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Development of a Multi-Site Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

Christine Moulton Clemson
University of Massachusetts Medical School

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Development of a Multi-Site Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

Submitted for fulfillment of Thesis for Masters in Clinical Investigation
Christine Clemson, PhD
November 5, 2009
DEVELOPMENT OF A MULTI-SITE PHASE II CLINICAL TRIAL
OF VALPROIC ACID (VPA) FOR RETINITIS PIGMENTOSA

A Masters Thesis Presented
By
Christine Moulton Clemson

The signature of the Master's Thesis Committee signifies
Completion and approval as to style and content of the Thesis

Gary Ostroff, Ph.D., Chair of Committee

Catarina Kafe, M.D., Ph.D., Member of Committee

Robert Brown, M.D. Ph.D., Member of Committee

Shalesh Kaushal, M.D. Ph.D., Member of Committee

The signature of the Dean of the Graduate School of Biomedical Sciences signifies that the
student has met all the master's degree graduation requirements of the school.

Anthony Carruthers, Ph.D.,
Dean of the Graduate School of Biomedical Sciences

Master's in Clinical Investigation Program

January 5, 2010
ACKNOWLEDGEMENTS

I would like to thank Shalesh Kaushal, M.D., Ph.D. not only for his idea to use VPA as a retinal therapeutic but also for the tremendous opportunity to take his concept from the preliminary stage to an approved trial as a project for a Master’s degree. This project allowed me to learn the specialized process of trial design and FDA approval in an incredibly constrained period of time. Thank you for the faith and trust you placed in me.

I would like to thank Robert Goldberg, Ph.D. for his tremendous mentorship and dedication to the MSCI students in general and to me in specific that consistently went above and beyond.

I would like to thank the Office of Research and Sheila Noone and Shayne Deal. They took the time to educate and guide me through a maze of new concepts and regulations. Their support during the IRB submissions and budget development was invaluable.

I would like to thank Lucie Lajuenesse in the Research Pharmacy for her help with drug sourcing and placebo design, her passion and dedication to her job and the patients she serves are inspiring.

I would like to thank Jenna Checchi for her help with the RP and AMD subject databases and being a much needed sounding board during many of the frustrating aspects of this project.

Mark Krebs at the University of Florida was instrumental in acquiring the visual field data correctly and in editing and contributing to the RP manuscript.

I would like to thank my fellow inaugural MSCI students: Olga Hardy, M.D.; Wendy Marsh, M.D.; Emily Weber-Lebrun, M.D.; Christopher Rosenbaum, M.D. and Stephen Hatch, M.D. I enjoyed learning, laughing and commiserating with you all.

Finally I would like to thank my family. It is great to reflect upon the process of my Ph.D. thesis years ago when our now teenaged son, Daniel, was only a toddler. Our family has grown considerably with his twin sisters, Rachel and Caroline. However, there are similarities in the family sacrifices and the heavy load that my husband, Conrad, bore. Conrad, you are truly a partner in every sense. Thank you.
OVERALL INTRODUCTION TO THESIS

The body of work presented here is a compendium of the multiple steps required for an investigator initiated trial of an existing medication (Valproic Acid- VPA) for a new indication (Retinitis Pigmentosa – RP). The chapters are listed in logical and chronological order of the process. In order to access patient records an expedited Institutional Review Board (IRB) application for retrospective chart review was submitted (Chapter 1). These records enabled the statistical analysis which not only laid the framework for the trial design, but also became the basis for two manuscripts (Chapter 2). Protocol development informed by the preliminary human studies (Chapter 3) was an instrumental part of the Investigational New Drug (IND) application (Chapter 3.5). This protocol along with the extensive case report forms that detail the intended data to be collected are included in the IND application. Because the Phase II clinical trial proposed attempting to identify the specific RP mutations of the subjects utilizing a National Eye Institute (NEI) study that enabled free genotyping services, two IRB applications were submitted (Chapter 3.6). The first was for approval of the NEI genotyping protocol, the second involved the VPA intervention. Two very different sources of funding for this trial were attempted (Chapter 4) – the NIH via the Challenge Grant mechanism and a private eye disease foundation (Foundation Fighting Blindness). In Chapter 5 I detail the alternate study designs that were considered and developed for this trial (and ultimately abandoned). Finally, in Chapter 6, I formally detail my suggestions to aid in the development of a comprehensive investigator initiated core facility at UMMMC.

The goal of this project was two-fold. The first was to learn the entire process of trial and protocol design both from a Umass Institutional perspective as well as from the perspective of the FDA. The second goal was the very real prospect of helping patients with a blinding disease. This work was successful on both counts. IRB approval was received for all the submitted applications. The complexity and uniqueness of many aspects of these submissions culminated in a comprehensive learning experience. The process of working with the Umass Research Pharmacy as well as developing the industry contacts and know-how to develop a workable and financially feasible placebo were both particularly important learning experiences. FDA approval of the IND submission was also received, and the process of pre-communication and delving into the considerable and ever-changing rules and regulations resulted in an extensive and valuable knowledge base. While the practicality of funding has limited the ability of this trial to move forward at this point, given the extensive framework laid by this body of work, we are actively pursuing other opportunities.

The third outcome of this work, while not as intentional, was the considerable process of determining the specific competencies and infrastructure that exist at UMMMC to enable investigator initiated drug intervention studies. While this institution is clearly moving rapidly in the direction of translational research, the many needs of these studies are often only clearly understood when the process is specifically undertaken. In completing the approval of this Phase II clinical trial, I was not only able to better understand and define the existing capabilities of UMMMC for this kind of research, I was able to add to that infrastructure when the existing knowledge or skill set was not available. In this
manner, I was able to inform and guide many of the support personnel who guided me and have become a part of the strategic direction of UMMC towards clinical translational research.
CHAPTER 1: RETROSPECTIVE REVIEW OF CHARTS OF PATIENTS TREATED OFF-LABEL WITH VPA AT UNIVERSITY OF FLORIDA

1.1 INTRODUCTION

The inception of the trial design required an analysis of the preliminary clinical data from patients treated off-label with VPA. Practitioners are strictly speaking allowed to prescribe their patients medications for indications other than what they are approved or marketed for. Dr. Kaushal treated both patients with RP, who have no real existing treatment options, and patients with Age Related Macular Degeneration (AMD), who failed standard therapy, with VPA. The scientific basis for using VPA as a retinal therapeutic is detailed exhaustively in the manuscript in Chapter 2 (page 19). In brief, prior work has shown that VPA has multiple biologic properties including apoptosis inhibition, microglial activation and even stimulation of photoreceptor differentiation from glial cells. In the Kaushal laboratory, VPA was identified as a potent molecular chaperone, increasing the yield of properly folded mutant rhodopsin, a protein important for many forms of RP. Further work from our laboratory has also shown that VPA can protect retinal cells from oxidative stress which is thought to be important in the progression of cell loss in RP and AMD.

VPA was approved by the FDA for use as a broad spectrum anticonvulsant in 1978 and is also used for acute and maintenance therapy of bipolar disease, for migraine prophylaxis, and occasionally for chronic pain syndromes. Therefore the pre-clinical, pharmacokinetic, manufacturing, safety and tolerability analysis were extensively completed previously. The off-label use of this medication allows for a preliminary analysis of its affect on retinal function as well as its tolerability in this specific patient population. Of course a clinical trial is required to rigorously analyze the efficacy and safety of VPA for retinal disease indications.

1.2 THE PROCESS

Dr. Kaushal had recently transferred here from University of Florida (UF), so our access to medical records were limited to only those patients that transferred their records to this institution. As this was my first foray into the IRB process, my initial approach was to familiarize myself with the resources in the UMMC Office of Research IRB website. My first goal was to understand whether the retrospective chart review (that would occur here at UMMC) of records of patients treated at a different institution (UF) would qualify for an exemption. This required extensive searching of the institutional web resources as well as the Collaborative IRB Training Initiative (CITI) materials. Ultimately a meeting was scheduled with Shayne Deal, a protocol specialist in the IRB office. I carefully detailed the information we proposed to collect and the complexity of the situation. She consulted with her superiors and ultimately confirmed that the chart review would be appropriate for an exemption.

I prepared and submitted the IRB exemption form and the data abstraction form and submitted it to Shayne for several rounds of pre-review and edits. Through this process it became clear that a
HIPPA waiver was also required so I prepared that as well. All three documents were submitted in hard copy to the IRB office.

1.3 Issues and Recommendations

While the Office of Research offers a variety of resources to investigators for human subjects’ research, the information is not centralized and often requires prior knowledge of where to look or who to contact to efficiently locate the information. The lack of centralization in human subjects’ research resources is clearly going to be addressed by the establishment of the UMass Center for Clinical and Translational Science and their co-pilot program to guide investigators through the process. It will be important not only to establish this conceptually however, as existing Office of Research staff will need to be continually informed and updated to the changing requirements and developing needs of the research community. While I now understand Umass IRB exemptions because I went through the process, it will be important to develop a tool that allows a naïve investigator to view and distill the entire process from start to finish. Electronic submission and tracking of the forms to the IRB office would streamline the process considerably.

The fact that Dr. Kaushal had recently transferred here ultimately served to be the biggest obstacle as access to medical records is strictly limited to those patients who plan on continuing to receive their care from Dr. Kaushal. Not only does this potentially bias the records, but also severely reduced the number of records we had access to. An additional and very real complication was that most of the records were faxed by the medical records Department at UF which was wholly inadequate for much of the outcomes of interest.

1.4 Outcome

Once the exemption was approved by the IRB, I was then given access to the records of UF patients as their records were transferred to UMMMC. A secure filing system was established in my office, and I began the considerable process of teaching myself to understand an Ophthalmologic patient record so I could abstract the required information. Through contact with the UMMMC Department of Ophthalmology clinic staff, and online web resources, I learned how to read and understand the clinic notes, and diagnostic measures and ultimately abstracted the data from approximately 14 RP patients and about 20 AMD patient’s records. I established password protected Excel spreadsheets and de-identified the data.

The adequacy of the medical records was addressed ultimately by my working with Mark Krebs, who is on staff at UF. I was able to identify the appropriate records for him and he would go to the medical records department, take the appropriate records to a high resolution color copy machine in another building to duplicate them. He would then send those records to me. This ensured both that all the data was preserved and that the reproduction of the visual fields was performed with no change in size. I was able to receive good data in this manner for seven RP patients that had baseline and follow up measures while on VPA.
## 1.5 Expedited IRB Application for Retrospective Chart Review of Pilot Data

### 1.5.1 IRB Exemption Application

<table>
<thead>
<tr>
<th>REQUEST FOR EXEMPTION</th>
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<tbody>
<tr>
<td>Shalesh Kaushal, MD, PhD</td>
</tr>
<tr>
<td>Christine Clemson, PhD</td>
</tr>
</tbody>
</table>

**Department:** Department of Ophthalmology  
**Campus:** University  
**Telephone Number:** 856-4808  
**E-mail address:** shalesh.kaushal@umassmemorial.org; christine.clemson@umassmed.edu  
**Title of project:** Retrospective Chart Review of Patients on Valproic Acid  

**Briefly describe the purpose of the study.**

This retrospective, chart-review of medical records transferred here from patients that Dr Kaushal previously treated at the University of Florida. There is no need for a HIPAA waiver given these are not currently patients at UMass and they signed the HIPAA form in Florida. The information to be abstracted was not collected for research, but is from the treatment of these patients by Dr. Kaushal who utilized both standard therapy and an off label medication – valproic acid. The retrospective chart review will be performed to assess these specific clinical outcomes in patients treated with oral valproic acid (VPA): 1) visual acuity, 2) visual field, 3) retinal anatomy, 4) perceived benefit as described in patient interviews and 5) safety profile. These outcomes will be used to assess the rates of vision loss (primary outcomes) and adverse events (secondary outcome) in patients prior to and during a regimen of oral valproic acid for a period of up to 12 months. This information will be used to inform our study design, IND, IRB and NIH grant submissions for a clinical trial here at UMass to determine the efficacy and safety of this medication for the treatment of retinal diseases.

**Briefly describe what procedures will be employed. If subjects are to be involved, describe how they will be involved, how they will be recruited or identified, and how long each procedure will take. Attach all surveys, interview questions, or other instruments to be used.**

This is a retrospective study. There will be no new procedures performed on patients. We will perform a thorough chart review of several diagnostic measures including Snellen Standard chart protocol, Electoretinography (ERT); Goldman perimetry, Optical Coherence Tomography (OCT), blood chemistry. The patients involved will have all signed medical records release forms to allow the transfer of their records to UMMHC. The majority of these patients will continue to be treated by Dr. Kaushal here at UMass. Patients that will transfer their care to UMass so as to continue to receive care from Dr. Kaushal will sign UMass HIPAA forms (the new patient information that will be collected at UMass is not, of course, covered under this exemption request).
Briefly describe how the data be recorded and who will have access to the data.

All data will be kept in a computer file, at all times to be accessed only by the primary investigator. A master Excel data collection sheet will be created for the statistical analysis. The paper data sheets information will be transferred to an Excel file for the final analysis.

Briefly explain the procedures to be taken to assure anonymity and confidentiality.

The patients will be de-identified by the creation of a master list assigning a study number to each patient. The database will be protected and will include the study number with a reference to the medical record number.

Please list all research personnel involved in the conduct of the study and their role in the study. All research personnel must complete a human subjects educational training program. Please visit our website at http://www.umassmed.edu/subjects/human/education/ for more information.

Shalesh Kaushal, MD, PhD Primary Investigator
Christine Clemson, PhD. Co Investigator

Citation of Exempt Category (check one):  ___ 1 ___ 2 ___ 3 _X 4* ___ 5 ___ 6

* If you have chosen exempt category #4, please complete the questions to follow.

EXCEPTIONS: Research involving vulnerable populations such as the mentally or cognitively impaired, prisoners, parolees, pregnant women, and fetuses cannot be exempt from review even though it meets the criteria below. Research using survey procedures or interview procedures upon children cannot be exempt. Research involving observation of children’s behavior cannot be exempt if the investigator is a participant in the behaviours observed.

Exempt Category #4: COMPLETE THIS SECTION IF YOU ARE REQUESTING PERMISSION TO STUDY EXISTING DATA, DOCUMENTS, RECORDS, AND/OR BIOLOGICAL SPECIMENS. Each section must be completed.

What is/are the type(s) of data/biological specimens to be used?

Patient demographic information including age, gender, diagnosis, comorbidities, medications and medical history will be obtained. Ocular treatments, retinal thickness, visual fields, length of treatment and dose of VPA, intraocular pressure, anterior and posterior exam data, retinal photographic changes, blood chemistry including chem 7, CBC and electrolytes, and patient comments on adverse effects and subjective improvement will be collected from the outpatient medical record.

What is the source of the data/biological specimens? Are these publicly available?

Data will be extracted from outpatient clinic charts of patients treated by Dr. Kaushal between January 2008 through the submission of this application.
Are data/biological specimens originally collected solely for research purposes?

Yes ___ No __X  

How are data/biological specimens identified when they are made available to your study team? (Please indicate by marking the appropriate box below.)

i. _____Direct Identifier (i.e., subject name, address, social security, medical record number, etc.). If receiving identifiers, this may require expedited or full IRB review.

ii. ___X_Indirect Identifier (i.e., an assigned code which could be used by the investigator or the source providing the data/biological specimens to identify a subject, such as a pathology tracking number or tracking code used by the source.)

iii. _____No Identifier (i.e., neither the researcher nor the source providing the data/biological specimens can identify a subject based upon information provided with the data/biological specimens.)

If (i) or (ii) is checked above and you are requesting permission to study biological specimens, will the identifier provided with the specimens be removed and destroyed upon receipt by your study team?  Yes ____  
No_____  Does not apply____X____

If (i) or (ii) is checked above and you are requesting permission to study archived data, will you abstract and record any subject identifiers as a part of the data collection process?  Yes ___X__  
No _____  Does not apply _____

Will any data or biological specimen(s) be collected from subjects after the submission of this application?  
Yes* _____  No ___X__  

*If yes, your research does not qualify for exemption from IRB review.

If you will have access to any protected health information for the data/specimen collection, you will be required to complete the HIPAA Waiver of Authorization and submit a signed copy for IRB review. Please visit our webpage 
www.umassmed.edu/subjects/human/HIPAA for the Waiver of Authorization.

Investigator’s Assurance: I certify that the information provided is complete and correct. I understand that as Principal Investigator, I have responsibility for the conduct of the study, the ethical performance of the project, and the protection of the rights and welfare of human subjects.

Principal Investigator’s Signature ____________________________  
Date 2-19-09 ______________________
1.5.2 HIPPA WAIVER

UMass Memorial Medical Center

HIPAA IRB WAIVER OF AUTHORIZATION

Principal Investigator: Shalesh Kaushal, MD PhD

IRB Docket # H-

**Protocol Title:** Retrospective Chart Review of Retina Patients on Valproic Acid

1. The use or disclosure of Protected Health Information (PHI) involves no more than a minimal risk to the privacy of individuals. Explain why? Include a detailed list of the PHI to be collected and a list of the source(s) of the PHI.

Patient demographic information including age, gender and medical history will be obtained. Ophthalmologic exam, diagnostic data and patient comments will be collected from the outpatient medical record.

2. Describe the plan to protect identifiers and indicate where PHI will be stored and who will have access (researchers must list all of the entities that might have access to the study’s PHI such as IRB, sponsors, FDA, data safety monitoring boards and any others given authority by law).

The patients will be de-identified by the creation of a master list assigning a study number to each patient. The database will be protected and will include the study number with a reference to the medical record number and name during data collection phase. Then it will be de-identified by removing the name and medical record for a final analysis. All data will be kept in a computer file, at all times to be accessed only by the primary investigator. A de-identified master Excel data collection sheet will be created for the statistical analysis.

3. When will identifiers collected during the study be destroyed? Also, please describe the procedure used to destroy the identifying data (electronically, paper, audio/video, photography, other).

The identifiers collected during the study will be destroyed upon completion of the statistical analysis of the study data. Electronic sources of data will only be stored on the hospital secure server and will be deleted from storage. Any paper containing identifying data will be shredded and placed in secured disposal bins available throughout the hospital.
4. Are research subjects contacted during the course of this research study? If yes, describe in detail, the recruitment plan.

Patients will be contacted only for them to complete a Medical Records Release form from the University of Florida to allow their records to be transferred to UMMHC.

5. The research could not practicably be conducted without the waiver because (explain below).

It would be an additional cumbersome step that is costly and bothersome to the patients, most of whom are severely handicapped due to vision loss. The Medical Records Release Form request already is a burdensome and time consuming step that is a direct result of Dr. Kaushal’s move here to Umass. Additional steps and forms will only serve to prolong establishing a clinical trial here at UMMS of this highly promising treatment for patients who are experiencing catastrophic debilitating vision loss.

6. The research could not practicably be conducted without access to and use of the PHI because (explain below).

The necessary data is contained within patient medical charts.

7. The HIPAA regulation requires reasonable efforts to limit protected health information to the minimum necessary to accomplish the intended purpose of the use, disclosure or request. Please note that researchers are also accountable for any PHI released under a waiver. Explain why PHI obtained for this study is/are the minimum information needed to meet the research objectives.

Patient demographics, comorbidities and other medications are required to establish that we have avoided a selection bias and to identify potential confounding factors. Ophthalmologic exam and diagnostic test information is required for the primary outcomes, assessing vision loss. Blood chemistry information is required for the secondary outcomes related to patient safety.

The information listed in the waiver application is accurate and all research staff will comply with the HIPAA regulations and the waiver criteria.

I assure that the information I obtain as part of this research (including protected health information) will not be reused or disclosed to any other person or entity other than those listed on this form, except as required by law. If at any time I want to reuse this information for other purposes or disclose the information to other individuals, or other entities, I will seek approval by the IRB.
UMass Memorial Medical Center

ACCOUNTING OF RESEARCH DISCLOSURES*  
Attachment A

Patient/Subject Name: __________________________________________________

Medical Record #: ___________________ DOB: ___________________

Information on the patient/study subject noted above was disclosed to the researcher listed below (or his/her designee) after approval was received for (check one):

☐ Data Collection for Review Preparatory to Research
☐ Decedent Research
X Waiver of Authorization

Name of Researcher: Shalesh Kaushal, MD PhD_____________________________

Department @ UMMS: Ophthalmology__________________ Phone: _508-856-4808_______

Brief Description of Information Disclosed: age, gender, race, history, blood chemistry, ophthalmologic diagnostic exams, patient comments

Disclosure made by UMass Memorial Medical Center.

Date: __________________

*This Accounting of Research Disclosures form should be used by the researcher in the event of PHI disclosures in any of the following circumstances:

1) The researcher’s request to conduct Data Collection for Review Preparatory to Research has been approved by the Office of Research
2) The researcher’s request of PHI solely for research on decedents has been acknowledged by the IRB chair or designee
3) The researcher’s Request for Waiver of Authorization has been approved by the IRB

After customizing this document with name and MR #, either place this form directly in the last section of the medical record (Incoming Letters and Reports) or send to:

Health Information Management  
UMass Memorial Medical Center  
55 Lake Avenue North  
Worcester, MA. 01655
CHAPTER 2: ANALYSIS OF DATA ABSTRACTED FROM PATIENT RECORDS

2.1 INTRODUCTION
While the natural history of RP has been described in the literature, the disease is quite heterogenous and is really a collection of many retinal dystrophic disorders. Therefore, it was important to use the data abstracted from the records of patients as a guide and a feasibility check on the study design. Specifically, the changes in outcome measures of interest (visual field, retinal thickness and visual acuity) are hard to predict among diverse RP patient populations, so this data was critical in designing the endpoints for the study. Additionally, the tolerability of VPA, even at relatively low doses in population of patients with RP and AMD is an open question, so any information abstracted on side effects and adverse events is valuable.

2.2 THE PROCESS
To get help in the rigorous biostatistical analysis of the data, I first contacted the UMMS institutional biostatistician, Stephen Baker. However, he didn"t have the time or the resources to dedicate to this project long term. An adequate analysis of this data would involve not only an understanding of biostatistics but also the specific ophthalmologic outcome measures (which are psycho-physical and inherently prone to measurement bias) and the patient population (which is extremely heterogeneous).

I was able to convince Carol Bigelow, PhD., who teaches the three Master in Clinical Investigation Biostatistics and Data Management classes, to partner with me on this analysis. Her time was quite limited, so we agreed to merge her understanding of data analysis with my burgeoning understanding of the science of RP outcome measures which was based in large part on the work by Eliot Berson at the Massachusetts Eye and Ear Infirmary. His group is highly regarded in their statistical approach which is informed by an in-depth understanding of the RP patient population and clinical measures. Carol Bigelow provided a preliminary analysis that became the template for the full analysis I performed on the RP patient data. I incorporated this completed analysis into the manuscript that follows (Chapter 2.5).

During the summer of 2009, a medical student intern, Jenna Checchi, who has considerable experience in data abstraction of chart records from her tenure at the NIH, worked with me to finalize abstraction of the complete AMD patient"s records. She also was instrumental in fine tuning both the RP and AMD Excel spreadsheets I had designed, to make them much more fascicle tools. We worked together on the AMD patient data to perform the analysis. This analysis was incorporated into the manuscript in Chapter 2.6.

2.3 ISSUES AND RECOMMENDATIONS
The lack of adequate biostatistical support staff at UMMMC is a known issue and one that is being addressed by the establishment of the new Department of Quantitative Health Sciences. It is important to emphasize that even relatively small projects such as this one, require considerable
investment of time and effort on the part of the biostatistical consultant. As more medical records were received, and other potential outcome measures were considered, the analysis was continually evolving. Fortunately between my training in biostatistics and the template analysis Carol had initially provided I was able to complete the analysis on my own with final feedback from Carol. I was also able to transfer this knowledge to the AMD study and adapt it to the specific outcome measures for that population, training Jenna in the process.

As with every aspect of this project, I embraced the fact that I would be primarily responsible for the data analysis as it provided me with yet another opportunity for experiential learning. I was glad, however, to have guidance and proofing by Carol Bigelow to ensure that the analysis was performed properly. As more and more Umass investigators pursue clinical research, the demand for biostatisticians will only increase. The current model of pockets of expertise dispersed among many different departments will not address this need. A robust supply of analysts, who are not fully occupied with other projects will be needed to provide core service to the UMMC research community.

While the analysis of the seven RP patients is suggestive of therapeutic benefit, given the low numbers, and extremely short length of follow up, the statistical analysis is considered speculative. The lack of sufficient data is what I would consider the largest issue to this analysis. The marginal statistical significance in the RP patient set is superior to the AMD results, which combine to paint a very different picture from what Dr. Kaushal sees in the UMMC Ophthalmologic Clinic.

The complications of the restricted patient population are such that that we cannot access more records from the UF patients who have been treated with VPA unless they happen to transfer their records to UMMC. It was hard to predict a priori how many patients would transfer their records from UF to UMMC and clearly, Dr. Kaushal’s expectations were optimistic. In retrospect, instead of proposing a larger randomized controlled trial as in Chapter 3 it would have been prudent to propose an intermediate trial. A small pilot study of standardized patients at the UMMC clinic that are consented, on a standard course of VPA and consistently analyzed for a variety of measures would provide more and better information than I could retrieve from this limited data set.

2.4 Outcome

Both manuscripts will be submitted to the British Journal of Ophthalmology. Rad Tzekof, PhD, a senior scientist with considerable expertise in eye studies who has recently joined our laboratory, is helping me to convert the visual field areas to the more robust degrees$^2$. Once this conversion is complete we expect to submit the manuscripts immediately.
2.5 MANUSCRIPT 1: VALPROIC ACID AS A POTENTIAL THERAPEUTIC FOR RETINITIS PIGMENTOSA

Original Article
Clinical science

Therapeutic Potential of Valproic Acid for Retinitis Pigmentosa

CM Clemson*, R Tzekov†, M Krebs‡, JM Checchi¹, C Bigelow*, S Kaushal**

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*These authors contributed equally to this work
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North, Worcester, MA 01655, Email: Shalesh.Kaushal@umassmemorial.org, Tel: 508-334-0677, Fax: 508-334-0699

Key words: Retinitis pigmentosa, valproic acid, visual fields, visual acuity.

Word count: 2,238 words
ABSTRACT

Background/aim: To examine the efficacy and safety of Valproic Acid (VPA) in patients with Retinitis Pigmentosa (RP).

Methods: Thirteen eyes were examined before and after brief treatment (average 4 months) with VPA. Visual fields (VF) for each eye were defined using digitized Goldmann Kinetic Perimetry tracings. VF areas were log transformed and vision loss/gain relative to baseline was calculated.

Results: Nine eyes had improved visual field with treatment, two eyes had decreased visual field and two eyes experienced no change, with an overall average increase of 11%. Assuming typical loss in VF area without treatment, this increase in VF was statistically significant (p<.02). An average decrease in logMAR scores was seen in these 13 eyes, which was significant (p<.02) assuming no loss in acuity without treatment. Side effects were mild and well tolerated.

Conclusion: Treatment with VPA does not provide significant harm and is suggestive of a therapeutic benefit to patients with RP. A placebo-controlled clinical trial will be necessary to rigorously assess the efficacy and safety of VPA for RP.
INTRODUCTION

Retinitis pigmentosa (RP) is a severe neurodegenerative disease of the retina characterized initially by night blindness, with progression to tunnel vision and eventual loss of central vision and total blindness. Targeted therapies for RP are complicated by the identification of more than 40 genes linked to the dominant and recessive forms of this disease. While a few new approaches for RP treatment have recently been investigated, including nutritional supplementation, light reduction, and gene therapy [1, 2], of these, vitamin A supplementation is the most promising [3-5], but its benefits are modest and side effects are problematic. Therefore, currently there is no significant treatment or cure for RP.

Recently we demonstrated the use of retinoids and other small molecules as pharmacological chaperones to increase the yield of properly folded RP mutant rhodopsins in heterologous cell culture [6]. We have tested whether other known small molecules can provide similar effects. We identified valproic acid (VPA) through this screen (S. Noorwez and S. Kaushal, manuscript in preparation). Prior work has suggested that VPA is a potent inhibitor of histone deacetylase (HDAC) [7] and the inflammatory response pathway via apoptosis of microglial cells [8-10]. In addition, VPA is known to down-regulate complement proteins [11] and increase the levels of various neurotrophic factors [12]. Thus, VPA has a unique biological profile suitable for treating retinal diseases. VPA was approved by the FDA for use as a broad spectrum anticonvulsant in 1978 and is also used for acute and maintenance therapy of bipolar disease, for migraine prophylaxis, and occasionally for chronic pain syndromes [13]. Collectively, this body of evidence suggests that VPA may be an appropriate therapeutic for patients with retinal dystrophies.

The preliminary clinical data presented here suggests that VPA has the potential to not only stop the progressive loss of visual field (VF) in RP patients, but can also improve VF; to the best of our knowledge, such an impact has not been demonstrated in a potential RP therapeutic. Results presented here will be used to inform a larger clinical trial to test the safety and efficacy of VPA for RP.

PATIENTS AND METHODS

This study is a retrospective chart review of patients with RP who were treated off label with VPA at the University of Florida Ophthalmology Department clinic between December 2007 and January 2009. This analysis was approved by the appropriate Institutional Review Board. Fourteen RP patients were identified; of these seven had adequate baseline and follow-up visual fields. (The visual fields from one eye of subject 5 were excluded due to poor quality.) The length of follow-up varied from 2 to 6 months. The dosage of VPA varied from 500 to 750 mg a day, which is lower than the dosage typically used for anti-convulsant therapy. Patient demographics, diagnosis, family history, genotype, best corrected visual acuity (BCVA - which was converted to the logarithm of minimal angle of resolution (logMAR)), dosage of VPA, length of treatment, blood chemistries and reported side effects were all recorded.

For each patient, intact baseline and follow-up visual field areas were defined using the existing Goldmann Kinetic Perimetry tracings (isopter V4e) from each eye. The tracings were digitized and the corresponding areas of functioning retina (in mm²) were calculated based on the method used by Dagnelie [14].

We defined the change in visual field (mm²) as a simple measure of percent change from baseline:
Percent change from baseline = 100 x ((Follow-up mm² – Baseline mm²)/Baseline mm²)

Improvement in visual field was defined as greater than 2% increase, a loss in VF area was defined as greater than a 2% decrease, while VF was considered unchanged if the follow-up value was within 2% of baseline.

Visual field loss in RP does not occur at a linear rate, and Massoff et al demonstrated it may decline exponentially, with an estimated loss of about 0.10 log units per year (16). VF areas (mm²) were log₉ transformed (logVF) and the difference between follow-up and baseline was calculated (ΔlogVF). To calculate average percent change in VF over the course of treatment the average difference across all eyes was calculated and converted to area (mm²). This value was used as the follow-up value in the above formula, and the baseline value used was 314 mm² (which was the average baseline from all subjects).

Using varying estimates from the literature regarding the natural history of visual field loss in RP patients [15-17], we hypothesized that patients without treatment would lose either 0.0, 0.011 or 0.033 logVF over the average length of treatment (4 months). Data was not assumed to be distributed normally and significance levels were calculated using the Wilcoxon signed ranked test. Statistical analysis was performed using Graph Pad Prism (La Jolla, CA).

Table 1. Study Sample Characteristics

<table>
<thead>
<tr>
<th>Patient #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Avg ± sd</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td></td>
</tr>
<tr>
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<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
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<td>21</td>
<td>46</td>
<td>16</td>
<td>23</td>
<td>31</td>
<td>52</td>
<td>36±16</td>
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<tr>
<td>Autosomal Dominant RP</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Length of VPA treatment (mths)</td>
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<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>4±1</td>
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<td>Avg. Dose of VPA (mg/day)</td>
<td>750</td>
<td>750</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>750</td>
<td>643±133</td>
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<tr>
<td>Eye</td>
<td>OD</td>
<td>OD</td>
<td>OD</td>
<td>OD</td>
<td>OD</td>
<td>OD</td>
<td>OD</td>
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<tr>
<td>Visual Field at baseline (mm²)</td>
<td>192</td>
<td>165</td>
<td>148</td>
<td>107</td>
<td>38</td>
<td>201</td>
<td>562</td>
<td>556</td>
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<tr>
<td>Visual Field at Follow up (mm²)</td>
<td>210</td>
<td>187</td>
<td>165</td>
<td>118</td>
<td>96</td>
<td>200</td>
<td>586</td>
<td>594</td>
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<td>Visual Acuity at baseline (logMAR)</td>
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<td>1</td>
<td>.544</td>
<td>.301</td>
<td>.176</td>
<td>.301</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

RESULTS

Table 1 summarizes the average characteristics of the RP patients included in this analysis. Patients’ ages ranged from 16 to 56 (average = 36), with five males included. The majority of patients (n=6, 86%) had a family history or reported genotyping suggestive of an autosomal dominant form of RP (ADRP). The length of treatment on VPA was short, with a range from 2 to 6 months. Overall, average visual acuity was 20/47 per eye (range 20/20 to count fingers at 3’ or 20/4000).
Analysis of Change in Functioning Retina

Visual fields were measured using kinetic perimetry; tracings were digitized and the areas determined by isopter V were converted into areas of functioning retina. Examples of baseline and follow-up perimeter tracings are shown in Figure 1A. The patient whose visual field is shown on Fig 1A (patient #6, Table 1) had two follow-ups within a short period of time (4 weeks) and VF results were stable, suggesting stability in vision function gain as a result of treatment. Line graphs of baseline and follow-up values of visual field areas for all seven study subjects, for each eye and the average values per patient are shown in Figure 1B. Baseline and follow-up data are plotted according to their time of measurement, thus accounting for duration of treatment; these graphs depict the individual slopes of change in visual field. Using a difference from baseline of ±2% as a criterion for change, nine eyes (5 right eyes and 4 left eyes) had improved intact visual fields after brief treatment with VPA, while two eyes lost VF area (one right eye and one left eye) and two eyes (one right and one left eye) had no change in VF. Table 2 lists the values for percent change from baseline and difference in logVF as described in Methods.

Some studies estimated an average visual loss of 0.10 log units per year (equivalent to ~10.5%/year) or about 0.033 log units (~3.52%) for 4 months (16), which is the average length of VPA treatment in this study. The change in logVF (ΔlogVF) from baseline is presented in Table 2 and Figure 2. The average change for all 13 eyes over the course of treatment was +0.164 (SD .298) log units, (range -0.012 to +0.942) corresponding to an average increase of about 35 mm². Assuming a baseline area of 314 mm² (the average baseline of subjects in this study), this translates to an 11% increase in area of functioning retina.

Table 2. Percent Change in Visual Field

<table>
<thead>
<tr>
<th>Patient</th>
<th>Eye</th>
<th>% Change in Vf Area</th>
<th>Δ logVF</th>
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<td></td>
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<td>13.9</td>
<td>.130</td>
</tr>
<tr>
<td>2</td>
<td>OD</td>
<td>11.3</td>
<td>.112</td>
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<tr>
<td></td>
<td>OS</td>
<td>10.2</td>
<td>.097</td>
</tr>
<tr>
<td>3</td>
<td>OD</td>
<td>156.4</td>
<td>.942</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>-0.4</td>
<td>-.004</td>
</tr>
<tr>
<td>4</td>
<td>OD</td>
<td>4.4</td>
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</tr>
<tr>
<td></td>
<td>OS</td>
<td>8.5</td>
<td>.065</td>
</tr>
<tr>
<td>5</td>
<td>OD</td>
<td>-10.2</td>
<td>-.107</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>OD</td>
<td>86.3</td>
<td>.022</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>27.7</td>
<td>.246</td>
</tr>
<tr>
<td>7</td>
<td>OD</td>
<td>1.3</td>
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<tr>
<td></td>
<td>OS</td>
<td>-11.2</td>
<td>-.120</td>
</tr>
<tr>
<td>Average</td>
<td>SD</td>
<td>23.3±48.8</td>
<td>.164±.298</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>9.4</td>
<td>.09</td>
</tr>
</tbody>
</table>

* - VF results excluded due to poor quality

Table 3. Statistical analysis of changes in VF on VPA relative to typical loss in RP patients.

<table>
<thead>
<tr>
<th>Null Hypothesis</th>
<th>Significance (Two Sided) of signed rank test</th>
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<td>Mean Change with no treatment</td>
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<td></td>
<td>Left eyes</td>
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<tr>
<td>0</td>
<td>.08</td>
</tr>
<tr>
<td>-0.011</td>
<td>.22</td>
</tr>
<tr>
<td>-0.033</td>
<td>.09</td>
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</tbody>
</table>

We performed an exploratory assessment to see if this effect was significant. We compared the change in VF for eyes on VPA to two theoretical rates of vision loss with no treatment. The first assumption was that there would be no loss of VF without treatment, while the second assumption was that eyes would lose an average of 0.033 log units or 3.5% (16). The third assumption was for a more conservative estimate of visual field loss based on Berson et al. (18). Significance levels were calculated using the Wilcoxon signed rank test (Table 3). A significant difference (p < .006) in VF loss was seen for eyes on VPA relative to the natural history of the disease (15). Even if one assumes a
slower rate of decline in visual field loss of 0.011 logVF unit or 1.5% for 4 months duration of VPA treatment (based on data from Berson et al. (18)), the difference is statistically significant (p<0.02).

Visual Acuity

An overall increase in visual acuity on VPA treatment was observed (Table 1). A decrease in logMAR units from baseline to follow-up is indicative of improved BCVA. When analyzed by eye, average logMAR for all right eyes decreased at baseline from 0.457 (SD 0.515) to 0.260 (SD 0.380) at follow-up while average logMAR values for the left eyes decreased from 0.300 (SD 0.332) to 0.153 (SD 0.113). The average change in logMAR across all eyes was a loss of 0.172 (SD 0.269) log units (range -0.824 to 0), which translates to a positive change in Snellen score of approximately 20/47 to 20/32. Assuming no loss in visual acuity without treatment this change in acuity was significant (p < 0.02).

Assessment of Possible Harm

We performed a conservative analysis to explore the possibility of any potential negative effects of VPA on patient's visual field. For purposes of this analysis, an event of negative effect of VPA was indicated by net loss in visual field from baseline greater than 2%. This is a conservative approach because, absent any treatment, the natural progression of RP includes a potential for significant short-term deterioration in visual field [15-17]. Of the 13 eyes examined, two experienced worsening of their visual field (Figure 1). No abnormal liver function or blood chemistries were noted in the study sample. The most common side effects were mild and included tiredness (10%) and stomach irritation (13%).

DISCUSSION

Retinitis Pigmentosa is a blinding disease with no robust treatment options. In this study we found treatment with valproic acid to be safe in patients with RP. The visual field areas of five of seven RP patients increased with a short treatment of valproic acid. Encouragingly, in one case (patient # 6), the significant improvement in functioning retinal area was confirmed at two time points (23 and 27 weeks). While visual acuity is not always a reliable outcome measure for RP given that photoreceptor degeneration typically begins in the periphery and progresses to the central macula in only the latest stages of disease, we observed an overall improvement in acuity while on VPA. These positive results are encouraging given that the VPA dose used in this study was about 60% lower than the typical dose for epilepsy or the dose used in a recently published clinical trial for amyotrophic lateral sclerosis [18].

While prior accounts of limited delay of progression of photoreceptor loss in RP patients have been reported with nutritional supplementation such as vitamin A [3-5] or treatments such as hyperbaric oxygen therapy [19], to the best of our knowledge, this is the first reported case of improvement of vision function in patients with RP as a result of pharmacologic treatment.

Valproic acid is widely used as an anti-convulsant and mood stabilizer and its efficacy in these capacities is likely mediated via its ability to affect GABA levels through glutamic acid decarboxylase and GABA transaminase modulation [20, 21]. It is interesting to speculate on how VPA may act as a retinal therapeutic. We first considered VPA for RP as it was identified using our heterologous cell culture screen for small molecules that can increase the yield of properly folded RP mutant rhodopsins (S. Noorwez and S.K., manuscript in preparation). However, other preliminary clinical data
on patients with age related macular degeneration suggests that VPA may be beneficial to ocular
diseases that are not known to have protein folding pathway deficiencies (Checchi et al., this issue of
journal), suggesting that VPA can work either on multiple pathways or in a protein folding independent
pathway. A variety of recent evidence suggests that VPA may work at the level of cell death
protection or inflammatory mediation as its neuroprotective properties have been well documented
[12, 22, 23], and it can down-regulate the photoreceptor-specific inflammatory response pathway via
apoptosis of microglial cells [8-10]. Furthermore, VPA is known to be a potent inhibitor of histone
decacetylase (HDAC) [7, 23, 24]. A particularly exciting property of VPA has recently been
documented that suggests that it has the unique ability to reverse photoreceptor damage: VPA can
induce cells to differentiate in culture [7]; moreover, it has been shown to stimulate glial cells to
differentiate into photoreceptor-like cells [25].

In summary, VPA offers an exciting new potential therapy for RP, a tragic blinding disease with no
good treatment options. The results of our preliminary clinical analysis in conjunction with the prior in
vitro data suggest that VPA may be an effective treatment for photoreceptor loss associated with RP.
However, only seven patients were analyzed and the length of follow-up was brief (an average of 4
months). Patients in this analysis were not thoroughly genetically characterized, and it is possible that
genetic variation in known RP genes might account for the variability in therapeutic response to VPA.
We plan to use this study as the basis for a placebo-controlled clinical trial with patients with well
characterized RP genotypes to fully evaluate the efficacy and safety of VPA as a treatment for RP.
Footnotes

Acknowledgments: The authors would like to thank Linda Stein for her efforts on this publication.

Funding: This study was supported in part by the Vision Research Fund at the University of Massachusetts Medical School.

Competing Interests: None.

Ethics Approval: Ethics approval was provided by the Institutional Review Board, University of Massachusetts Medical School.
REFERENCES


Figure Legends

**Figure 1:** Visual field after treatment with VPA

- **A.** Goldmann Kinetic Perimetry tracings from patient 6 at baseline (left) and after 6 months of VPA treatment (middle-red), overlap of baseline and follow-up (right).  **B.** Change in Visual Field: Baseline and follow-up VF areas are graphed for each individual patient, length of follow-up varied for each patient. Areas were analyzed by right eye, left eye and average of both eyes. Numbers correspond to the individual subjects.

**Figure 2:** Change in visual field. Goldmann Kinetic Perimetry tracings (isopter V4e) from each eye were digitized and areas (mm2) were calculated as described in methods and log transformed. Scatterplots of change in log transformed VF over the course of treatment are shown for left eyes, right eyes and all eyes combined. Mean value is shown by thin bar and standard deviation is represented by upper and lower dark bars.
Figure 1

Figure 2
2.6 MANUSCRIPT 2: VALPROIC ACID AS A POTENTIAL THERAPEUTIC FOR AGE-RELATED MACULAR DEGENERATION

Valproic Acid as a Potential Therapeutic for Age-Related Macular Degeneration

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Key words: macular degeneration, valproic acid, visual acuity, apoptosis, pilot study

Word count: 2,349 words
ABSTRACT

Background/Aim: Small, pilot, retrospective study to assess efficacy and safety of valproic acid (VPA) as treatment for age-related macular degeneration (AMD).

Methods: Twelve patients with non-exudative (14 eyes) and exudative (8 eyes) AMD were treated off-label with VPA 500-750 mg/day for 23 weeks (±11.8). Treatment efficacy was assessed by change in best-corrected visual acuity (BCVA) (as logMAR). Patients were queried to assess subjective change in visual perception after treatment.

Results: Overall, BCVA improved in nine eyes, remained unchanged in nine eyes and worsened in four. However, in patients taking >500 mg/day, BCVA improved in eight eyes (57.1%), was unchanged in six eyes (42.9%) and did not worsen in any eyes. Eight patients (66.7%) reported subjective improvement in visual perception, which corresponded to improvement of BCVA in at least one eye. One patient discontinued treatment due to fatigue.

Conclusions: This is the first report to describe improvement of BCVA and subjective visual perception in AMD patients after treatment with VPA, which was well-tolerated in most patients. Due to small sample size and short duration of treatment, it is difficult to make definitive conclusions on treatment efficacy. A clinical trial is warranted to rigorously assess efficacy and safety of VPA in AMD.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 60 in the developed world [1] and is characterized by loss of central visual function, including visual acuity. AMD is categorized into two major forms: an exudative form and a non-exudative form.

Recent emerging technologies and novel therapeutics have adequately targeted the physiological aspects and progression of exudative AMD, which has a faster disease progression and poorer visual prognosis than non-exudative AMD. Various treatment options have emerged to suppress choroidal neovascularization, the landmark symptom of exudative AMD, such as laser coagulation, photodynamic therapy, and anti-VEGF therapy [2]. There is evidence that these treatments stabilize [2, 3] and perhaps improve [2] visual function in exudative AMD. Disease recurrence and potential unwanted systemic effects [2] suggest that there is a place for alternative treatment modalities for this form of the disease.

Currently, treatment strategies considered for non-exudative AMD have failed to stop disease progression or reverse vision loss. The Age-Related Eye Disease Study (AREDS) found that a combination of nutritional supplements (zinc and vitamins A, C, and E) slows the progression of AMD from intermediate to advanced stages over the course of several years [4]. Statins have been studied as a treatment option to clear subretinal deposits (drusen), which are associated with all forms of AMD, but, at the present time, there is insufficient evidence regarding their efficacy [5]. Subthreshold laser treatment also failed to produce protective effects in terms of drusen clearing [6]. Neither prophylaxis with vitamin supplementation nor treatment with statins specifically addresses the physiological characteristics of non-exudative or exudative AMD.
Numerous contributing factors are suspected [7], but most investigators agree that smoking and genetics are consistently associated with AMD [3]. Similar but less pronounced changes to Bruch’s membrane and the retinal pigment epithelium (RPE) can also be caused by normal physiological aspects of aging [7], which amplifies the importance of efforts to find a viable treatment option. AMD is likely a growing public health concern, especially in light of the aging “baby boomer” population. Exudative AMD only accounts for 10%-20% of incident cases of AMD, but remarkably accounts for 90% of those with severe vision loss [8, 9]. Non-exudative AMD can also lead to significant vision loss in the elderly [7], and there is still a dearth of prospective treatment candidates that adequately address the unique pathophysiological processes of this condition.

The accumulation of drusen and pigmentary abnormalities in RPE cells are characteristic of both forms of AMD. There is an ongoing debate about the components and origin of drusen, which likely arise from unprocessed and/or underprocessed cellular material contained in RPE cells that has been exocytosed [10]. This material in the form of debris accumulates in the subretinal space, promoting chronic inflammation that perturbs the function of RPE and the outer retina [7]. Consequently, photoreceptors, which rely on the components of the blood-retina barrier to maintain their environment, are unable to survive due to the dysfunction and subsequent loss of RPE integrity and changes in the permeability and composition of Bruch’s membrane. In addition, exudative AMD is marked by the appearance of choroidal neovascularization, usually affecting the macula. Newly formed choroidal blood vessels transcend Bruch’s membrane and leak exudate or blood in the surrounding space, causing separation of Bruch’s membrane from the RPE or neurosensory retina and leading ultimately to a scar formation [7].

Valproic acid (VPA) is a fatty acid that is used primarily as anti-convulsant therapy and was approved for this use by the Food and Drug Administration in 1978 [11]. Patients have demonstrated excellent tolerability of VPA compared to other treatment options [12]. Since then, therapeutic indications for VPA have been broadened, including the treatment of migraine and bipolar disorder [11], and VPA is currently under investigation for cancer treatment [13]. Research in this laboratory and others has identified biological properties of VPA that indicate that it could be used as a suitable treatment for retinal diseases. Recently, our laboratory has demonstrated the effectiveness of VPA to mitigate oxidative apoptosis of human RPE cells in culture. Additionally, we have other evidence that suggests that VPA is neuroprotective in mouse models (manuscript in preparation). VPA was identified as one of the small molecules that demonstrated effectiveness as a chaperone. Our companion manuscript (Clemson et al., this journal issue) demonstrates that VPA may also be effective in the treatment of Retinitis Pigmentosa. Others have shown that VPA induces the release of tissue-protective cytokines and attenuates the signs of inflammation in neural tissue [14]. VPA has also been shown to inhibit the action of the membrane attack complex in complement in RPE cells [10], probably due to VPA’s properties as a histone deacetylase inhibitor [15, 16]. Considering that diminishing integrity of the RPE is characteristic of AMD [7], these data suggest that VPA may be able to target specific pathology considered as a crucial part of AMD pathogenesis. In addition, VPA attenuates microglial overactivation [17, 18], a process which takes place in the sub-neuroretinal space during inflammatory response [19]. Inflammation by complement activation has been
associated with AMD pathogenesis [20]. Inhibition of angiogenesis in human endothelial cells by VPA [21] suggests that pathologic choroidal neovascularization could stabilize in exudative AMD. These findings, combined with the numerous neuroprotective properties of VPA [22, 23], strengthen the case for VPA use as a retinal therapeutic, particularly for AMD.

Here, we present the results of a small, pilot, retrospective study that sought preliminary evidence regarding the efficacy and safety of low doses of VPA as treatment for AMD.

METHODS

The appropriate Institutional Review Board approved the retrospective chart review for this study. All patients were treated at the Department of Ophthalmology, University of Florida – Gainesville during the period December 2007 to December 2008. The data presented here were not collected with the intent to study VPA.

Fifteen patients with the diagnosis of AMD in both eyes received a prescription for an off-label use of VPA; 12 of them returned for a follow-up visit and were included in the study. The study cohort comprised four males and eight females with a mean age of 77.9 (± 6.4) years. Seven patients presented with compound disease (non-exudative AMD in one eye and exudative AMD in the other eye; one patient had exudative AMD in both eyes). Visual acuity data from 22 eyes were available and included: 14 eyes with non-exudative AMD and 8 eyes with exudative AMD (see Table 1). One eye with the diagnosis of a geographic atrophy form of AMD was excluded from this analysis.

VPA dosage varied from 500 to 750 milligrams (mg) per day, a lower dose compared to that typically prescribed as a maintenance dose for epilepsy, which is the primary indication for VPA. All patients were started on a dose of 500 mg daily. In eight patients who tolerated the 500 mg dose well, the daily dose was increased to 750 mg. Length of treatment varied from 8 weeks to 38 weeks (mean duration = 23.1 ±11.8). The following data were extracted: patient demographics, diagnosis, best corrected visual acuity (BCVA), reported systemic side effects and subjective improvement of vision at follow-up. Hepatotoxicity was monitored periodically with serum liver function tests.

BCVA was measured using a Snellen chart at a distance of 20 feet. Values were converted to a logarithm of minimum angle of resolution (logMAR) score for statistical analysis. A decrease in logMAR score is indicative of improved visual acuity. Additionally, change in visual acuity is presented by lines gained or lost over the course of VPA treatment.

In order to detect any dose-dependent changes in BCVA, patients were stratified by average daily dose of VPA: those taking 500 mg/day, and those taking >500 mg/day.

RESULTS

Outcome measures for non-exudative and exudative AMD eyes are described in Table 1. Eight Caucasian females and four Caucasian males were studied, ranging in age from 65 to 87 years.
<table>
<thead>
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<th>Patient ID</th>
<th>Average VPA daily dose (mg)</th>
<th>Length of treatment (weeks)</th>
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<th>Type of AMD</th>
<th>logMAR change</th>
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<td>DRY</td>
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</tr>
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<td>4</td>
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<td>19.0</td>
<td>OD</td>
<td>WET</td>
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Table 1. Clinical and treatment characteristics of the patients in the study. Eyes with non-exudative form of AMD are coded as ‘DRY’, and patients with the exudative form of AMD are coded as ‘WET’. N/A – data not available; *data excluded from analysis.

The average baseline visual acuity for the study cohort was 0.62 (±0.62) logMAR units, corresponding to a Snellen acuity of approximately 20/60. The average change in BCVA at the time of follow-up for all eyes included in this analysis (n=22) was an improvement of -0.05 logMAR (±0.23) units, equivalent to 0.5 lines (±2.3 lines). However, the two treatment groups (500 mg/day and >500 mg/day) showed different responses to treatment. With results from both eyes averaged, the 500 mg/day treatment group showed an average worsening of visual acuity of 0.09 (±0.10) logMAR units, whereas the >500 mg/day treatment group showed an improvement in visual acuity of -0.16 (±0.16) logMAR units or 1.6 lines, and this difference was statistically significant (p<0.05, see also Fig. 1). Additionally, a one-sample t-test between the treatment group taking >500 mg/day and a theoretical value of 0 (indicating no change) yielded a result (p=0.05) suggestive of significant BCVA improvement.

At baseline, non-exudative AMD eyes presented with a mean acuity of approximately 20/60 (logMAR=0.50). Those with non-exudative AMD in the 500 mg/day treatment group showed a slight worsening in visual acuity of 0.02 (±0.12) log MAR units, while those in the group treated with >500 mg/day had a slight improvement in average visual acuity of -0.06 (±0.08) log MAR units. The difference between the two groups was not statistically significant. Additionally, a
one-sample t-test between the treatment group >500 mg/day and a theoretical value of 0 (assuming no change in vision over treatment) was not statistically significant (p=0.097), but indicates a trend towards improvement (Figure 2).

A similar analysis was performed for the eyes with exudative AMD. The baseline visual acuity of the eyes with exudative AMD was 0.87 (±0.79) logMAR units, equivalent to approximately 20/160. As with non-exudative AMD eyes, patients treated with 500 mg/day showed a slight worsening in visual acuity of 0.16 (±0.19) logMAR units, while the group treated with >500 mg/day had a slight improvement in average visual acuity of -0.33 (±0.35) logMAR units, equivalent to an improvement of 3 lines. The difference between the two groups was not statistically significant (Mann Whitney test, p=0.057), but suggests a trend. The result of a one-sample t-test between the treatment group of >500 mg/day and a theoretical value of 0 was not significant (p =0.15) (Figure 3).

Table 2 describes a subjective assessment of visual function correlated with visual acuity averaged from both eyes. Eight of 12 patients (67%) reported improvement in visual acuity due to VPA treatment. Improvement in BCVA was measured in six of those eight patients (75%).

<table>
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</tbody>
</table>

Table 2. Comparison between subjective reporting in visual perception and BCVA change at the end of the treatment period. Of the 12 patients, three reported no change, one patient did not offer an opinion, and eight reported.
subjective improvement in visual acuity over the course of treatment. Of these eight patients, 6 logMAR scores actually improved and 2 did not change. ± = improvement, Ø = no change, and -=worsening.

Two patients complained of onset of fatigue during VPA treatment. Patients also reported episodes of heartburn, weight loss, tremor, upset stomach, diarrhea, and dizziness while on VPA. Of those patients who reported a side effect, each patient experienced only one side effect. One patient discontinued treatment due to fatigue. The patient did not have any co-morbid conditions and was not taking any medication that could account for the reported fatigue.

DISCUSSION

The results from this small retrospective study indicate that VPA could be considered as a new approach in the treatment of AMD. BCVA in eyes with the exudative or non-exudative form of AMD improved significantly in patients on a dose greater than 500 milligrams VPA per day.

Typically in the context of clinical trials, significant changes in visual acuity are reported as a change of three or more lines (by ETDRS or Snellen chart); for AMD patients, it is likely that any measurable improvement or stabilization of disease progression would be clinically relevant. The condition of these patients is expected to deteriorate with time and to our knowledge, no therapeutic that has been indicated for use in both exudative and non-exudative AMD has demonstrated a potential to stabilize or reverse the damage caused by AMD.

Our analysis indicates BCVA improvement in 75% of patients reporting subjective improvement. In light of the fact that subjective reports encompassed both eyes, and our analysis indicated a differential effect based on each eye, it is difficult to rigorously correlate the objective measures of improvement with subjective reports. It will be important in future studies to carefully distinguish subjective changes in photopic (and scotopic) visual function in non-exudative and exudative AMD eyes separately.

Patients from other studies have demonstrated excellent tolerability of VPA when used as an anti-convulsant at larger dosages than those used in this analysis [12], and our patients showed similar tolerance. Side effects reported by patients in this study are consistent with side effects reported from VPA treatment [24]. All but one patient reported side effects that were transient and subsided without intervention or by changing the time of administration to taking VPA after a meal. There were no co-morbidities in the patient who discontinued treatment that could account for severe fatigue.

There are several limitations in this chart review that are important to consider when interpreting our results. These data were collected retrospectively. Patients were not randomized into treatment groups, AMD in the patients was not graded, and neither patients nor researchers were masked to the type of treatment received. In addition, this small subject pool was selected from one clinical site and was not population based. These shortcomings in study design would be addressed by the creation of a randomized clinical trial. To improve accuracy of BCVA measurement, it will be important to use the ETDRS chart exclusively in lieu of the Snellen chart.
Given that these data were not collected from a rigorously designed clinical trial, and not all pertinent patient data were collected to detect potential statistically or clinically significant outcomes, our results give promise to the notion of VPA as a retinal therapeutic, but are not conclusive. This analysis provides for the first time some clinical indication to support the growing body of basic science research implicating VPA as a candidate for non-exudative and exudative AMD treatment. A randomized placebo-controlled clinical trial will be necessary to rigorously assess the dosage, efficacy and safety of VPA for AMD.

Footnotes

Acknowledgments: The authors would like to thank Linda Stein for her efforts on this publication.

Funding: This study was supported in part by the Vision Research Fund and by the Clinical/Translational Research Pathway, Office of Medical Education, both at the University of Massachusetts Medical School.

Competing Interests: None.

Ethics Approval: Ethics approval was provided by the Institutional Review Board, University of Massachusetts Medical School.

REFERENCES


Figure legends

Figure 1. Change in BCVA at the follow-up visit compared to the baseline visit for patients treated with 500 mg VPA per day (n=4) or >500 mg/day (n=6). Unpaired t-test between the two groups demonstrated significant difference (p<0.02). One-sample t-test (treatment group vs. no-change) for the treatment group of >500 mg/d resulted in p=0.05, suggestive of BCVA improvement.

Figure 2. Change in BCVA at the follow-up visit compared to the baseline visit for eyes with the diagnosis of non-exudative AMD treated with 500 mg VPA per day (n=3) or >500 mg/day (n=7). One result per patient was included; in cases where two eyes had the same diagnosis, the result was averaged. One-sample t-test (treatment group vs. no-change) for the treatment group of >500 mg/day resulted in p=0.10, suggesting a trend for BCVA improvement.

Figure 3. Change in BCVA at the follow-up visit compared to the baseline visit for eyes with the diagnosis of exudative AMD treated with 500 mg VPA per day (n=3) or >500 mg/day (n=4). One result per patient was included; in cases where two eyes had the same diagnosis, the result was averaged.
Figure 1

Change in BCVA at follow-up
(average of OD & OS)

Figure 2

Change in BCVA for eyes with non-exudative AMD
(average of OD & OS, if available)
Change in BCVA for eyes with exudative AMD
(average of OD & OS, if available)

Figure 3
CHAPTER 3: CLINICAL TRIAL DEVELOPMENT

3.1 INTRODUCTION
This aspect of the project was the most labor intensive, and although through this effort I authored countless documents, there was a wealth of my work in this regard that was not recorded in the corresponding submitted documents. This is an indication of the large amount of behind the scenes information gathering and connection building that was required. Since I hope to annotate below the unrecorded processes important for trial development, the introductory section to this chapter is the most lengthy. Additionally, this aspect of the project intersected the most with the missing infrastructure/core expertise here at UMMC. Therefore the Issues and Recommendations section at the end of this introduction is also the most comprehensive.

While many steps were taken concurrently, the general order of the process as I undertook it was: 1) study design; 2) protocol development; 3) placebo development; 4) case report form design and production; 5) IND submission and 6) IRB submission.

The lynchpin step in the process was to produce the protocol. This document is the basis for the IRB and IND submissions. The protocol is the distillation of the specifics of the trial incorporating the fine detail of every aspect of the study from the exact procedures performed at every visit to the definition of adverse events.

Trial design is based on incorporation of the preliminary studies and known rates of progression of RP into a power analysis. Additionally the structure of the study design is deeply dependent upon the disease and patient population. I had never developed or even seen a study protocol prior to this project, and finding good models to use as templates was difficult. These kinds of documents are highly proprietary, and the ones I could get access to weren’t necessarily the most appropriate for an ophthalmologic study. This was even more true for the case report forms, it was hard to find any available electronic copies that contained relevant ocular diagnostics.

In planning the trial, I found that ultimately the cost associated with an investigator initiated trial is rate limiting, and the concepts of sound study design and the realities of fiscal concerns are very much in competition. For example, the cost of the drug for the entire study period is about $7000. The cost to manufacture an ideal placebo is about $50,000. This exemplifies the constant push and pull during the design process; understanding what was feasible was just as important as what the right steps were.

3.2 THE PROCESS
I considered multiple trial designs for this study, basing them on established prior studies in neurodegenerative disorders such as the delayed start, crossover and futility designs often used in Parkinson’s Disease. The first design I settled on (and still to this day believe is the best for our circumstances) was a one-armed self-controlled study. Given the extreme heterogeneity of the RP disease progression and genotype, I was concerned about controlling for the treated subjects with
unrelated controls. I proposed a rigorous genotyping analysis coupled with a longitudinal baseline screening of subjects to define the rates of vision function loss for each subject. This design, which was modified and vetted over a period of many months, ultimately was informally rejected by the FDA. The details of this trial design can be found on page 191 as this was the design included in the Challenge grant submission.

3.2.1 Communication with the FDA
Pre-communication with the FDA was happening in tandem with the data analysis and study design. Dr. Kaushal’s prior contact with the Ophthalmologic Products Division Chair, Wiley Chambers, M.D. was instrumental. During the six months from trial development to IND submission, I communicated with Dr. Chambers via phone calls and email. Fortunately this division of the FDA is small and streamlined. Dr. Chambers emphasized that his division preferred informal communications during the entire process such that when the IND was submitted they had thorough knowledge of its contents. (The process is such that his staff would have about 10 to 20 days with which to decide to put a study on “clinical hold” or by default allow it to proceed. Constant communication with the investigators allows them to review the protocol over a longer period of time, and even shape the study to some degree).

It was during these pre-communications with Dr. Chambers that I learned a central tenet of this aspect of human subjects’ research: Find out what the FDA wants. Despite his acceptance of the soundness of the one-armed self-controlled study (and his agreement that it’s a great design for RP subjects), Dr. Chambers asserted that as a rule placebo controlled trials are considered more rigorous by the FDA. At his insistence, I then redesigned the trial as a randomized, placebo controlled study. This single aspect doubled the numbers we needed to enroll, increased the costs to the point that I question the feasibility that we will ever get fully funded with no pharmaceutical backing, and also meant that we needed to partner with a second site as 90 patients was an untenable recruitment goal for UMMC.

The second site was selected by Dr. Kaushal – the Retina Foundation of the Southwest. The principal investigator at this site, David Birch, PhD is a highly regarded clinical trialist in RP and was a great resource to me. His clinical trial coordinator, Kirsten Locke RN, worked closely with me to coordinate the equipment and operating procedures between sites. Furthermore this clinic has an extensive set of families and fully characterized RP patients. Ultimately the addition of this site added immeasurably to our study.

Utilizing the data from the preliminary human study, with help and guidance both from Stephen Baker and Carol Bigelow, I performed a power calculation to understand how many subjects we would need to power the study. It was determined that 90 subjects total (45 placebo and 45 treated) were required. The details of my analysis are included below in the protocol (page 65) and the Challenge grant application (page 191).

The whole process of submitting an Investigational New Drug application to the FDA, for the uninitiated such as myself, involves a steep learning curve and a lot incredible and frustratingly
difficult information gathering. There is no available core expertise within the UMMC community so my knowledge was gained through a combination of on-line resources (primarily the FDA CDER website) and communication with knowledgeable contacts such as Wiley Chambers, David Birch and Marg Humphries RN, who is the clinical trial coordinator for the ongoing gene therapy trial here at UMMC.

The IND submission for this trial, given that it is for a new indication for a well established medicine and is an investigator initiated study simplified the process. However, there were many new and changing regulations (the requirement for posting to the clinicalTrials.gov website for example), that even the experts at the FDA were unsure of how to implement.

### 3.2.2 Case Report Forms

An unexpected (and extremely time consuming) requirement for the IND submission was the inclusion of case report forms (CRFs). The creation of these documents cemented the fine details of every piece of data we expected to collect on each subject. With screening, baseline and four follow-up clinic visits, multiple follow up phone calls and repetitive measures of many in-depth ophthalmologic tests, I created a set of about 150 case report forms (a sample set is included in Chapter 3.5.1 page 84). In order to do this I had to understand not only what we were proposing to measure, but also the details of the many pieces of new ocular equipment we were proposing to use. Ultimately, as with much of this project, the CRF creation required an invaluable in-depth understanding of the data we would collect. The CRFs were extremely helpful in coordination of processes and equipment between the two-sites. I also see the value of these forms as I currently work with the Business Systems Department in the UMMMC Information Services to create a data management tool for this trial. These forms lay a very firm foundation for the database, so much so that Business Services will be implementing the submission of CRFs as part of the workflow for clinical trial data management processes in the future.

### 3.2.3 Placebo Development

Placebo development was another unexpected aspect to the study design. I initially worked with Lucie Lajuenesse, the Research pharmacist here at UMMC, to both source the VPA and develop a workable placebo. Identifying exactly which lot of the generic form of VPA (absolutely required for the IND submission) was anything but straightforward. With quite a bit of effort and help from Madeline Karcasinas in purchasing, I was able to find the name of the supplier (McKesson) that the hospital can purchase the study drug from. (Typically UMMC trials of this sort have pharmaceutical sponsors who provide both placebo and study drug). I contacted this supplier (who is rarely the actual manufacturer of the drug), and was able to get a lot # of the study drug that would at least partially cover our initial VPA dosing. (Wiley Chambers informed me that a simple amendment to the IND application could be filed if and when the lot# changed).

VPA is oil soluble and is dispensed in large soft-gel capsules. The inexpensive method of placebo creation that is typically used here at UMMC is to over-encapsulate the study drug (ie. put it into another larger empty capsule). Then a standard placebo tablet is also over-encapsulated into the same size empty capsule. In theory this placebo solution seemed functional, but in practicality it did
not work. First, we would need about 50,000 capsules of both the study drug and the placebo. The research pharmacy here at UMMMC does not have the resources for this. Second, the “standard” placebo was actually a tablet and was easily identifiable versus the study drug as it shook inside the empty capsule while the study drug was immobilized in the empty capsule. Even if we expected that patients would not figure out the difference, clearly the clinic staff would be unblinded as they administered the vials of study drug and placebo. Third, the only empty capsule that would accept the large 250mg VPA capsule was a size 00 – which is very large and hard to swallow. At this point I started the quest for a workable placebo from extramural sources.

Lucie referred me to a local pharmaceutical compounding center, Boulevard Pharmaceutical Compounding in Worcester. The proprietor, Joe Rosetti, is an eccentric, loveable 75 year old man with lots of experience and long-winded stories about the nature of his business. His facility was certainly capable of over-encapsulating the study drug. We worked together to come up with a cheaper solution to the placebo. He could not find a smaller capsule to accept the VPA so he would fill the same large, size 00 capsules with powdered methylcellulose (brand named Avicel). This would at least have a closer appearance to the over-encapsulated study drug. I had Joe provide me with 100 capsules of a placebo created in this manner and Jenna Checchi pilot tested this placebo on 5 staff members in Dr. Kaushal’s clinic and laboratory. One person felt that it got stuck in their throat and one person refused to try to swallow it once he saw the actual capsule size. Given that VPA can cause difficulty swallowing, it seemed clear that a new solution should be found. Additionally, the cost of this low-tech solution was about $15,000.

I next contacted Frontage Laboratory, a contract pharmaceutical manufacturer. They worked with me to develop a quote to manufacture a small, hard capsule filled with the VPA excipient oil (soft gels are expensive to produce and rarely manufactured by small facilities). The cost to provide this placebo was about $40,000. Besides the cost, the downside of this solution was that the placebo still didn’t look like the study drug. However, since over encapsulation was not involved, the size of both the study drug and the placebo was much smaller.

Throughout this entire process I was continually contacting manufacturers of VPA in an attempt to entice them to be involved in the study and provide materials for the trial. My first contact was to Abbott, who holds the original patent on Valproic Acid (Depakene). While this patent has long expired, the extended release version (Depakote) was still under their patent protection and I reasoned that Abbott would absolutely want a new indication for this soon to expire intellectual property. If you have ever tried to reach someone at a big (or small) pharma company, you learn quickly that it is difficult to get the names and contact information of the decision makers. However, through friends at Abbott here in Worcester, and a lot of “creative” conversations with the receptionists at Abbott’s facilities in Illinois, I was able to speak directly with the medical directors who make the decisions on resources for new indications for VPA. I was told emphatically on many different occasions, from multiple people at Abbott, that they had exhaustively partnered with investigators such as ourselves over the years who were studying VPA. They had committed untold resources in an attempt to find new indications, and none were successful. The official position was
that Abbott was letting their patent protection expire and was not investing any more money in investigator-initiated studies on this medication.

I also contacted four manufacturers of generic VPA (with the continuing mergers of many of these pharmaceutical companies it is difficult to tell exactly who is manufacturing the drugs and the information on the FDA website is clearly outdated). It turns out that Catalent Pharmaceuticals, who manufactures VPA, also has a small contract manufacturing business. They could produce 50,000 identical soft gel placebos in their pilot facility AND source 50,000 capsules of an identical lot of study drug (at cost). This solution cost about $45,000 (plus the cost of the study drug). This solution was clearly the most robust in terms of keeping the trial blinded and keeping the capsule size to a minimum. Catalent also provided stringent placebo manufacturing standards and could guarantee that the placebo was identical to the study drug in excipients since they also manufactured VPA. I chose to proceed with the Catalent placebo solution.

3.2.4 The IRB Applications
The next part of the process was to prepare and submit the IRB applications. While this process was lengthy, I fully understood the scope of the process so this effort was not unexpected. Because the genotyping of the subjects was to be covered under a separate protocol from the National Eye Institute, a separate IRB application was required. I found that genetic analysis is an area of concern for the UMMMC IRB and felt that this previously approved NIH protocol was scrutinized even more thoroughly and engendered more comments and revisions than the VPA intervention study application that followed. The consent forms were a particularly grueling aspect as the wording on the consent form from the NEI was not always in acceptable standard UMMMC language. Each change to this consent had to be approved both by the Umass IRB and the NEI protocol liaison. Additionally, since we wanted this free genotyping service to be available to all UMMMC Ophthalmology patients regardless of whether they were enrolled in a clinical trial or not, I created two separate consent forms for these distinct patient populations which added yet another layer of complexity.

The application process involved several rounds of pre-submission of the applications to the IRB. The application form and the consent forms were scrutinized by the IRB office and a series of changes were requested. The Research Pharmacy office produced the Institutional Pharmacy form that is required for the application (they usually need about 2 weeks to produce this). Once these changes were made, 20 hard copies of the application and extensive supporting material were officially submitted (including one copy with original signatures). The UMMMC copy center required extensive lead time for this job so I relied on Fedex/Kinkos to copy and collate the documents.

After the committee review, there was another round of edits and inclusions to address their concerns. Once these changes were made and approved, there was a cumbersome process of swapping out modified pages into the existing documents in an attempt to not have to reproduce the 20 hard copies of each portfolio again.

3.3 Issues and Recommendations
3.3.1 BIOSTATISTICAL RESOURCES
I envision a “one-stop shopping” resource for investigators that would be housed at the Umass Center for Clinical and Translation Science web portal. A critical component of this resource would be educational links as well as connections to in-house core services for trial design and biostatistical analysis. From power analysis to statistical analysis of pre-clinical studies, this would provide the critical framework for the study design. These designated biostatisticians would be involved with the project from inception to final data analysis. They would also be involved in contributing to the specifics of the protocol including detailing the statistical methods used to analyze the trial data during and after the completion of the study. This information is not only critical for ensuring the soundness of the study design, but also will define the endpoints for early termination due to safety concerns. Finally, these biostatistics consultants would be part of the data management team as their history with the specific project will be instrumental in influencing the design of the database. During review of the protocol and data by the FDA or other entities, the statistician would be already up to speed and available to aid in communication and clarification.

3.3.2 ELECTRONIC SUBMISSIONS
Electronic submission of IRB forms would alleviate the need for the cost and hassle of manually producing multiple copies of hundreds of pages of documents. Moreover, with the dynamic nature of the review process, it is clear that hard copies complicate the process, making it more prone to errors and omissions. (This is not to mention the cost to the environment).

As the electronic submission of both application and trial data are increasingly being required by the FDA, Information Services at UMMMC will need to understand these requirement and develop and maintain both the hardware and software compatible for these very specialized requirements. This is an opportunity for the institution to proactively design an enterprise solution instead of the typical development of highly specialized and insulated pockets of expertise that often appear when there is no centralized solution.

While not always appreciated as a critical path, preparing, copying and binding the portfolio of documents required for these kinds of submissions is a critical piece of the equation. There is a general confusion about the resources and capabilities for copy and document production services here at UMMMC. For instance, if you call the help desk, you will invariably be told, that there is no Copy Center here on site. However, if you know a priori about the Copy Center on B level (or can find it by doggedly searching the UMMMC website) you will find that small scale projects can be easily produced in-house. Larger projects are sent to an off-site facility, but they often take at least a week to deliver the job. However, it would be great to have the ability to not only get projects simply reproduced or bound, but to coordinate these jobs with smart sets of the specific requirements that are associated with each submission. For example, an online tool that will assemble your IRB application (much like a grant generator) into the correct order and notify the researcher if a critical piece is missing. This correctly assembled document (that automatically inserts correct logos, cover letter addresses and validated electronic signatures) could then be sent to a designated copy center that produces the proper number of copies and delivers a complete portfolio to the correct recipient.
In this manner the process is not only clearly communicated and streamlined, but even the copy center staff are educated as to the particulars of these kinds of documents.

It would be extremely helpful for the Clinical Research Office to provide sample and templates for protocol development. I used Microsoft Word and Powerpoint to create the CRFs (using hard copy samples generously provided from Marg Humphries and Kirsten Locke as templates for some of the forms). In hindsight, these software programs were wholly inadequate as form creation and font conversion issues disallow proper printing from certain printers. Therefore, templates and software packages for CRF generation would also be important additions to the resources provided by the Office of Research.

3.3.3 FDA Knowledge Base Development

It will be important to have online resources available at the Umass Center for Clinical and Translation Science web portal that educate investigators as to the FDA requirements, but also maintain a current set of links to the appropriate contacts in each division. Correlatively, UMMC should recruit and/or develop in house FDA liaisons whose not only help investigators and trial coordinators navigate the requirements; but would also be responsible for establishing and developing relationships with key personnel within the FDA. Each division works differently. Some, like the Blood and Biologics Division, prefer “formalized” pre-communications regardless of whether the study is sponsored by an investigator or pharmaceutical company. Other divisions, like the Anti-Infective and Ophthalmologic Division, prefer informal communications as the more formal process is encumbering and slows things down. Still other divisions have distinctly different policies based on whether an investigator or pharmaceutical company is the sponsor. Most of these policies are unofficial and as dynamic as the turnover of personnel at the FDA. Therefore, they are only well understood by constant direct communication with key decision makers.

3.3.4 Research Pharmacy

The Research Pharmacy at UMMC is grossly understaffed and currently in a facility far too small for even their limited capabilities. Major resources should be invested in recruitment and infrastructure for this critical piece of human subjects” research at UMMC. Some specific services the Research Pharmacy should expand are: placebo design and production (including developing a network of outsourcing pharma resources); developing a dosing consulting service that can be utilized in the trial design phase; and development of networked online tools for randomization so remote trial sites (both UMMC clinics and their co-sites) can communicate during recruitment in real time.

3.4 Outcomes

After submission to the FDA we received a standard communication by mail acknowledging receipt of our application and detailing when we could begin recruitment if we received no other communication to the contrary (that date 9/4/2009 was exactly 30 days from their receipt of the application). Also in the letter was a notification that we had not addressed the requirement of reporting to
This was confusing to me as I had communicated with Dr. Chambers directly about this and he indicated that we would not have to submit to this website until we were ready to recruit. The critical question for me was (and I have read the legislation that resulted in this new regulation many times and it is not clear on this point) - are we allowed to claim an exemption due to the fact that we are not ready to start recruiting for at least 6 months after the IND submission? I sent several emails to the designated clinicaltrials.gov official at the NIH and received no response. The phone number listed on the NIH website was no longer in service and I left several messages at the new number provided and received no response. Several phone calls to the FDA administrator listed on the letter made it clear that: 1) The FDA really is not sure how to proceed when the trial may not happen for sometime after the IND application is submitted and 2) The FDA clearly has a responsibility to show that all IND applications have the proper clinicaltrials.gov form 3674– but they are not prepared to guide investigators in how to fill the form out. Ultimately, with the approval of Maureen Parker, the program management staff chief at the FDA Ophthalmology division, I submitted the form 3674 (page 83) claiming an exemption to clinicaltrials.gov due to the fact that we were not prepared to publicize the trial until we were funded.

The IND application was reviewed without incident and through their lack of communication to the contrary, we received the de facto approval for this trial as of September 4, 2009.

The IRB applications were both approved pending minor modifications which were immediately addressed. We are currently approved to implement both the NEI genotyping and VPA intervention in the Ophthalmology clinic.
3.5 IND SUBMISSION TO THE FDA

3.5.1 Table of Contents

Investigational New Drug Application for Valproic Acid to Treat Retinitis Pigmentosa

August 3, 2009
Sponsor-Investigator: Shalesh Kaushal, MD PhD
University of Massachusetts Worcester

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   c. Claim for Categorical Environmental Exclusion

3. Form 1572
   a. Sponsor Investigator CV
   b. Protocol Outline
   c. Case Report Forms

3.5.2 COVER LETTER

August 3, 2009

Wiley Chambers, MD
Division of Anti-Infective and Ophthalmology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltville, MD 20705-1266
Re: Initial IND submission
Valproic Acid for treatment of Retinitis Pigmentosa

Dear Dr. Chambers,

Enclosed, for your distribution, are three copies (1 original and 2 photocopies) of our IND application for the use of Valproic Acid (VPA) in adult patients with Retinitis Pigmentosa (RP) that we have discussed with you.

**Rationale**
In vitro data supports that VPA has multiple biologic properties that make it an ideal candidate for a retinal therapeutic. First, we have shown that VPA effectively increases yields of properly folded mutant rhodopsin, and that VPA protects cells from oxidative stress induced apoptosis. Work by others has demonstrated that VPA is a potent inhibitor of histone deacetylase (HDAC) and the inflammatory response pathway via apoptosis of microglial cells. Importantly, we have preliminary clinical data that suggests that VPA has the potential to not only stop the progression but may also reverse loss of visual field in patients with RP.

**General Investigational Plan**
This is a two-site, interventional, prospective, placebo-controlled, blinded study of 90 subjects with retinitis pigmentosa undergoing treatment with oral VPA for a total of 12 months (45 treated and 45 controls). For the intervention, VPA dosage will vary by weight and will be lower than the recommended for anticonvulsant therapy (from 500 to 1000 mg total daily dose).

The main measure of visual function will be visual fields as measured by semi-automated kinetic perimetry (SKP). Visual function will be quantified at baseline screening and at 12 months after start of study medication in order to determine whether VPA administration affects visual/retinal function. Secondary outcome measures of visual function will include static perimetry measurements to test the sensitivity values with the central 30° and the 25 item National Eye Institute Visual Function questionnaire to assess quality of life (QOL). Outcomes for efficacy for both eyes will be determined.

Participants will be followed closely for adverse reactions to VPA. Clinic visits at 2 and 6 months will include safety labs, physical and ocular exams. Participants will be contacted by telephone on months not scheduled for clinic visits. Safety variables will include the incidence of adverse events, marked changes in visual acuity, changes in vital signs, marked changes in clinical laboratory data (especially liver and pancreatic function) and findings during physical examinations.

This application has been reviewed and approved by the University of Massachusetts, Worcester IRB; John Sullivan, MD, the Vice Provost for Research and Terry Flotte, MD, Exec. Dep. Chancellor and Dean of the Medical School at the University of Massachusetts, Worcester.

If you have any questions, please direct them to me as the sponsor-investigator of this IND application at (508) 334-0687 or Shalesh.Kaushal@umassmemorial.org

Sincerely,

Shalesh Kaushal, MD PhD
Chair and Associate Professor
Department of Ophthalmology
University of Massachusetts Medical School
### 3.5.3 Form 1571

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**

**INVESTIGATIONAL NEW DRUG APPLICATION (IND)**  
**(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)**

| Form Approved: OMB No. 0910-0014. Expiration Date: May 31, 2009 See OMB Statement on Reverse. |
| NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40). |

#### 1. NAME OF SPONSOR  
Shalesh Kaushal, MD PhD

#### 2. DATE OF SUBMISSION  
08/01/2009

#### 3. ADDRESS (Number, Street, City, State and Zip Code)  
University of Massachusetts Medical School  
55 Lake Avenue North Rm S6-410  
Worcester, MA 01655

#### 4. TELEPHONE NUMBER (Include Area Code)  
508 334 0687

#### 5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)  
Depakene, Valproic Acid, 250 mg oral capsule

#### 6. IND NUMBER (If previously assigned)  

#### 7. INDICATION(S) (Covered by this submission)  
Retinitis Pigmentosa

#### 8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:  
- [ ] PHASE 1  
- [X] PHASE 2  
- [ ] PHASE 3  
- [ ] OTHER (Specify)


- (NDA) 018081  
- (ANDA) 073229  
Study drug manufactured by Catalent Pharma Solutions, 250 mg soft gel capsules lot# 3888975; soft gel capsule placebo to be manufactured by Catalent Pharma Solutions, CMC materials for placebo attached.

#### 10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

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#### 11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)  
- [X] INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)  
- [ ] RESPONSE TO CLINICAL HOLD  
- [ ] PROTOCOL AMENDMENT(S):  
- [ ] INFORMATION AMENDMENT(S):  
- [ ] IND SAFETY REPORT(S):  
- [ ] NEW PROTOCOL  
- [ ] CHEMISTRY/MICROBIOLOGY  
- [ ] INITIAL WRITTEN REPORT  
- [ ] CHANGE IN PROTOCOL  
- [ ] PHARMACOLOGY/TOXICOLOGY  
- [ ] FOLLOW-UP TO A WRITTEN REPORT  
- [ ] NEW INVESTIGATOR  
- [ ] CLINICAL  
- [ ] OTHER (Specify)  
- [ ] RESPONSE TO FDA REQUEST FOR INFORMATION  
- [ ] ANNUAL REPORT  
- [ ] GENERAL CORRESPONDENCE  
- [ ] REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED  

CHECK ONLY IF APPLICABLE

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

- [ ] TREATMENT IND 21 CFR 312.35(b)  
- [ ] TREATMENT PROTOCOL 21 CFR 312.35(a)  
- [ ] CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY
12. **CONTENTS OF APPLICATION**

This application contains the following items: (Check all that apply)

- [x] 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- [x] 2. Table of Contents [21 CFR 312.23(a)(2)]
- [ ] 3. Introductory statement [21 CFR 312.23(a)(3)]
- [ ] 4. General Investigational plan [21 CFR 312.23(a)(3)]
- [ ] 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- [x] 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - [x] a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - [ ] b. Investigator data [21 CFR 312.23(a)(6)(ii)(b)] or completed Form(s) FDA 1572
  - [ ] c. Facilities data [21 CFR 312.23(a)(6)(ii)(b)] or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data [21 CFR 312.23(a)(6)(ii)(b)] or completed Form(s) FDA 1572
- [x] 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
  - [x] Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- [ ] 8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)]
- [ ] 9. Previous human experience [21 CFR 312.23(a)(9)]
- [ ] 10. Additional information [21 CFR 312.23(a)(10)]

13. **IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION?**

   - [ ] YES
   - [x] NO

   **IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION?**

   - [ ] YES
   - [x] NO

   **IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.**


   Shalesh Kaushal, MD PhD

15. **NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG**

   Shalesh Kaushal, MD PhD

I agree not to begin clinical investigations until 30 days after FDA’s receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. **NAME OF SPONSOR OR SPONSOR’S AUTHORIZED REPRESENTATIVE**

   Shalesh Kaushal, MD PhD

17. **SIGNATURE OF SPONSOR OR SPONSOR’S AUTHORIZED REPRESENTATIVE**

18. **ADDRESS (Number, Street, City, State and Zip Code)**

19. **TELEPHONE NUMBER (Include Area Code)**

20. **DATE**
Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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<td>Center for Drug Evaluation and Research</td>
<td>Center for Biologics Evaluation and Research (HFM-99)</td>
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<td>Central Document Room</td>
<td>1401 Rockville Pike</td>
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"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.
3.5.4 Study Protocol

Project Title

A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa Protocol #H-13371

Trial Sites and Site Principal Investigators

University of Massachusetts Worcester
Shalesh Kaushal, MD PhD, Chair and Assoc. Professor
Christine Clemson, PhD Co-Investigator
Department of Ophthalmology
University of Massachusetts Medical Center
Biotech 5, Suite 250
381 Plantation Street
Worcester, MA 01605

Retina Foundation of the Southwest (RFSW)
David G. Birch, Ph.D.
Chief Scientific and Operating Officer
Director, Rose-Silverthorne Retinal Degeneration Laboratory
Retina Foundation of the Southwest
Adj. Professor of Ophthalmology
Director, Visual Electrophysiology
University of Texas Southwestern Medical School
9900 North Central Expressway, Ste. 400
Dallas, TX 75231

Total enrollment: 90 subjects
Expected initiation: Q4 2009
Expected Duration: Twenty-Four months from first-subject-in to last-subject-out.
Recruitment: 9 months (last-subject-in).
Treatment: 360 days of oral valproic acid. Follow up: 3 months after last treatment
Background and Rationale
RP is a severe neurodegenerative disease of the retina characterized initially by night blindness with progression to tunnel vision and eventual loss of central vision and total blindness. Targeted therapies for RP are complicated by the identification of more than 30 genes linked to the dominant and recessive forms of the disease. Further compounding this complexity is the rarity of this disorder: although RP is one of the most common inherited eye diseases with an incidence of ~1:3000, its prevalence is relatively rare. RP affects approximately 100,000 individuals in the U.S., qualifying it as an orphan disease. Given the huge costs associated with the preclinical and clinical phases of drug development, pharmaceutical companies are generally reluctant to invest in developing new therapeutics for RP. While a few new approaches for RP treatment have recently been investigated including nutritional supplementation, light reduction and gene therapy (Delyfer et al., 2004; Gaby, 2008; Hartong et al., 2006), of these, vitamin A supplementation is the most promising, but its benefits are modest and side effects are problematic. Therefore, currently there is no therapy to substantially alter or reverse the progression of RP.

Scientific Rationale
Recently, we have demonstrated the use of retinoids and other small molecules as pharmacological chaperones to increase the yield of properly folded RP mutant rhodopsins in heterologous cell culture (Noorwez et al., 2008). We have tested whether other known small molecules can provide similar effects. We identified valproic acid (VPA) through this screen. In vitro data supports that VPA has multiple biologic properties that make it an ideal candidate for a retinal therapeutic. First, our in vitro assay shows that VPA effectively increases yields of properly folded mutant rhodopsin (Figure 1, Appendix A. Pre-Clinical Data). Second, VPA protects cells from oxidative stress induced apoptosis (Figure 2, Appendix A. Pre-Clinical Data), most likely through upregulation of the heat shock response (not shown). Other work demonstrates that VPA is a potent inhibitor of histone deacetylase (HDAC) (Gottlicher et al., 2001) and the inflammatory response pathway via apoptosis of microglial cells (Chen et al., 2007; Dragunow et al., 2006; Kim et al., 2007).

Preliminary Clinical Data
Seven RP patients were treated off-label with oral VPA (250 mg BID). Visual fields were measured using kinetic perimetry (Figure 3, Appendix B. Pilot clinical study). Results varied from patient to patient, however 6 of 7 patients showed no progression of their disease on VPA, one patient experienced a loss of VF and 5 patients experienced an increase in their visual field (e.g. Figure 3, Appendix B), which no other therapeutic has previously shown. Overall, we detected an average increase in visual field/month (Figure 4, Appendix B. Pilot clinical study). These results suggest that VPA has the potential to not only stop the progression but may also reverse loss of visual field.

Study Objectives
RP is an incurable and untreatable group of heterogeneous retinal degenerative diseases that cause severe visual loss. There is currently no therapeutic that substantially slows the progression of this disease, and certainly none that can restore vision in RP patients. The objective of this study is to provide efficacy information on the ability of VPA to both slow the progression of visual function loss and/or to restore of visual function in patients with RP and collect safety and tolerability information. This collective data will be used for larger Phase III studies for patients with RP.

Study Design and Methods
This is a two-site, interventional, prospective, placebo-controlled, blinded study of 90 subjects undergoing therapy with oral VPA. Patients will undergo clinical examinations and evaluations of retinal function and structure prior to consideration of the subject as a candidate for clinical trials. Clinical examinations will
include refraction, static and kinetic perimetry, fundus photography and visual acuity. Measures of visual function will include full-field electroretinography. Optical coherence tomography will be used to measure retinal structure. Methods of these measures are detailed below. During these evaluations, medical and ophthalmic histories will be elicited from subjects and their families to ensure that there are no comorbid medical or ocular genetic conditions that may prevent study participation. While the equipment proposed for use in this trial is state of the art and as such will provide the highest level of quantitation available, the quasi-subjective nature inherent in many standard ocular tests make day-to-day variation an important confounder to our analysis. All diagnostic measures will be calibrated and standardized such that intervisit and interocular variances for each outcome measure will be quantified and included in our analysis. This will involve sequential repeated measures for the same patients on these machines.

The study design flow chart can be found in Appendix C. Study Schedule Flow-chart.

Subgroup Analysis
It is likely given the vastly different nature of the proteins involved in RP, that certain therapies will have varying beneficial effects on patients with different mutations. Indeed our preliminary clinical analysis suggests a varied response to VPA among the 7 RP patients treated (Figure 4, Appendix B. Pilot clinical study), and indicates that certain individual or patient populations may preferentially respond to this medication. Patients included in this preliminary clinical analysis, were not well characterized in regards to their RP genotype. To examine this in more detail, we propose to enroll around 20 patients with P23H opsin mutations, and perform molecular genotype analysis on each enrolled patient. Performing stepwise regression analysis adjusting for each mutation, we will correlate primary and secondary outcome measures with genotype to determine if VPA has a general benefit to all patients or if it effect is specific for certain populations of RP patients.

The genotyping in families with autosomal dominant pedigrees will be done through the NEI eyeGENE protocol. Genotyping is not a prerequisite for this study. If participants are interested in obtaining genotyping information, blood samples will be collected after informed consent and will be mailed to the NEI eyeGENE coordinating center and shipped to the appropriate testing facility where it will be screened for the most common RP mutations. Due to the rarity and sporadic nature of the many mutations associated with RP, it is likely that specific mutation information will not be identified for over half of our enrolled patients, however, the additional information gained from the patients that can be genotyped will be valuable in understanding the potential mode of VPA action and targeted effectiveness of therapy.

Outcomes
Primary Endpoint- Visual Field

**Intact visual field will be quantified at screening, baseline and at the end of the study (12 months after start of study medication) in order to determine whether VPA administration affects visual/retinal function. Visual fields will be measured using the Octopus 900 semi-automated kinetic perimetry (SKP) module (see page 59 Visual Field)**

Visual Field

; the specific stimulus used will be defined for each patient based on their intact visual field upon screening. The same stimulus will then be used for all subsequent analysis.

The study is powered to detect a change in mean visual field area using semi-automated kinetic perimetry, as the primary endpoint (see page 65). Secondary analyses will be exploratory, but in order to test several
additional endpoints we will also adjust for multiple comparisons either using the very strict Bonferroni adjustment or by relying on an omnibus test. Secondary outcome measures of visual function will include static perimetry measurements to test the sensitivity values with the central 30°; best corrected ETDRS visual acuity; color contrast sensitivity as measured by the Chroma Test; retinal anatomy as measured by Optical Coherence Tomography (OCT) and rod and cone responses as analyzed by electoretinography (ERG), fundus photography; the 25 item National Eye Institute Visual Function questionnaire to assess quality of life (QOL); efficacy as predicted by specific mutation; the dose response profile of VPA as measured by serum VPA levels and the toxicity and safety profile of VPA in RP patients. Outcomes for efficacy for both eyes will be determined.

Inclusion Criteria

To be eligible for the study, subjects must fulfill all of the following criteria:

- Understand and sign the IRB-approved informed consent document for the study.
- Age ≥ 18 years.
- Weight ≥40 Kg and ≤158.9 Kg
- Diagnosis of Retinitis Pigmentosa including photoreceptor degeneration established by visual field constriction, night blindness, marked reduction of ERG responses, and the clinical signs of RP including waxy pallor of the optic nerve, vascular attenuation and/or the presence of intraretinal pigment on clinical examination.
- Visual acuity of 20/200 or better in at least one eye.
- All subjects of reproductive potential must commit to using an acceptable method of barrier or hormonal contraception up to at least 3 months after stopping the study drug.
- Females who have attained menarche must have a negative pregnancy test at study entry.
- Willingness to comply with the protocol.

Exclusion Criteria

Potential participants meeting any of the following criteria will be excluded from the study:

1. Medical problems that make consistent follow-up over the treatment period unlikely (e.g. stroke, severe MI, end stage malignancy), or in general a poor medical risk because of other systemic diseases or active uncontrolled infections.
2. Other retinal diseases: Glaucoma, retinal inflammatory disease, (Note: CME is allowable), cataract worse than +2 NS or herpes simplex virus of the eye.
3. Intact visual field of 5° or less.
4. Diabetes or cancer.
5. A hemoglobin concentration below the lower limit of normal (less than 14 gm/dL); a platelet count below the lower limit of normal (less than 140K/mm³) or an absolute neutrophil count below the lower limit of normal (less than 1600/mm³ at study entry).
6. Suspected liver dysfunction determined by having alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin values elevated above the upper limit of normal.
7. History of pancreatitis by clinical features and/or laboratory abnormalities in the last 12 months.
8. Renal dysfunction based on serum creatinine using the MDRD equation.
9. Subjects suffering from urea cycle disorders will be excluded.
10. Subjects with history of neurological conditions including epilepsy, history of brain injury, encephalitis, or any organic brain syndrome will be excluded.
11. Subjects with a history of schizophrenia, schizoaffective disorder, bipolar disorder, suicidality or organic mental disorders will be excluded.
12. Subjects already receiving valproic acid or other anti-convulsants will be excluded.
13. Sensitive to or have ever had an allergic reaction to Valproic Acid.
14. Sensitive to or have ever had an allergic reaction to peanuts as peanut oil is an inactive ingredient in valproic acid capsules and the placebo.
15. At least 2 weeks since prior drugs specifically known to interact with valproic acid including: aspirin, felbamate, rifampin, amitriptyline/nortriptyline, carbamazepine, clonazepam, diazepam, ethosuximide, lamotrigine, phenobarbital, primidone, phenytoin, tolbutamide, warfarin, or zidovudine
16. Pregnant or Lactating mothers who are breast feeding their babies will not be eligible.
17. RP patients involved in other clinical trials within the last 3 months are ineligible for this study.

Study Drug
The scientific rationale for VPA as a retinal therapeutic was described above. It is critical to emphasize however, that the extensive history and well established safety and tolerability profile of VPA makes it an ideal candidate for a Phase II study, which streamlines the time to treatment in humans considerably relative to new drug design. VPA was approved by the FDA for use as a broad spectrum anticonvulsant in 1978 and is also used for acute and maintenance therapy of bipolar disease, for migraine prophylaxis, and occasionally for chronic pain syndromes (Henry, 2003).

VPA is well tolerated in most patients and adverse events are rare (reviewed in Peterson and Naunton, 2005). The primary concern is hepatotoxicity which is rare in low risk patients occurring in fewer than 0.29 in 10,000 patients (Bryant and Dreifuss, 1996). Subjects will be carefully screened for comorbid conditions and concomitant medications to ensure that only patients at the lowest risk for serious adverse events are enrolled (see Exclusion Criteria).

In the event of a non-serious adverse effect such as gastric disturbance, the participant will be counseled to take the medication with food. If that does not resolve the issue, or if the non-serious effect is not gastric related (such as feelings of lethargy), the drug dose will be lowered. If that does not resolve the issue, or the adverse event is more serious, then the participant will be withdrawn from the study.

Dose Rationale
Treatment dosages were selected based on our proof of concept preliminary studies described above and known safety and tolerability profiles of VPA. For the intervention, VPA dosage will vary by weight (Table 1) and will be less than the starting dosage recommended for anticonvulsant therapy (2).

### TABLE 1: VPA DOSAGE SCHEDULE BY WEIGHT

<table>
<thead>
<tr>
<th>Pounds (lbs)</th>
<th>Kilograms (Kg)</th>
<th>Total Daily Dose (mg)</th>
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<tr>
<td>22 - 54.9</td>
<td>10 - 24</td>
<td>250</td>
</tr>
<tr>
<td>55 - 87.9</td>
<td>25 - 39.9</td>
<td>500</td>
</tr>
<tr>
<td>88 - 131.9</td>
<td>40 - 59.9</td>
<td>750</td>
</tr>
<tr>
<td>132 - 164.9</td>
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<tr>
<td>165-197.9</td>
<td>75-89.9</td>
<td>1250</td>
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Excluded fr
Source of VPA and Placebo

The study drug will be a soft gel 250 mg valproic acid capsule, purchased from Catalent Pharma Solutions (2725 Scherer Drive North, St. Petersburg, FL 33716, 866-720-3148), lot # 3888975. The placebo will also be manufactured by Catalent Pharma Solutions, and will look identical to the study drug. It will be a soft gel capsule of same, color, size and shape. The placebo capsule will be filled with peanut oil, the identical excipient in the study drug.

Examination Requirements

Screening Visit

The Screening visit consists of the following examinations and procedures:

1. Explanation of study and a copy of the Consent forms (if not mailed ahead of the visit)
2. Signing of the Informed Consent for the trial
3. Signing of the Informed consent for genotyping (not necessary for enrollment in study)
4. Complete medical and ocular history
5. Urine test for pregnancy (if female and of child bearing capacity)
6. Blood draw for hepatic and pancreatic function screen (and genotyping if enrolled).
7. Visual acuity examination
8. Ocular examination
9. Semi-Automated Kinetic Perimetry, with static measurements in the 30° central field (in Duplicate)
10. Fundus photographs

Baseline Visit

Qualified participants will be asked to return to the clinic within 30 to 120 days after the Screening Visit. Randomization will occur only after the participant is confirmed to be eligible. Participants are considered eligible if they meet all the inclusion criteria, and do not meet one or more exclusion criteria and return to the clinic within 120 days following the Screening Visit, and sign the randomization consent form.

Participants must be re-qualified if randomization does not occur within 120 days of the Screening Visit. Re-qualification requires that the responses to each of the eligibility questions be verified and ocular exams and fundus photographs re-performed.
The UMMMC research pharmacy will assign bottle numbers. The master randomization list for both centers will be maintained at the UMMMC Coordinating Center.

The Baseline Visit consists of the following examinations and procedures:

1. Signing of the genotyping consent form (if not signed at the Screening Visit)- not a prerequisite for study
2. Blood draw for safety labs and genotyping.
3. Urine test for pregnancy (if female and of child bearing capacity)
4. Ocular Examination
5. Visual acuity and refraction at 3 meters via the Electronic Visual Acuity Tester (EVA) using the Electronic ETDRS (E-ETDRS) Testing Protocol
6. Semi-Automated Kinetic Perimetry, with static measurements in the 30° central field (in Duplicate)
7. Optical Coherence Tomography (OCT) in duplicate
8. Color-Contrast Sensitivity Analysis (Chroma Test) in duplicate
9. Full-Field Electroretinogram
10. Quality of Life Questionaire(QOL)
11. Concomittant Medications
12. Distribution of Study Medication (or placebo) and administration directions.
13. Assignment of Bottle Numbers

Participants who consent to participate will be contacted by telephone within 24 hours to answer questions and assure full understanding of dosing instructions and procedures.

Follow-up Visits
In-clinic follow-up visits will occur at 60, 180 and 360 days after initiating VPA treatment for evaluation of their clinical status and to assess adverse events. Participants will be asked to provide information on any side effects they are experiencing. Subjects will be followed up with phone calls after the week 1 and at month 1, 3, 4, 5, 7, 8, 9, 10 and 11. The purpose of these phone calls is to assess adherence to study medication, assess adverse events, schedule additional clinic visits if needed, and clarify study procedures. These phone calls will be particularly useful as we expect that quite a few patients may live at some distance from the clinic sites. In all cases, participants will be followed for a period of 3 months after the study ends.

The in-clinic follow-up visits will consist of the following examinations and procedures:

1. Safety Labs
2. Concomitant Medications
4. Ocular examination
5. Adverse Event assessment
6. Collection and re-issuance of study medication bottles
7. Assessment of study drug adherence via self-report, VPA blood levels, and pill counting
8. Semi-Automated Kinetic Perimetry, with static measurements in the 30° central field (in Duplicate) (at month 12 follow-up visit)
9. Optical Coherence Tomography (OCT) in duplicate (at month 12 follow-up visit.)
10. Color-Contrast Sensitivity Analysis (Chroma Test) in duplicate (at 12 month follow-up visit.)
11. Full Field Electoretinogram (ERG) (at month 12 follow-up visit.)
12. Fundus Photogaphy (at 12 month follow up visit).
13. Quality of Life Questionaire(QOL) (at 12 month follow up visit).

The full schedule of study visits can be found in Appendix D. Scheduled Study Evaluations Table.

Study Assessments

Visual Field
Visual field measurements will be made as described for patients with severe vision loss (Nowomiejska et al., 2005; Nowomiejska et al., 2008) using the Octopus 900 (Haag-Streit International) with the semiautomatic kinetic perimetry (SKP) module. Stimuli of selected size and luminance according to the Goldmann classification are moved along user-defined vectors having a constant angular velocity of 3° per second. Vectors are drawn manually using an electronic pen. The stimulus is moved almost perpendicularly towards the presumed scotoma border from nonseeing towards seeing areas of the VF. Fixation is monitored by a digital infrared camera, which provides a highly magnified image of the tested eye. The stimulus movement along each vector is terminated by the response of the patient, who is instructed to look straight ahead at the fixation point (green cross) and press a button as soon as the stimulus is perceived. The respective stimulus location is marked on the screen automatically by the software with a size- and intensity-specific symbol, and after several repetitions with different vectors, the symbols are connected, and enabling isopters are drawn in selectable color. The area enclosed by an isopter is automatically quantified by the software using triangulation in square degrees of eccentricity.

Refractive and Best-Corrected Visual Acuity (BCVA)
Visual acuity is measured at a distance of 3 meters on a calibrated computer screen, using the program EVA-ETDRS. A separate sequence will be used for each eye. Patients will be allowed as much time as necessary and encouraged to read each letter, and asked to guess if unsure. The vision score is then calculated by the program.

Color Contrast Sensitivity
The ChromaTest psychophysical vision testing system (CH Electronics) will be used to measure color contrast sensitivity. For this test the subject is seated at a fixed distance from a large format standardized and calibrated NEC Spectraview LCD monitor. Alphabetical letters displayed on a background of equiluminance at a constant angle and size create an image that tests the central 6.5 degrees of the retina. The computer finds the endpoint of the test by a Modified Binary Search method; if response is correct, on the next presentation the color difference between letter and background is halved. If response is incorrect, the color contrast is doubled. Incorrect responses prolong the test, but do not influence the final threshold. This method of determining thresholds leads to finite steps which reach a plateau at the color contrast sensitivity threshold at a test sensitivity of 1% (Wong et al., 2008). The thresholds for each major color axis will be defined for each patient at baseline.
**Optical Coherence Tomography (OCT)**
Spectral–domain OCT (Spectralis – Heidelberg Engineering) will be used to estimate the existence and the extent of retained photoreceptors. In patients with stable fixation, the OCT studies will involve groups of raster scans to sample the retinal region of interest.

**Fundus Photography**
Pupils will be dilated to 6 mm or larger with two sets each of 2.5% Neo-Synephrine and 1% Mydriacyl, or equivalent. Contact lens examinations should be avoided prior to photography. A modified 3-standard field color photography and fundus reflex procedure will be used.

**Full-field Electroretinogram (ERG)**
Full field ERGs will be performed according to ISCEV standards. Special protocols for the recording of ‘submicrovolt’ ERGs have already been used in two clinical trials that included patients with relatively severe forms of retinitis pigmentosa (RP). For this proposal, methods of recording submicrovolt ERGs will be similar to those previously used in very severe retinal degenerative diseases (Jacobson et al., 1998). Full-field 29 OR 30 Hz flicker will be presented with the standard stimulus on the 7 cd.m\(^{-2}\) white background and 100 sets of flicker trains consisting of three consecutive responses will be recorded.

**Quality of Life (QOL)**
QOL will be assessed using the 25-Item National Eye Institute Visual Function Questionnaire (Mangione et al., 2001). The questionnaire will be administered in an interview format at the baseline visit and at the 12 month visit.

**Genotyping Analysis**
The genotyping test will be performed as a part of the eyeGene clinical research study at the National Institutes of Health (NIH). 10 ml of whole blood will be obtained by routine phlebotomy using plastic vacutainers containing K2 EDTA. All samples will be stored exclusively at room temperature with overnight shipping. Participants will be screened for the most common RP mutations including: ABCA4, RHO, RDS, IMPDH1, PRPF31, PRPF3, RP1, PRPF8, NR2E3, TOPORS, RPGR, RP2, CNGA1, CRB1, C1QTNF5/ CTRPS, MERTK, PDE6A, PDE6B, RGR, RLBP1, RPE65, TULP1, CA4. Dr. Kaushal or Dr. Asdourian will provide pre and post-test genetic counseling to all participants.

**Serum VPA Assay**
Compliance is an issue in self administered study drug clinical trials. Medication monitoring will occur at every follow up visit. Patients will be instructed to bring prescription bottles to every visit for counting. Additionally, serum VPA levels will be assayed at regular intervals for bioavailability determination as well as validation of participant compliance to protocol. Serum concentrations will be assayed by a fluorescence polarization immunoassay system (Ax-Sym analyzer; Abbott Diagnostic Division, Irving, TX).

Since the results of this test would obviously unblind any research staff, arrangements will be made to have the VPA blood levels held by the clinical testing lab facility until the end of the study. Given that the VPA serum level is being used primarily for a research question, and likely does not afford useable safety
information, we feel this will not compromise subject safety. If however, serious adverse events occurred, then this information would be available if and when a subject is unblinded.

**Randomization, Masking and Unmasking**
The research pharmacy at UMMMC will be responsible for randomization. Two codes will be used for the two types of capsules (placebo and VPA) provided to patients. All patients will be assigned to receive capsules following a computer-generated block randomization.

**Capsule Code**
The capsule code information will be kept on a password-protected computer with the password known only to the capsule coordinator in the research pharmacy at UMMMC. The randomization code for the groups will consist of 2 single-letter identifiers for the two capsule types (A or B). The capsule codes are a temporary identifier of capsule bottles as the capsule coordinator will place a label with each individual’s ID number over the capsule code. This will prevent laboratory personnel from associating the patient ID with capsule code assignment.

**Coordinating Center**
UMMMC will be the coordinating center and the research pharmacy will randomly assign the study intervention.

Participants and investigators will be masked to the treatments. Participants will be unmasked if deemed clinically necessary by the examining physician and if the Study Chair and Data Safety and Monitoring Board (DSMB) Chair are in agreement. A written request for unmasking, after approval by the Study Chair and DSMB Chair, will be made to the Coordinating Center, who will inform the site Principal Investigator of the treatment assignment. All instances of unmasking must be reported to the IRB, the DSMB and the FDA.

**Monitoring Participants and Criteria for Withdrawal**

**Data Safety and Monitoring Board**

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines.

The procedures outlined in the protocol and case report forms will be carefully reviewed by the Investigators and staff prior to Study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and well being of subjects.

Amendments will be submitted to the IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the Informed Consent form will be revised and if applicable, subject’s consent to continue participation will again be obtained.

To ensure safety of human subjects and integrity of data in this trial, a data and safety monitoring plan will be established. The levels of monitoring will include:

1) Dr. Shalesh Kaushal, MD, PhD as and Dr. David Birch as site Principal Investigators, will continuously monitor patient safety and be responsible for reporting serious and unexpected adverse reactions as regulated to the FDA, DSMB and IRB.
2) The DSMB will provide safety oversight of the trial, to monitor the progress of the study, and to recommend modification of the trial, as appropriate. The DSMB will review safety data after the first two months of oral dosing and after 6 months of oral dosing. Serious and unexpected adverse reactions will be reviewed by the DSMB or subcommittee.

3) Approval of the IRB will be obtained before enrolling subjects in this clinical trial. Following the beginning of enrollment, the IRB will conduct continuing reviews of the trial at intervals appropriate to the degree of risk to human subjects.

A detailed Data and Safety Monitoring Plan will be submitted to the IRB prior to the accrual of human subjects.

**Adverse Experience Reporting**

All adverse events, either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported. Any serious adverse event (SAE) regardless of severity or potential association with the study drug, must be documented in study records by the site Investigator and promptly reported to the Coordinating Center (within 24 hours of learning about the event). Non-serious adverse events can be collected in a routine manner using case report forms.

**Obligations of Site Investigators**

Site Investigators will report all adverse events, regardless of their severity or potential association with the study drug. When submitting adverse event information to the Coordinating Center, a site Investigator may not delegate someone other than a listed study physician the responsibility for reviewing the accuracy of the contents of the adverse event report. When reporting an adverse event, the site Investigator must assign a severity grade to each event and also declare an opinion on the relatedness of the event to the study drug.

Serious adverse events are defined below on page 63. For any such event, the Coordinating Center must be notified within 24 hours of when the Investigator first learns of the occurrence of the event. Adequate information must be collected with supporting documentation.

**Serious Adverse Event Reporting Responsibilities of the Site**

When an SAE is identified, the site Investigator (or the site Study Coordinator) shall promptly:

A. Notify the site PI (if a different person) in person or by telephone about the SAE.
B. The site PI (or another designated study physician) is responsible for reviewing and approving the serious adverse event report contents (including the event description, grading of event severity, and attribution of relatedness to the study drug).
C. Submit the initial serious adverse event report to the UMMC Coordinating Center within 24 hours of recognizing the event. Submission to the local IRB is based on each site’s responsibilities per the site’s IRB.
D. The adverse event report and each page of any attached materials must describe the study participant only by their coded study identifier(s). Any personally identifying information (e.g., name, telephone number, address, etc.) must be removed or obscured before delivery to the Coordinating Center.
E. If the Coordinating Center requests additional information, or if further pertinent details become available (e.g., laboratory reports, follow-up evaluations, discharge summaries, autopsy reports, etc.), promptly submit them to the Coordinating Center.

F. If a death occurred, complete the death case report form. Be sure to include a statement regarding the causality assessment on the form.

G. If a hospitalization occurred for more than 24 hrs, complete a serious adverse event form.

**Obligations of Coordinating Center**
The UMMC Coordinating Center, must immediately investigate each reported serious adverse event and notify the FDA (and other relevant regulatory authorities), the DSMB, and all participating investigators within 15 days of any adverse experience that is associated with the use of the study drug and that is both serious and unexpected.

**Serious Adverse Events Defined**
A serious adverse event (SAE) is defined for this protocol as an adverse event of Grade 3, 4 or 5.

**Grading Severity of Adverse Events**
The site Investigator must grade the severity of all reported adverse events into one of four categories: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening) or Grade 5 (death).

**GRADE 1—MILD**
Transient (< 48 hours) or mild discomforts, no or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities, nonprescription or single-use prescription therapy may be employed to relieve symptoms (e.g., aspirin for simple headache, acetaminophen with codeine for post-surgical pain). Mild adverse events may be listed as expected consequences of the therapy for any given protocol, and standard supportive measures for such an expected event do not necessarily elevate the event to a higher grade.

**GRADE 2—MODERATE**
Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required, hospitalization possible.

**GRADE 3—SEVERE**
Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely.

**GRADE 4—LIFE-THREATENING**
Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable. This grade is used when the participant was, in the view of the Investigator, at substantial risk of dying at the time of the adverse event or it was suspected that use or continued use of the study drug would have resulted in the participant’s death. (This does not include a reaction that, had it occurred in a more serious form, might
have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.)

**Grade 5 - Death**
A death (Grade 5 event) occurring during the study, whether or not considered treatment-related.

**Relatedness of Event to Study Drug**
The site Principal Investigator (or an authorized study physician) must submit an attribution for the relatedness of the reported adverse event to the study drug. The attribution should take into account both the temporal association and any known physical, physiological or toxicological information regarding the study drug that could reasonably infer causality. Relatedness should only be considered for the study drug and not for any standard study examination or diagnostic procedures. The five attribution categories are:

1) **Definitely Related**—Clearly related to the study drug.
   An adverse event that follows a temporal sequence from administration of the study drug; follows a known response pattern to study drug; and, when appropriate to the protocol, is confirmed by improvement after stopping the study drug; and by reappearance of the reaction after repeat exposure; and cannot be reasonably explained by known characteristics of the participant’s clinical state or by other therapies.

2) **Probably Related**—Likely related to the study drug.
   An adverse event that follows a reasonable temporal sequence from administration of study drug; follows a known response pattern to the study drug, is confirmed by improvement after stopping or lowering the dosage; and cannot be reasonably explained by the known characteristics of the participant’s clinical state or other therapies.

3) **Possibly Related**—May be related to the study drug.
   An adverse event that follows a reasonable temporal sequence from administration of study drug and follows a known response pattern to the study drug, but could have been produced by the participants' clinical state or by other therapies.

4) **Probably Not Related** – Likely not related to the study drug
   An adverse event that either does not follow a reasonable temporal sequence from administration of study drug or have a known response pattern to the study drug. Stopping the medication or reducing the dosage and rechallenge may or may not be performed to adequately support no relationship.

5) **Definitely Not Related**—Clearly NOT related to the study drug.
   An adverse event that does not follow a reasonable temporal sequence after administration of the study drug and is not a known response pattern to the study drug and most likely is explained by the participant’s clinical disease state or by other therapies. In addition, a lowering the dosage or stopping the medication and a negative rechallenge to the study drug would support an unrelated relationship.

**Withdrawal Criteria**
Participants may choose to withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other protocols. Participants who develop an adverse reaction to the study drug or a serious
complication associated with or aggravated by continuation of study drug may be withdrawn from the study drug. Following study drug discontinuation, participants will return for a final assessment.

**Monitoring Guidelines**

At a minimum, the DSMB will review the study data at the time points defined in the section entitled “Interim Safety Analysis on page 66 to identify any issues with safety or the general conduct of the study. The DSMB may recommend temporary suspension, or to close enrollment, or stop the study at any time due to safety concerns, demonstration of efficacy or lack of efficacy, or slow enrollment.

Before recommending closing enrollment or stopping the study, the DSMB will consider:

- Internal consistency of primary and secondary results.
- Distribution of baseline prognostic factors among the treatment groups.
- Consistency of primary and secondary results across clinical centers.
- Sensitivity of the results to adjust for missing data and the possible impact of missing data from missed participant visits for assessment of the primary and secondary response variables.
- Any other considerations that the DSMB may want to review.

**Statistical Considerations**

**Sample Size and Power**

Attainable recruitment goals and functional outcome data from our preliminary analysis were both used to estimate sample size for the Phase II trial. Our pilot analysis demonstrated a potential dramatic annual change in VF annually in VPA treated RP patients (Figure 4). Reports in the literature allow us to conservatively estimate a 5% reduction in VF annually in untreated RP patients (Berson et al., 2002). If we reduce our estimate of delta from that calculated in the pilot study to boost the statistical validity of the trial, and assume a 60% difference in the rate of visual field change in Phase II, statistical significance for a two-sided test using a significance level of 0.05 and 80% power would require around 40 patients per group.

In general, RP patients are highly motivated to comply as evidenced in the similarly designed RFSW based Phase I trial of DHA where drop-out rates were 0% at year 3 and 7% at year 4. Because we will likely enroll sibling pairs into the trial, the total number of “active” participants has been increased from 80 to 90 to permit statistical compensation of these sibling pairs.

**Efficacy Analyses**

The primary efficacy variable is the mean change in Visual Field Area (VFA) from baseline to 12 months using semi-automated kinetic perimetry (SKP) using the Octopus 900 (Haig-Strait).

Secondary efficacy variables will include: static perimetry measurements in the 30° central field; mean
change from baseline in Best Corrected Visual Acuity (BCVA), Color contrast sensitivity and changes in ERG, Optical Coherence Tomography (OCT), fundus images and vision-related quality of life (NEI-VFQ25).

Safety Analyses
Safety variables will include the incidence of adverse events, marked changes in visual acuity, changes in vital signs, marked changes in clinical laboratory data (especially liver and pancreatic function), and findings during physical examinations.

Interim Safety Analyses
Participants will be followed closely for adverse reactions to VPA. Clinic visits at 1, 2 and 6 months will include safety labs and subjects will be qualitatively assessed by physical and ocular exams. Participants will be contacted by telephone on months not scheduled for clinic visits.

Statistical Methods
Data will be analyzed using student t tests (paired and unpaired). Multiple predictor regression models will be created using exponential change (to better approximate normality) in VF area, sensitivity measurements in the 30° central field, visual acuity, color contrast sensitivity, ERG amplitude and central foveal thickness as outcomes. Predictor covariates will be age, age at presentation, VF area at baseline, genotype, inheritance pattern, average rate of VF loss (as predicted by screening and baseline values), average serum VPA value and dose of VPA. Analysis will be performed based on an intention to treat analysis.

The study is powered to detect a change in mean visual field area using semi-automated kinetic perimetry, as the primary endpoint. Secondary analyses will be exploratory, but in order to test several additional endpoints we will also adjust for multiple comparisons either using the very strict Bonferroni adjustment or by relying on an omnibus test.

Potential Risks
Potential risks to study subjects include the well known and characterized risks associated with administration of the therapeutic agent and with study procedures. Valproic acid can cause serious and fatal hepatotoxicity especially in individuals with liver disease, organic brain disease, serious seizure disorders, congenital metabolic disorders, those on multiple anticonvulsants and children under the age of 2. Therefore individuals with contraindicating diseases and concomitant medications as well as children under 18 will be excluded from this study. The risk of hepatotoxicity usually occurs within the first 6 months of treatment and decreases considerably in older age groups. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting.

In the pilot study (Appendix B. Pilot clinical study) no abnormal liver function or blood chemistries were noted with patients on 500 mg total daily dose of VPA. The most common side effects were mild and included tiredness (10%) and stomach irritation (13%).

Valproic acid can cause serious and fatal pancreatitis. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms such as abdominal pain, nausea, vomiting, and/or anorexia to death. Cases have been reported shortly after initial use as well as after several years of use.
Valproate can produce teratogenic effects such as Spina Bifida, therefore woman of child bearing potential will be screened for pregnancy prior to administration of the study agent and must maintain use of contraception during the study period.

The risks associated with ophthalmic procedures include redness, discomfort or allergic reaction to topical medications used to dilate the pupil prior to visual function tests. High blood pressure, cardiac dysrhythmias and closed angle glaucoma may be exacerbated by some of these medications and light sensitivity may be experienced when the pupil is dilated. Corneal abrasions may result from the contact lenses used in performing electroretinography testing. The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Patients will be recruited from the Department of Ophthalmology at the University of Massachusetts Medical Center; the Retina Foundation of the Southwest and through the Foundation Fighting Blindness. This protocol will be listed in the Clinical Trials Data Bank of the NIH. Potential study patients who demonstrate an interest in participating in the study will receive an explanation of the terms, procedures, and requirements of the study from an investigator of the research team in language they can understand. They will receive a copy of the Informed Consent Form to read and share with family or friends. Subsequently, an investigator will answer questions and request the patient's permission to participate in the study. Volunteer participants who sign a study-specific patient informed consent form approved by the Institutional Review Board will then be scheduled for a screening evaluation to determine their eligibility. Children under 18 are not included in this study.

Protections Against Risk

The subjects will be informed of possible consequences of the study from one of the delegated study staff members in a language they can understand. They will be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. They will be asked to follow-up with necessary safety evaluations if they have received study agent prior to their desire to withdraw. They will be given full information regarding potential side effects of VPA and the procedures involved. The medical history and physical examination performed prior to study agent administration will identify patients with medical conditions that would increase the risks associated with study procedures and those subjects will be excluded from participation. The administration of the study agent and all procedures related to the study will be performed by trained and licensed medical and health professionals. They will be provided with contact numbers for any questions or concerns arising regarding the possible effects of the VPA and encouraged to call if they feel that an adverse event is occurring. In the event of an adverse event associated with the clinical trial, immediate medical care will be provided.

Patients will be followed closely, especially in the first 6 months for known adverse reactions to VPA. Safety labs regarding liver and pancreas toxicity will be drawn prior to and periodically during dosing with VPA. Results of all laboratory and safety exams performed to ensure subject eligibility and safety will be reviewed by an investigator during the study. Subjects with known risk factors such as liver disease, pancreatic conditions, metabolic disorders, organic brain diseases, seizure disorders and those on anti-convulsants will be excluded from the study. Female subjects of child bearing potential must have a negative pregnancy test at the baseline visit and prior to study agent administration. Female subjects of reproductive ability must be
willing to use effective contraception for the duration of the study, one year. Lactating mothers will not be included in this study.

We will not include children under 18 in this study due to increased risk of adverse events with VPA in children combined with the fact that the majority of RP patients recruited will be over 18.

The Data Safety Monitoring Board (DSMB) will be established with members who have an understanding of the disease, ethics, and biostatistics. They will review the study results and notify the PI of their findings and recommendations for study continuation or modification. The DSMB will be charged with monitoring the conduct of the trial and assessing patient safety on an ongoing basis. This group will review all safety data, including serious adverse events, adverse events, and laboratory data. Confidentiality of the subjects will be maintained in the process of review by the DSMB. The DSMB will provide committee recommendations after each review. Adverse events will be reported to the IRB, NIH, and FDA as regulated to insure the safety of subjects.

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines.

Confidentiality and Access to Source Data/Documents
Confidentiality will be assured by limiting access to the subject database to key research personnel. Individual identifiers will be stored in the computerized database and will also be the only identifier on analyzed and stored subject specimens. Access to the database will be controlled by a user code. The log identifying the subject names with the subject numbers, as well as Case Report Forms, Informed Consent Forms, laboratory study reports, and demographic profiles will be kept locked in an investigator’s office. The subjects will be informed of the information stored and the review of that information by the DSMB, UMass and RFSW IRB, and UMass and RFSW clinical facility personnel, Data Management and Statistical personnel, research staff, and personnel performing the procedures.

Sources of Materials
Research material obtained from identifiable living human subjects includes reports of: history and physical assessments, blood, urine, pregnancy tests, perimetry, optical coherence tomography, visual acuity measurements, color contrast sensitivity and electroretinography measurements, clinical assessments, adverse events, and autopsies. Copies of case report forms, original test results, subject medical records, signed subject informed consent, correspondence, and any other documents of the subjects, relevant to the conduct of the study will be kept on file by the principal investigator. All material or data collected as part of the study will be obtained specifically for research purposes.
References


Appendix A. Pre-Clinical Data

**FIGURE 1:** VALPROIC ACID ALLOWS MUTANT P23H RHODOPSIN TO PROPERLY FOLD TO THE LEVEL OF WILD TYPE.

HEK293 cells stably expressing an inducible mutant P23H rhodopsin expression vector were grown to confluence and tetracycline was added to induce opsin expression. 3mM VPA was added for 48h. Rhodopsin was purified by immunoaffinity methods. Yields of folded p23H opsin were quantified by spectrophotometry. In the presence of 11-cis retinal, folded mutant rhodopsin levels (red) increase from baseline (blue) to that of wild type (green).

**FIGURE 2:** VPA RESCUES RETINAL PIGMENTED EPITHELIUM CELLS FROM HYDROQUINONE (HQ) INDUCED APOPTOSIS.

ARPE-19 cells are protected from HQ mediated apoptosis by the presence of VPA.
Appendix B. Pilot clinical study

FIGURE 3  PERIMETRY TRACING OF A PATIENT TREATED WITH VPA
Goldmann Kinetic Perimetry tracings (using V4e isopter) of Patient One before and after treatment with VPA 250 mg twice daily.
A. Goldmann Kinetic Perimetry tracings (isopter V4e) from each eye (e.g. Figure 3) were digitized and areas were automatically calculated. We defined percent change in visual field relative to baseline and accounted for duration of treatment.

B. Assessment of the statistical significance of the observed changes in visual field, relative to baseline was exploratory. Three null hypotheses were considered: (1) $H_0$: Median percent change per month with no treatment = 0; (2) $H_0$: Median percent change per month on no treatment = -0.5 percentage points; (2) $H_0$: Median percent change per month on no treatment = -1.0 percentage points. Significance levels were calculated using the signed rank test.
Appendix C. Study Schedule Flow-chart

**FIGURE 5: STUDY VISIT SCHEDULE**

Cells outlined in red represent clinic visits with full battery of outcome measures.
## Appendix D. Scheduled Study Evaluations Table

**TABLE 3: Scheduled Study Evaluations**

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<th>Screening</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
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\(^a\) If enrolled  
\(^b\) Ophthalmic examinations include: slit lamp examination; tonometry, indirect ophthalmoscopy and retinal biomicroscopy.  
\(^c\) Quality of Life Assessed using the 25-Item NEI Visual Function Questionnaire  
\(^d\) For subjects that withdraw from the study at any time before visit 5.
Clinical Manufacturing of Placebo Valproic Acid Softgels and Sourcing of Active Valproic Acid Softgels

QTE-UOQ-0001.01

Confidential for University of Massachusetts

Prepared for Christine Clemson, PhD
222 Maple Drive, Higgins Building
Shrewsbury, MA 01545
Phone: 774-258-0425

Catalent Contact: Sarah Hauer
Phone: 410-663-0394
July 28, 2009

Section 1. Scope of Work
Catalent will source one active batch of Valproic Acid 250 mg softgels size 19 mm – off white in color (lot # 3888975 – Manufactured by Catalent Pharma, St. Petersburg, FL, distributed by Watson Pharma, Inc., Corona, CA 92880 USA). Catalent will manufacture one batch of placebo (50,000 capsules) of identical size, shape and excipient fill to study drug. The following sections provide additional detail for the “Project” and the associated costs.

Section 2. Activities/Specifications

2.1. Project Activities

2.1.1. Catalent’s Responsibilities

2.1.1.1. Project Initiation

2.1.1.3. Clinical Batch Manufacturing
Catalent will perform the following activities required for the manufacture of one placebo CGMP batch of Valproic Acid softgels:

- Order excipients and sample for release.
- Generate Master Batch Records and Production Batch Records for UMASS’ approval.
- Prepare gel mass using the current, opaque colored gel mass formulation, sufficient for manufacture of the clinical batch.
- Manufacture one (1) CGMP placebo batch (50,000) of 19 mm soft-gel off-white capsules using identical excipient fill to study drug (peanut oil based fill).
- Perform in-process encapsulation testing (fill and shell weights, seal checks).
- Perform a drying profile for the batch based on hardness.
- Bulk package softgels for shipping to a packaging site designated by UMASS.
- Provide required batch documentation to UMASS.

2.1.1.4. Excipients Sourcing and Testing
Catalent will provide access to released excipients for clinical manufacture to include the following:

- Source and supply excipients and components in support of manufacture.
- Store materials in a controlled CGMP warehouse.
- Review documentation for each excipient.
- Ensure test methods used are in compliance with USP.
- Provide access to released excipient(s) for use in batch manufacture.
- Provide Certificate of Analysis as required.

2.1.1.5. Release of Clinical Batch
Catalent will perform the following batch release testing activities:

- Review documentation for the batches.
- Write specifications for the placebo finished product.
- Perform release testing for the placebo batch consisting of appearance, absence of active, and MLT per USP/EP/JP Harmonized Method.
- Perform MLT one-time validation (as per USP/EP/JP Harmonized Method) for the placebo batch.
- Report results and issue Certificate of Analysis.
- Complete QA audit of batch paperwork.
- Provide batch paperwork and batch release documentation to UMASS.

Section 3. Cost Proposal
Section 4. Invoicing and Payment Terms

Section 5. Scheduling/Deliverables

5.1. Scheduling
Catalent must receive a signed Quotation, a signed protocol, and all raw materials/intermediates/final product samples in order for this project to be scheduled. Subsequently, a Purchase Order number (where applicable) must be received within 28 days of receipt of the signed quote. Once scheduled, UMASS will be notified by Catalent of the anticipated start and completion date of the project activities.

5.2. Deliverables
   5.2.1. Reports and Certificates of Analysis
   A report and/or Certificate of Analysis will be issued upon completion of each project phase.

   5.2.2. Communication
   In order to establish a collaborative relationship between UMASS and Catalent, both parties will appoint a Project Manager to serve as a point of contact to oversee progress on this project. Upon initiation of the project, Catalent and UMASS will establish a communication plan, that may include conference calls, visits, and timelines. UMASS communication is encouraged. To foster project planning, reviews/updates, and coordination meetings, Catalent will administer project team conference calls as reasonably required.

Section 6. Additional Project Terms

6.1. Safety

6.1.1. Catalent’s Responsibilities
Catalent will assess all vendor and UMASS MSDS and all handling data for the samples/materials associated with this project. If categorized as a CDS and/or Category 4 or above, the samples/materials will require special handling precautions and will be subject to a Hazardous Material Fee for all handling and testing directly associated with the samples/materials. If applicable, this Hazardous Materials Handling Surcharge has been included in the project costs.

6.2. Methods/Documentation

   6.2.1. Catalent’s Responsibilities
   Catalent will review all project-related documentation and methods received from UMASS associated with this project.

6.3. Samples/Materials

   6.3.1. Catalent’s Responsibilities
Catalent will, as necessary, log in all samples/materials according to current Standard Operating Procedures. The sample/material lot numbers will be recorded in the laboratory notebooks at the time of use. Upon issuance of the final report or Certificate of Analysis, Catalent will issue a request for approval of destruction of any remaining clinical supply materials/samples, during which time samples/materials will be stored in quarantine at Catalent for a period of 30 days. After a 30-day quarantine period, if additional storage is required, Catalent will issue a QAR for the additional cost.
3.5.6 CLAIM FOR CATEGORICAL EXCLUSION

August 3, 2009

I claim categorical exclusion (under 21 CFR 25.31[e]) for the study(ies) under this IND. To my knowledge, no extraordinary circumstances exist.

Shalini Kaushal
**3.5.7 Form 1572**

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<td>STATEMENT OF INVESTIGATOR</td>
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<tr>
<td><em>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</em></td>
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**NOTE:** No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. **NAME AND ADDRESS OF INVESTIGATOR**
   Shalesh Kaushal, MD PhD
   Chair and Assoc. Professor of Ophthalmology
   University of Massachusetts Medical School
   Rm. S6-410
   Worcester, MA 01655

2. **EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.**
   - ✔ CURRICULUM VITAE
   - ☐ OTHER STATEMENT OF QUALIFICATIONS

3. **NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED**
   University of Massachusetts Memorial Medical Center - Memorial Campus
   119 Belmont Street
   Worcester, MA 01605
   Retina Foundation of the Southwest (RFSW)
   9900 North Central Expressway, Ste. 400
   Dallas, TX 75231

4. **NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.**

5. **NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).**
   University of Massachusetts Medical School
   Institutional Review Board
   Human Subjects Office S1-859
   55 Lake Avenue North
   Worcester, MA 01655
   Western Institutional Review Board (WIRB)
   3535 Seventh Ave. SW
   Olympia, WA 98508-2029

6. **NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S)**
   - David Birch, PhD (RFSW)
   - Christine Clemson, PhD (UMMMC)
   - George Asdourian, MD (UMMMC)
   - Gary E. Fish, M.D (RFSW)
   - Rand Spencer, M.D. (RFSW)
7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.
   A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa H-13371

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

   □ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF
   THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

   ✗ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF
   SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE
   INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND
   LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE
   REPORT FORMS TO BE USED.

9. COMMITMENTS:

   I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make
   changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or
   welfare of subjects.

   I agree to personally conduct or supervise the described investigation(s).

   I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure
   that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21
   CFR Part 56 are met.

   I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

   I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

   I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations
   in meeting the above commitments.

   I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in
   accordance with 21 CFR 312.68.

   I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and
   approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated
   problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except
   where necessary to eliminate apparent immediate hazards to human subjects.

   I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR
   Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572

STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

2. Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate
   this information along with other technical data into an Investigational New Drug Application (IND).
   INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR

11. DATE
Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltville, MD  20705-1266

Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (HFM-99)  
1401 Rockville Pike  
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.
A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa H-13371 
Outline

1. **Indication Investigated**: Retinitis Pigmentosa (RP) 
2. **Number of Subjects**: 45 treated; 45 controls (90) total – split evenly between 2 sites. 
3. **Subject Characteristics**: Diagnosis of RP, age 18 or greater. 
4. **Clinical Observations and Laboratory tests performed**: visual fields as measured by semi-automated kinetic perimetry (SKP), best corrected ETDRS visual acuity; color contrast sensitivity as measured by the Chroma Test; retinal anatomy as measured by Optical Coherance Tomography (OCT) and rod and cone responses as analyzed by electroretinography (ERG), fundus photography; the 25 item National Eye Institute Visual Function questionnaire to assess quality of life (QOL); genotyping, complete blood counts and comprehensive metabolic screening, urine pregnancy tests and serum VPA levels. 
5. **Estimated duration of study**: 15 months (12 months treatment plus 3 months follow up). 
6. **Case Report Forms**: Attached
3.5.9 CLINICAL TRIALS.GOV WAIVER (FORM 3674)
### 3.5.10 Sample Case Report Forms

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# 3.6 IRB Applications

## 3.6.1 Genotyping Application

### Section II

**Protocol Summary Sheet**

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<td>Shalesh Kaushal</td>
</tr>
<tr>
<td>Degree:</td>
<td>MD PhD</td>
</tr>
<tr>
<td>Faculty Title:</td>
<td>Chair and Assoc Professor</td>
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<tr>
<td>Department:</td>
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<tr>
<td>Total # of subjects at off-site locations:</td>
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<tr>
<td>Email Address:</td>
<td><a href="mailto:Shalesh.kaushal@umassmemorial.org">Shalesh.kaushal@umassmemorial.org</a></td>
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</table>

**Title of Study:**

National Ophthalmic Genotyping and Phenotyping Network, Stage 1 — Creation of DNA Repository for Inherited Ophthalmic Diseases

**Contact Person Name:**

Christine Clemson, PhD

**Phone #:**

856-4808

**University:**

Memorial: x

**Identify Condition being studied:**

Retinitis Pigmentosa

**Shriver Center:**

Marlborough:

Shriver Center:
Source of Funding: NIH/NEI

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Please provide IDE# if not approved by FDA

### Drug Information

In the table below, list all drugs being used. If the drug is considered investigational by the FDA you must include the IND# assigned by the FDA. Please "X" approved or investigational.

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### Use Space Below for Comments or Additional Drug Information

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**SECTION V**

**DESCRIPTION OF RESEARCH PROJECT**

**PERSONNEL ENGAGED IN THE RESEARCH STUDY.** List all personnel engaged in the study. This list must agree with that in Section VI (Delegation of roles/responsibilities).

**Shalesh Kaushal, M.D. PhD. (UMMC)** will serve as a Principal Investigator of this study providing pre and post test genetic counseling to participants who choose to be genotyped.

**Christine Clemson, PhD. (UMMS)** will serve as the Study Coordinator of this trial, collecting all relevant clinical information, sending it to the coordination center and collating all genotype information as it is returned.

**George Asdourian, M.D. (UMMMC)** will serve as a co-investigator and will help provide pre and post test genetic counseling to participants who choose to be genotyped.

**Judith Colbert, R.N. (UMMMC)** will serve as the study nurse coordinator for the UMMC site, she will perform the blood draws and prepare and mail the samples to the coordinating center.

**2. GENERAL STATEMENT OF PROBLEM**

**Purpose:** Include concise hypothesis to be tested by proposed research.

Molecular genetics has the potential to revolutionize the diagnosis and treatment of inherited eye diseases. Progress in research on inherited eye disease would be augmented by the availability of patient DNA coupled to robust, anonymous phenotypic information. The National Ophthalmic Genotyping Network (eyeGENE) has been created to answer this need. With the creation of a national DNA and blood repository for inherited eye disease, samples will be gathered from clinical centers around the nation, such as UMMHC and will be coupled to anonymous, phenotypic descriptors. If requested, a portion of the sample submitted by a clinician will be used for appropriate, CLIA-certified molecular diagnostics that can be used in patient care. Once a sufficient repository is created, researchers will be able to request aliquots for their laboratory experiments. Participants will be provided the option to be re-contacted if an approved clinical study for which they might qualify is offered.
3. BACKGROUND AND SIGNIFICANCE:

a. Provide a summary of the facts which led to selection of the problem.

Over the past 15 years, nearly 500 genes that contribute to inherited eye diseases have been identified. Disease-causing mutations are associated with many ocular diseases, including glaucoma, cataracts, strabismus, corneal dystrophies and a number of forms of retinal degenerations. This remarkable new genetic information highlights the significant inroads that are being made in understanding the medical basis of human ophthalmic diseases. As a result, gene-based therapies are actively being pursued to ameliorate ophthalmic genetic diseases that were once considered untreatable.

To date, no other ophthalmic research groups/societies have attempted to carry out a study of this type and proportion. Once the repository is established, it would provide an outstanding tool for researchers and clinicians in the ophthalmic community. This repository of DNA and blood, coupled with phenotypic information, would be used by researchers for testing hypotheses related to eye disease. We hope, in the future, this study will enhance recruitment for clinical trials in inherited eye diseases.

The overall goals of eyeGENE are as follows:

To provide a repository of DNA and blood coupled to anonymous phenotypic information for researchers
To provide molecular diagnosis to patients with inherited eye diseases
To establish genotype-phenotype correlations for rare eye diseases
To enhance recruitment for clinical trials and investigations in inherited eye diseases

Specifically, Dr. Kaushal will enroll his patients in this protocol to determine, if possible, the specific mutation responsible for their eye disease. This information will not only be used for patient care, but for facilitating specific sub group analysis in our ongoing clinical trials here at UMMHC.

b. Please describe the Investigator’s previous work on the problem.

In November 2003, the National Eye Institute convened a national meeting of researchers, clinicians, and genetics professionals to discuss the creation of a National Ophthalmic Genotyping Network (eyeGENE). The consensus from this meeting was that having a national repository of DNA and blood samples that was available to researchers and was anonymously coupled to important, select clinical and genotypic data would be a major asset to vision research. If mutation analysis of known genes were performed according to CLIA standards, then this information could also be directly used to enhance patient care and to facilitate the use of clinical molecular testing in ophthalmology and optometry.

Dr. Kaushal has been involved in genotyping his patients as part of standard of care in his practice for many years. He is skilled at genetic counseling of patients with eye diseases who present with a variety of mutations and concomitant inheritance and disease severities.

c. What are the aspects that justify the use of human subjects, human data, or specimens as part of this research?

The ability to detect disease-causing mutations in many individuals with inherited ophthalmic diseases offers significant benefits for patients and their families. It is now possible to provide genetic testing for patients afflicted with ocular diseases by screening for these genes. This remarkable opportunity, however, has now created the challenge of providing genetic information to individuals who want to know whether they could benefit from the treatments that are being developed. Unfortunately, this type of molecular testing is not widely available.

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To date, no other ophthalmic research groups/societies have attempted to carry out a study of this type and proportion. Once the repository is established, it would provide an outstanding tool for researchers and clinicians in the ophthalmic community. This repository of DNA and blood, coupled with phenotypic information, would be used by researchers for testing hypotheses related to eye disease. We hope, in the future, this study will enhance recruitment for clinical trails in inherited eye diseases.

4. DETAILED DESCRIPTION OF RESEARCH PLAN (especially as it affects the subject)

Include a schematic representation of what the research will entail (e.g. a table with the number of visits and what will happen at each visit or flow diagram of subject’s involvement over time).

The following information will be collected on all participants, regardless of the nature of their disease: 1) name; 2) contact information; 3) date of birth; 4) gender; 5) race; 6) family history. Medical, ophthalmologic, and genetic history will also be obtained and will be used to prepare a pedigree for each family. Demographic information and clinical information specific for the participant’s disease will be collected, such as the duration of symptoms, presence of night blindness, visual acuity, and the amplitude of a combined response electroretinogram.

Participants will undergo phlebotomy to provide a blood sample to the repository. Phlebotomy may be performed at the laboratory of the participant’s choice. Around 24 to 30 ml of blood will be drawn from adults; the volume of blood drawn will be within NIH guidelines for children and will be no more than 7 ml/kg/6 week period and no more than 3ml/kg in a single draw. A minimum of 5 ml of blood is required from children and a minimum of 15 ml of blood is required from adults to be able to participate.

Molecular genetics testing will be performed in a CLIA-certified lab, and individual participant results will be given back to the referring clinician, although it may take several months to complete the sample analysis. Participants who wish to receive results of the testing will receive pre- and post-testing genetic counseling. Referring clinicians are required to certify that they are able to provide or arrange for both pre- and post-testing genetic counseling before they are permitted to enroll participants in the study.

b. Inclusion/Exclusion Criteria - As appropriate, explain what steps will be taken to insure that subjects meet the criteria (e.g. healthy, not pregnant, etc).

**Inclusion Criteria**

To participate in this protocol,  
1a. The participant must present with characteristics that meet minimal clinical criteria. For a Diagnosis of Retinitis Pigmentosa this includes photoreceptor degeneration established by reduced visual acuity, visual field constriction, night blindness, marked reduction of rod and cone ERG responses, and presence of intraretinal “bone-spicule” pigment on clinical examination.

OR

1b. The participant must be a relative of an affected participant if analysis would help with the interpretation of an affected participant’s test results or to obtain some useful information as decided by the eyeGENE Research Study Group.
The participant must be willing and able to provide a suitable blood sample.

**Exclusion Criteria**

1. Severe systemic disease that compromises the ability of the referring clinician to obtain an adequate eye examination.
2. Any disease or condition that makes it unsafe for a subject to provide a blood sample of at least 5 mL for children and at least 15 mL for adults.
3. Inability to cooperate with phlebotomy and clinical examination.
4. Those with impaired decision-making capability who do not have a legally-authorized representative.

c. Discuss the number of experimental and control subjects, and explain the statistical basis for the numbers.
The total number of participants to be enrolled for the entire eyeGENE study is 1,250; approximately 250 per year for five years. At UMMHC, Dr Kaushal expects to enroll about 30 patients a year for 5 years.

d. Does the study involve randomization?

Yes  No  x

If yes, please describe process.

e. How long will each subject be enrolled in the study?
The amount of time that each subject is involved with the eyeGENE study depends on how they choose to be affiliated with the study:
If the participant wishes to take part in research, but do not want results of genetic testing or does not want to be re-contacted for future clinical study, the name and contact information of the participant will not be collected. Age at the time when sample was donated will be recorded instead of date of birth.
If the participant wishes to take part in research and in future clinical trials, but does not want results of genetic testing, the sample will remain identifiable in the central eyeGENE database to the personnel at NEI only.
If the participant does not wish to be re-contacted in future clinical trials but wants the results of genetic testing, two years after clinical molecular diagnosis is complete the name and contact information of the participant will be removed and the date of birth will be converted to age (CLIA regulations require holding onto identifiable samples for two years after the sample has been processed if molecular test results are given back to the participant.).
If the participant wants to be re-contacted for future clinical studies and wants the results of genetic testing, the samples will remain identifiable to personnel of NEI only.
If the participant is an unaffected relative of an affected participant, s/he will not be contacted for future clinical studies, nor receive the results of genetic testing. The sample will remain identifiable in the central eyeGENE database to the personnel at NEI only.

f. Provide a brief overview of what participation in the study will mean to each participant in terms of what he/she will experience. Describe in order, each procedure, how long each procedure will take and how often each procedure will be performed. Include doses & route of administration of any drugs and whether
the procedure or drugs would always, sometimes or never be required as part of the subject’s standard of care.

Genetic testing is sometimes included as standard of care. Participants will undergo phlebotomy to provide a blood sample to the repository. Phlebotomy may be performed at the laboratory of the participant’s choice. Around 24 to 30 ml of blood will be drawn from adults; the volume of blood drawn will be within NIH guidelines for children and will be no more than 7 ml/kg /6 week period and no more than 3ml/kg in a single draw. A minimum of 5 ml of blood is required from children and a minimum of 15 ml of blood is required from adults to be able to participate.

Molecular genetics testing will be performed in a CLIA-certified lab, and individual participant results will be given back to the referring clinician, although it may take several months to complete the sample analysis. Participants who wish to receive results of the testing will receive pre- and post-testing genetic counseling. Referring clinicians are required to certify that they are able to provide or arrange for both pre- and post-testing genetic counseling before they are permitted to enroll participants in the study.

g. Is any aspect of this research study being conducted in the Medical School or a non-UMMMC facility? If yes, please explain.

no

h. Will hospitalization be required as part of this research study?

Yes  No  x

If yes, how long will subjects be hospitalized?

i. Will there be any material inducements or recruitment incentives given to research staff or research subjects as part of this research study? (e.g., direct payments, free hospitalization, care)

Yes  No  x

If yes, explain how much, the pay schedule, or any partial payments that will be given.

DISCLOSURE OF CONFLICT OF INTEREST

Investigators should disclose any financial arrangement they may have with a company whose product figures prominently in their research or financial arrangements they may have with company making a competing product. The relationship should also be described in the informed consent documents. In the case where the only relationship is that a company is sponsoring the research study, it is sufficient to prominently identify the sponsor on the front page of the consent form and to simply state “NONE” in the consent form under Conflict of Interest.

Is there a conflict of interest?  Yes  No  x

6. RELATIONSHIP TO STANDARD THERAPY.
Describe the standard therapy that patients would receive if not in the research study. Explain how this research intervention deviates from or replaces generally accepted standard therapy and justify the deviation. The alternative to participating in this study is not to participate. This study does not provide treatment and does not replace any therapy that the participants’ doctors give them.

7. DESCRIBE THE POTENTIAL BENEFITS OF THIS PROJECT.
Include hoped-for benefit to society, to the group of subjects or to individual subjects. In most cases there will be little or no direct benefit of this study to participants. Some subjects may benefit from the genetic testing and counseling provided under this protocol. The study will yield generalizable knowledge about eye disease genetics.

Address the risk/benefit ratio of the study. If there are no direct subject benefits, this should be stated.

This is a minimal risk study for adults. For minors, the research is category I: the research presents minimal risk to study participants.

8. DESCRIBE THE POTENTIAL RISKS TO SUBJECTS INCLUDE PSYCHOLOGICAL, ECONOMIC, LEGAL OR SOCIAL RISKS AS WELL AS PHYSICAL RISKS.

Include the following information:

a. Estimate likelihood of occurrence, severity, and duration. If generally accepted quantitative estimates are available based on previous data, these should be stated. Otherwise, qualitative estimates such as “rare”, “occasionally”, or “frequently” may be used. The committee needs scientific information about drug/device side effects so as to best judge the pros and cons of the study. Do not simply cut and paste the consent form “Risk” section into this part of the protocol.
The only physical risk or discomfort associated with this study is from phlebotomy to obtain the blood sample. Drawing blood may cause pain and carries a small risk of bleeding, bruising, dizziness and/or infection at the injection site.
Medical information will only be obtained from an eye examination done as part of standard clinical evaluation for the subject’s condition.

b. Explain what steps will be taken to protect against its occurrence, minimizing the harm, methods for early detection of harm, and what procedures will be followed to avoid serious injury (e.g. withdraw from study or dose reduction).
While it is anticipated that the results of the molecular genetic studies will result only rarely in new information regarding a participant’s clinical diagnosis, genetic information resulting from these studies, if available, might affect their ability to obtain insurance coverage or employment. In order to minimize this risk, when results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified and pedigree structures are disguised in a fashion consistent with maintaining the scientific integrity of the report. In most cases, the NIH will not release any information about
research involvement without written permission. However, if the participant signs a release of information form, the NIH will give the requestor information from the participant’s medical record.

This study involves the evaluation of a genetic condition and information relating to the family, such as adoption and paternity, may be revealed or information may become available about unsuspected family members who are affected. This information will be maintained in confidential laboratory documents and medical records.

Genetic pre and post test counseling will be provided to participants.

d. Do you, as the PI, have equipoise regarding the study? That is, are you comfortable with the risks in relationship to the knowledge gained? If the study involves randomization, do you believe in the equality of the treatment arms?

For a repository collection instrument such as described here, equipoise is not relevant.

9. CONFIDENTIALITY CONSIDERATIONS: EXPLAIN STEPS THAT WILL BE TAKEN TO INSURE THE CONFIDENTIALITY OF INFORMATION THAT IS OBTAINED IN THE COURSE OF THIS RESEARCH PROJECT. INCLUDE THE FOLLOWING:

a. How will identifiers be used?

Data and samples of all participants will be barcoded. Samples and data from subjects who did not wish to receive genetic test results or to have future contact will be irreversibly de-identified.

All of those participants who want their sample to be anonymous and who do not wish to receive CLIA test results will have their samples coded and de-identified. The CLIA labs will have to de-identify any sample before they use it for their own research purpose. Similarly, in future outside researchers will only receive an anonymous sample with pertinent clinical information, but without any identifiers.

The NIH will not release any information about research involvement without written permission. However, if the participant signs a release of information form, the NIH will give the requestor information from a participant’s medical record. As a result of releasing results, genetic information resulting from these studies might affect a participant’s ability to obtain insurance coverage or employment.

b. Where will data be stored?

The application is being housed and run by NIH’s Center for Information Technology (CIT). CIT access to the server is limited to those performing setup and maintenance activities on the CIT servers. Access to the database, either via the web application or direct SQL Server connection, is controlled by a User ID and password. Password complexity is determined by the HHS Secure One program and implemented in the database access programs. Access to the web server is via secure http protocol (https). Support and maintenance is either performed locally within the NIH network or by encrypted VPN access.

CIT will implement and report on the NIST 800-53 security controls for a "moderate" security system. Annual review of the security controls will be performed. The certification will be renewed every 3 years.

c. Besides the UMMS IRB and their representatives, who will have access to the research data?

Access to participant data is only available as follows:
eyeGENE staff access is limited to the eyeGENE Director, the eyeGENE Coordinator, and the NEI Molecular Diagnostic Lab Assistant Director.

eyeGENE support staff with access to all data is limited to the developer and maintenance staff, NEI IT security and software maintenance, and eyeGENE security study staff.

Physicians, or those acting on behalf of a physician, may access their own participant’s data. Genetic testing results are “read-only” for such individuals, once the results are marked final by the CLIA lab. They will not have access to identifying information for patients they did not personally submit.

CLIA diagnostic lab personnel will have full read access to data from participants that are referred to their lab for molecular diagnosis. Their ability to modify data in the participant file will be limited to inputting mutation data on the participant samples analyzed in their laboratory. CLIA lab personnel will able to see the patient identification number, their date of birth, their gender, and their other disease-specific phenotypic information. They will NOT be able to view the patient name, referring physician or other contact information.

A strict audit trail is maintained of any access to patient information by any eyeGENE user, which records the date and time of access and the name and organization of the user, which is reviewed periodically, which is used as a double-check to ensure that no unauthorized access to patient data has ever occurred.

No information will be released to third parties other than the CLIA labs except or as requested by the participant in writing.

d. When will the data/specimens be destroyed?
CLIA regulations require holding onto identifiable samples for two years after the sample has been processed if molecular test results are given back to the participant. CLIA labs will be required to destroy identifying patient information after this period has elapsed.

e. In the future, might other use be made of specimens collected as part of the research? If yes, please describe.
Samples and data from subjects who wish to receive CLIA genetic test results or to be contacted in the future will be linked to identifiable information that is kept in the eyeGENE database is protected by multiple levels of security.

10. ECONOMIC CONSIDERATIONS:

In the course of this research project, might the subjects experience any additional expenses as a result of study participation? This includes both out-of-pocket costs and expenses that might not be covered by medical insurance.

Yes  x  No

If yes, please explain and justify.

No patient or their insurance company, regardless of whether they are enrolled in an UMMHC clinical trial, will be responsible for the costs associated with genetic analysis of the blood sample.
As a collaborating site, the investigators will adhere to the NEI eyeGENE protocol. The NEI eyeGENE protocol does not provide for funding of tasks other than the genotyping of the sample. As with other standards of care, patients or their insurance companies will be responsible for certain aspects of the procedure: phlebotomy, shipping, eye examinations and genetic counseling. The eyeGENE initiative allows for the funding of sample analysis, the cost of which would normally fall on the patient or their insurance company if that patient were not enrolled in the eyeGENE study. The cost of phlebotomy and shipping, for the patient is estimated to be $87 USD if they elect to pay out of pocket.

If however genotyping must be completed for data collection as part of enrollment in a UMMHC protocol, this is no longer “standard of care” because the patient is a subject of research study and the responsibility of cost if slightly different. UMMHC protocols that involve the study of genetic information will be able to provide funding for all aspects of sample collection and analysis.

b. Please explain potential increase in standard hospital costs if any.

N/A

11. DESCRIBE THE CHARACTERISTICS OF THE SUBJECT POPULATION.

a. The subject population includes:

    - ADULTS
    - CHILDREN

b. Is the subject population restricted in respect to any of the following characteristics?

    | Please “x” those that apply | Yes | No |
    |-----------------------------|-----|-----|
    | Age Range                   | x   |     |
    | Health Status               | x   |     |
    | Gender                      |     | x   |
    | Racial/Ethnic composition   |     | x   |

If you responded YES to any of the above, include a clear rationale for this restriction.
Severe systemic disease that compromises the ability of the referring clinician to obtain an adequate eye examination.
Any disease or condition that makes it unsafe for a subject to provide a blood sample of at least 5 mL for children and at least 15 mL for adults.

12. WILL THE STUDY POPULATION SPECIFICALLY INCLUDE A POPULATION OF SUBJECTS CONSIDERED “VULNERABLE”? VULNERABLE POPULATIONS ARE CHILDREN, MENTALLY IMPAIRED, PREGNANT WOMEN, PRISONERS, OR FETUSES.

    - Yes    x    No

If yes, please explain.
Children will be enrolled in this protocol if they have one of the diseases being studied. Pregnant women may be enrolled if they have one of the diseases being studied.

13. WHAT IS THE SOURCE OF THE SUBJECT POPULATION?

Participants will be patients of the UMMMC Ophthalmology clinic.

14. EXPLAIN ANY STEPS TAKEN TO INSURE THAT THE SUBJECT POPULATION IS REPRESENTATIVE.

No restriction on the form or genotype of ocular disease will be instituted and as such it is expected that the recruited patients will be representative of all patients.

15. HOW AND WHERE WILL SUBJECTS BE RECRUITED FOR THE STUDY? CONSULT THE IRB GUIDELINES FOR THE RESTRICTIONS ON RECRUITMENT OF EMPLOYEES, STUDENTS, AND INPATIENTS. ATTACH COPIES OF ALL RECRUITMENT MATERIALS TO BE USED AS PART OF THIS RESEARCH STUDY. THESE MATERIALS MUST BE APPROVED BY THE IRB BEFORE BEING USED. Recruitment guidance can be found on our website under HSC Forms.

Recruitment will not be performed with the use of advertisements. Potential participants thought to be appropriate for genetic testing either for additional data, for clinical trials, or for standard of care will be approached by the investigator or co-investigator. Potential participants will be approached in the clinic setting at the time that the investigator or co-investigator discovers that participation is possible. Relatives will be identified by the potential participant and will be contacted by study personnel with the potential participant’s cooperation and permission.

16. WILL PROTECTED HEALTH INFORMATION (PHI) BE USED AS PART OF THIS RESEARCH STUDY? PLEASE VISIT OUR WEBSITE FOR MORE INFORMATION ABOUT PHI OR THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA).

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<td>X (in some cases)</td>
<td>X (in some cases)</td>
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Depending on whether the participant chooses to enroll in research that requires the storage of protected health information: see section 4e.

If yes, please answer the following questions.

How and where will the PHI be accessed (i.e. meditech, database, medical records, another site)?

- Database, medical records

Will a subject’s PHI be accessed before the subject is enrolled in the study?

- NO

Please list the PHI to be used as part of this research study (i.e. name, DOB, medical record #).

- Name, DOB, Contact information (address, phone #)
17. METHOD FOR OBTAINING INFORMED CONSENT

a. Are you requesting a waiver of the requirement for obtaining consent?

Yes  No  x

Do not complete the following questions if you are requesting a waiver of informed consent.

18. WILL VERBAL CONSENT BE OBTAINED?

Yes  No  x

If yes, will an unsigned “fact sheet” be given to subjects before verbal consent is obtained?

Yes  No

If yes, please provide a copy of the “fact sheet”.

19. WILL A SIGNED CONSENT FORM BE REQUIRED?

Yes  x  No

AS A GROUP, ARE THESE SUBJECTS EXPECTED TO BE COMPETENT TO GIVE CONSENT FOR THEMSELVES?

Yes  x  No

If no, please explain why and how consent will be obtained.

21. EXPLAIN THE CIRCUMSTANCES UNDER WHICH CONSENT WILL BE OBTAINED. HOW WILL YOU INSURE THAT POTENTIAL SUBJECTS HAVE ADEQUATE TIME TO CONSIDER THEIR OPTIONS, AND THAT POSSIBLE COERCION IS MINIMAL?

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study. The participants must have the ability to understand and sign an informed consent form, or have a legally-authorized representative to sign for them. All affected participants will receive the standard consent, while unaffected relatives will receive a separate consent.
If the participant requires the consent to be in larger font in order to read it well, this will be provided. If participants are visually impaired to the point of being unable to read the consent, they can take the consent back with them to read it over with a family member or with the use of magnifying devices. If the participant chooses, the investigator can also read the consent verbatim to the participant and answer any questions that may arise. We do not anticipate a large percentage of potential participants to be unable to read. Should a potential participant be illiterate, the consent will be read verbatim and care will be taken to ensure comprehension by the participant of the information presented in the consent as the document is read.

22. IF THE SUBJECT POPULATION INCLUDES MINORS, AND SIGNED CONSENT WILL BE OBTAINED, WILL AN ASSENT FORM BE USED AS PART OF THE CONSENTING PROCESS? CONSULT IRB GUIDELINES FOR INFORMATION ABOUT CHILDREN IN RESEARCH STUDIES.

Yes x No Minors enrolled Verbal consent requested

NOTE: In general, it is expected that minors from age 8 to 15 will read and sign an assent form. Older adolescents (16 and 17) will usually read and sign the same consent form as the parents signed. The assent form template is available on our website.

23. IF YES, PLEASE EXPLAIN WHO WILL APPROACH THE MINORS AND HOW AND WHERE THE ASSENTING PROCEDURE WILL TAKE PLACE.

Children will be enrolled in this protocol if they have one of the diseases being studied. Phlebotomy will only be done on those able to cooperate and can provide a minimum of 5 ml of blood sample. Consent will be obtained from parents or guardians; assent will be sought from minors older than 7. Genetic information will be released to the parents or guardians, if requested. For those reaching age 18 with stored samples in the study, if they express an interested in being contacted about research participation, they will sign a new consent form. It will be the responsibility of the study coordinator to contact these patients to arrange for consent to be obtained. At that time, these now adult patients will again be made aware of their rights concerning the study.
SECTION VI
CERTIFICATION OF APPROVAL
PI Name: Shalesh Kaushal, MD PhD

DELEGATION OF ROLES/RESPONSIBILITIES*: Checklist/Signature List

<table>
<thead>
<tr>
<th>Name and Credentials</th>
<th>Role*</th>
<th>Signature</th>
<th>Department/Campus</th>
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<tbody>
<tr>
<td>Shalesh Kaushal</td>
<td>PI</td>
<td></td>
<td>Ophthalmology/UMMMC</td>
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<td>MD PhD</td>
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<tr>
<td>Christine Clemson</td>
<td>Study Coordinator</td>
<td></td>
<td>Ophthalmology/UMMS</td>
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<tr>
<td>PhD</td>
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<tr>
<td>George Asdourian</td>
<td>Co-I</td>
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<td>Ophthalmology/UMMMC</td>
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<td>MD</td>
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<tr>
<td>Judith Colbert RN</td>
<td>Study Nurse Coordinator</td>
<td></td>
<td>Ophthalmology/UMMMC</td>
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*Roles: (choose appropriate # below)
1. Sub or Co-Investigator 2. Study Nurse Coordinator 3. Study Coordinator 4. Other:
Dr Kaushal and Asdourian will provide pre and post genetic counseling, Dr. Clemson will coordinate all communication with eyeGENE coordinating center; Judith Colbert will mail blood samples to eyeGENE coordinating center.

**Delegation of Responsibility Codes: (choose all that apply)
A. Consent Subjects
B. Take Medical History
C. Conduct Physical Exam
D. Phlebotomy
E. Monitor Vital Signs/Nursing Assessment
F. Maintain Regulatory Documents
G. CRF Completion and Query Resolution
H. SAE/AE Monitoring/Reporting
I. IRB Communications and Continuing Review
J. Other (explain):

Although the Principal Investigator is ultimately responsible for every element of study activity, this form serves to clarify to whom the PI has delegated specific study activities and responsibilities
3.6.2 Genotyping Consent Form

UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL
COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH
CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

Title: National Ophthalmic Genotyping Network, Stage 1 – Creation of Repository for Inherited Ophthalmic Diseases. Study # 06-EI-0236

Principal Investigator: Shalesh Kaushal, MD, PhD

Sponsor: National Eye Institute (NEI) at the National Institute of Health (NIH)

Research Subject’s Name: _____________________________ Date: __________

Invitation to Take Part and Introduction

We invite you to take part in a research study here at the University of Massachusetts Memorial Medical Center (UMMMC), that is a part of a larger study at the National Institutes of Health (NIH). First, we want you to know that:

Taking part in this NIH sponsored research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive. If you have such beliefs, please discuss them with your doctor before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at the UMMMC clinic, or with family, friends or your personal physician or other health professional.
In the remainder of this consent, we will use the word “you” to mean either “you” or “your child,” as applicable.

**Purpose of Research**
The purpose of this study is to better characterize and understand the genes involved in eye disease. A “bank” of DNA, blood samples, and eye examination information will be created for use in future studies on eye diseases.

The main goal of this research is to understand genetic eye conditions and to identify the genetic factors responsible for causing such diseases. DNA samples from a large number of people with different eye diseases is needed. The eyeGENE network has been set up to enroll people with eye disease, to obtain information on their eye examinations, and to collect blood from which the genetic material, DNA, will be extracted. The information and samples obtained will be used to test for genes that might be involved in the eye disease in your family and will also be placed in a repository to make it available to other researchers, now and in the future, who are studying eye diseases.

If you are planning to take part in this research study, we would also want you to know that:

You or your insurance company will have to pay for the cost of drawing the blood and shipping it to NEI, as well as the genetic counseling. However, analysis of the genetics sample will be completed at no cost to you.

If you decide that you do not want to participate in this study you should know that there are several other genetics testing laboratories you can approach to obtain your genetic test results on a fee-for-service basis.

You will be asked to provide a blood sample and information on your eye condition and family history, as well as demographic information.

Your sample will be kept at a DNA and blood repository at the NEI.

Your personal and medical information will be kept in a secure database.

You will need to choose whether 1) you wish to receive genetic results back and 2) if you wish to be re-contacted for future clinical or research studies and, if additional tests for your disease are found, if you wish to receive the results for these new tests.
The amount of personal information you need to provide depends on whether you wish to receive results or wish to be re-contacted. Your personal information needs to be maintained in the secure eyeGENE database if you wish to be re-contacted.

The time period to obtain genetics testing results back may vary from 3 months to one year depending on your disease and the genes that are being tested.

To be eligible for this study, you must meet the following criteria:

1. You or your child must have one of the eye diseases we are currently studying. Your UMMC ophthalmologist will make this determination.

2. You/Your child must be able to provide a blood sample for genetic testing.

You may not be eligible for this study if:

1. You have any disease that makes it impossible to obtain the eye examination information that we need for the study or to obtain a blood sample.

2. You are unable to provide consent for yourself and do not have a legally-authorized representative to provide consent for you.

Procedures

The study doctors believe that you/your child qualifies as a potential participant in this trial based on your/your child’s clinical data. We will provide information on your medical history and about eye conditions in yourself and your family to the NEI coordinating center. You will need to provide a blood sample. For the blood sample, about 5 to 6 teaspoons of blood will be drawn from a vein in your arm. Less blood will be drawn from those younger than 12 years.

Your sample along with medical details will be sent to eyeGENE, who will check all the information provided and if they agree that you are eligible then they will send your sample for testing for specific genes that are known to contribute to your condition. The remaining blood will be stored for use in future approved research studies.

The eyeGENE coordinating center will send your sample for testing in an approved clinical laboratory that is a part of their network. If you would like to receive the results
of your genetic testing, they will be sent to our clinic and your physician will share the results with you. You will be required to sign a second consent form (a DNA diagnostics form) and receive genetic counseling from a UMMC Ophthalmology clinic physician. The genetic counseling will help you to understand the implications of genetic testing and of the results of your genetic test. You will only receive results from yourself and/or your minor children.

Please indicate whether you would like to receive the results of your initial genetic testing by initialing the box next to your choice.

A1. _____ I would like to receive the results of my genetic testing that will be performed at this time. I understand that the results will be sent to my doctor, who will give them to me. I agree to meet with my doctor who will provide genetic counseling and assist me in understanding the results of the testing.

The time period to obtain genetics testing results back may vary from 3 months to one year or more depending on your disease and the genes that are being tested.

A2. _____ I do not want to receive the results of the genetic testing that will be performed at this time.

The blood that is stored may be tested in the future for genes that are not currently known. Please indicate whether you would like to receive the results of future genetic testing by initialing the box next to your choice.

B1. _____ I would like to receive the results of any genetic testing on my sample that may be performed in the future. I understand that the results will be sent to my doctor, who will give them to me, I agree to meet with a genetic counselor who will assist me in understanding the results of the testing.

B2. _____ I do not want to receive the results of any genetic testing that may be performed in the future.

The eyeGENE network will maintain medical examination and family history information on you as well as your DNA and blood sample. Other researchers may like to study the medical information on your eye disease and your sample. Researchers who use samples and medical information with approval of eyeGENE in the future will
not know your name. Your personally identifying information will not be disclosed to any other people without your consent.

In the future, researchers will be able to see the results of your genetic testing and some information about your eye condition. Examples of such information will include the nature of your eye disease status, age when you were evaluated, demographic information (such as your age, gender, and race/ethnicity). Other information such as pictures of your eye or your history of other diseases may also be available. Researchers may view this information to study other diseases or conditions, or for other purposes. Researchers will NOT be able to view your name, date of birth or contact information. Your DNA/ blood sample will ONLY be used for research studies related to vision.

**Use of Blood and DNA Samples and Results from this Study**

If the results of any genetics study, in which your DNA/blood was included, are reported in medical journals or at scientific meetings, your name will not be used, nor will you be identified in any other manner. Family trees may be published but they would be trimmed and masked to minimize the possibility of patient identification.

**Future research participation**

We hope that researchers using samples and information from the eyeGENE repository will also develop new clinical studies of eye disease in the future, and we would like to be able to offer you information on new studies that might interest you. Participation in future studies is completely voluntary. You do not have to participate in any additional studies in order to participate in this study.

Please let us know if you would like eyeGENE to contact you about future studies. If you would like us to hold onto your contact information and let you know if such a study arises, please indicate so below:

___YES, please re-contact me if you become aware of a clinical study that I may qualify.
Please note, that in order to make our records as accurate as possible, we request that you notify us of any contact information changes. Please send an email with the updated address to the eyeGENE Coordinator at eyeGENEinfo@nei.nih.gov or contact the eyeGENE coordinator at 301-435-3032.

NO, please do not re-contact me for further studies.

Risks, Inconveniences and Discomforts

Risks of Drawing Blood – A needle will be used to draw blood from a vein in your arm. You may experience some discomfort at the site of needle entry, and there is a risk of bruising. There is a very small risk of fainting or infection.

Risks of genetic testing - Genetic testing can provide information about how health or illness is passed on within your family. This knowledge may affect your emotional wellbeing. This information can cause stress, anxiety, or depression. Some genetic testing can also determine if people are directly related. These tests sometimes show that people were adopted or that their biological parent is someone other than their legal parent. If these facts were not known previously, they could be troubling. Genetic counseling will be available to help you understand the nature and implications of your and your family’s genetic findings. We will not discuss such information with you unless it has direct medical implications for you or your family, which is unlikely.

Genetic information about you will not be revealed to others, including your relatives or your insurance company, without your written permission. Similarly, you will not receive information about other family members. You may only receive information about yourself or your minor children. Parents are entitled to copies of their minor child’s medical records without consent of the child.

Problems, such as with insurance or employment discrimination, may occur if you disclose information about yourself or agree to have your research records released. We will not release any information about you or your family to any physician, insurance company or employer unless you sign a document allowing release of the information.
Potential Benefits

You may benefit from participating in this study by learning more about the genetic basis of your eye disease. We also hope to gain knowledge that may help you, your family members, or others with eye disease in the future.

Right of Withdrawal

You have the right to withdraw from the study at any time and for any reason.

Upon your request, we can remove your sample at the repository or permanently remove all identifying information from the repository and the collaborating DNA diagnostic lab. Your sample can be destroyed (when possible) on your written request.

However, we are not able to retrieve portions of your sample that may have been already distributed to researchers. If your sample has already had all identifying information removed, we would not be able to identify your sample in order to destroy it.

Compensation/Cost of Participation

You will not be paid to participate in this study. Genetic testing will be provided at no cost, however, you or your insurance company will be responsible for the costs of drawing blood and for shipping the blood sample to NEI, and for the eye examinations and genetic counseling.

Alternatives to Participation

You do not have to participate in this study in order to have genetic testing or genetic counseling for your eye disease. These services can be provided through your health care provider. This study does not provide treatment and does not replace any therapy that you may be receiving from your own physician. You may choose not to participate in this study.
Confidentiality

Your samples and medical information will be assigned a unique specimen code. Only the specimen code will be used to identify them. The identifiable information that you provide is protected in a secure eyeGENE database with multiple levels of security and only limited authorized eyeGENE personnel will be granted access to this information. No researchers using your samples or medical information will receive any information that could personally identify you, unless you have opted to be re-contacted in the future and have given us permission to provide your information to the researcher.

To help protect your privacy, eyeGENE has obtained a Certificate of Confidentiality for this research study. With this Certificate, the researchers cannot be forced, for example, by court subpoena to disclose information that may identify you, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. However, the Certificate cannot be used to resist a demand from the Department of Health and Human Services or other offices in the United States Government for audit and evaluation purposes, nor does it preclude voluntary disclosure.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family or researchers from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Although every reasonable effort will be made to protect the confidentiality of your medical records, a potential risk for possible breach of confidentiality exists and absolute protection cannot be guaranteed.

Information kept at the University of Massachusetts Medical Center: You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law. The study doctor and other people associated with this research will keep information about your participation in locked files. They will restrict access to the information in these files to persons directly involved with the research.

Information available to other people: Representatives of the Food and Drug Administration (FDA) and the Data and Safety Monitoring Board may review your medical and research records to assure the quality of the information used in the research. The FDA may photocopy your medical and research records to verify information submitted to the FDA.

An Institutional Review Board (IRB) is a group of people who are responsible for assuring the community that the rights of participants in research are respected.
Members and staff of the IRB at this medical center may review the records of your participation in this research. A representative of the Board may contact you for information about your experience with this research. If you wish, you may refuse to answer any questions the representative of the Board may ask.

**YOUR QUESTIONS:** The study doctor is available to answer your questions about this research. The Chairman of the IRB is available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from participating in this research. You may telephone the Chairman of the IRB during regular office hours at (508) 856-4261

**YOUR WILL HAVE A COPY OF THIS CONSENT FORM TO KEEP.**

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

**CONFLICT OF INTEREST DISCLOSURE**

NONE
CONSENT TO PARTICIPATE IN THE RESEARCH PROJECT

Title: National Ophthalmic Genotyping Network, Stage 1 – Creation of Repository for Inherited Ophthalmic Diseases.

P.I. Name: **Shalesh Kaushal, MD, PhD**

Subject’s Name:

I understand the purpose and procedures of this research project and the predictable discomfort, risks, and benefits that might result. I have been told that unforeseen events may occur. I have had an opportunity to discuss the risks and benefits of this research with the investigator and all of my questions have been answered. I agree to participate as a volunteer in this research project. I understand that I may end my participation at any time. I have been given a copy of this consent form.

__________________________ Date:

Subject’s signature

*Subject’s Legal Representative, if appropriate:*

Name: _____________________ Relationship to Subject: ______________

(Print)

__________________________ Date:

Legally Authorized Representative or Family Member Signature

Witness Name: _________________________________
STATEMENT OF PERSON OBTAINING CONSENT

I, the undersigned, have fully explained the details of this clinical study as described in
the consent form to the subject named above.

______________________________ Date: __________________
Signature of person obtaining consent

INVESTIGATOR’S DECLARATION

As the principal investigator or co-investigator on this study, I attest to the following:

• the nature and purpose of the study and study procedures, as well as the
  foreseeable risks, discomforts and benefits have been explained to the above-
  named subject
• this subject has been given the opportunity to ask questions and to have those
  questions answered by knowledgeable research staff
• this subject meets the inclusion/exclusion criteria for this study

I have considered and rejected alternative procedures for answering this research
question.
3.6.3 Genotyping Assent Form

UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

ASSENT TO PARTICIPATE IN RESEARCH

Title: National Ophthalmic Genotyping Network, Stage 1 – Creation of Repository for Inherited Ophthalmic Diseases. Study # 06-EI-0236

Principal Investigator: Shalesh Kaushal, MD, PhD

Sponsor: National Eye Institute (NEI) at the National Institute of Health (NIH)

My name is ________________________________.

Name of person obtaining assent

We are asking you to take part in a research study because we are trying to learn more about eye diseases that affect people. We are interested in people who may have an eye disease, which was passed onto them from their family members or was present from the day they were born.

If you agree to be in this study the doctor will look at your eyes. Depending on what type of eye disease you have, he will perform different tests, which may include shining a bright light, using eye drops, or taking photographs of your eye/back of your eye. Your doctor will explain everything to you.

As a part of this research, your doctor will take about one tablespoon of blood from your arm and send it to the National Eye Institute for research and tests. He may numb the area with some cream first. You still might feel a little pinch or pressure.

You may have a little bleeding from the area where the doctor takes blood and you might have a bruise.

You may benefit from participating in this study by learning more about how and why people can get your eye disease. We also hope to gain knowledge that may help you, your family members, or others with eye disease in the future.
Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say “yes” you can still decide not to do this.

Your participation is entirely voluntary. If you don’t want to be in this study, you don’t have to participate. Remember, being in this study is up to you and no one will be upset if you don’t want to participate or even if you change your mind later and want to stop.

You can ask any questions that you have about the study. If you have a question later that you didn’t think of now, you can call me at 508-334-6855 or ask me next time.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

**ASSENT TO PARTICIPATE IN THE RESEARCH PROJECT**

Title: National Ophthalmic Genotyping Network, Stage 1 – Creation of Repository for Inherited Ophthalmic Diseases.

Subject’s Name:_______________________________

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions. I agree to take part in this study.

____________________________________________ Date:

Subject’s signature

____________________________________________ Date: ________________

Signature of person obtaining assent

____________________________________________ Date: ________________

Signature of Investigator

**3.6.4 GENOTYPING HIPPA AUTHORIZATION**

UMass Memorial Medical Center
AUTHORIZATION TO DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES
The privacy law, Health Insurance Portability & Accountability Act (HIPAA), protects my individually identifiable health information (protected health information). The privacy law requires me to sign an authorization (or agreement) in order for researchers to be able to use or disclose my protected health information for research purposes in the study entitled: **National Ophthalmic Genotyping and Phenotyping Network, Stage 1 — Creation of DNA Repository for Inherited Ophthalmic Diseases**

I authorize UMass Memorial Medical Center to disclose my protected health information to:

- UMass Medical School including the researcher Dr. Shalesh Kaushal and his/her research staff
- Federal and State authorities that oversee research
- The eyeGENE National Ophthalmic Disease Genotyping Network

Protected health information (PHI) that may be disclosed includes all “x” boxes, and PHI which is listed in the sections titled “other” below.

*[PI, “X” relevant boxes below, double click on box to “X”]*:

<table>
<thead>
<tr>
<th>General Records</th>
<th>Statutorily Protected Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Cardiac Studies (Heart)</td>
<td>□ Abortion</td>
</tr>
<tr>
<td>□ Consultations</td>
<td>□ Alcohol / Drug Abuse</td>
</tr>
<tr>
<td>□ Discharge Summaries</td>
<td>□ Psychiatric Health</td>
</tr>
<tr>
<td>□ EEG/EMG/Sleep Studies</td>
<td>□ Sexual Assault Counseling</td>
</tr>
<tr>
<td>□ Emergency Service Records</td>
<td>□ Domestic Violence Counseling</td>
</tr>
<tr>
<td>□ Home Health Records</td>
<td>□ HIV / AIDS Test Results / Treatment</td>
</tr>
<tr>
<td>□ Hospice Records</td>
<td>□ Sexually Transmitted Diseases</td>
</tr>
<tr>
<td>□ Immunization Records</td>
<td>□ Rehabilitation Notes (PT/OT/Speech)</td>
</tr>
</tbody>
</table>

Other (Specify): Name, Date of Birth, Contact information, race, ethnicity, results of genetic testing, family history, medical history, information about your eye disease, results of ophthalmic tests

My protected health information will be disclosed as listed above for the following reasons:

The purpose of this study is to better characterize and understand the genes involved in eye disease. A “bank” of DNA, blood samples, and eye examination information will be created for use in future studies on eye diseases.

I do not have to sign this Authorization. If I decide not to sign the Authorization:

- It will not affect my treatment, payment or enrollment in any health plans, or affect my eligibility for benefits.
- I will not be allowed to participate in the research study.
If I sign the Authorization, I understand that:

- I have the right to withdraw, or revoke, the Authorization.
- If I revoke the Authorization, I will send a written letter to: Dr. Shalesh Kaushal, Dept of Ophthalmology, Rm S6-410; UMMS, 55 Lake Ave. N, Worcester, MA 01605 to inform him or her of my decision.
- If I revoke this Authorization, researchers may only use the protected health information already collected for this research study.
- If I revoke this Authorization my protected health information may still be used and disclosed should I have an adverse event (a bad effect).
- If I change my mind and withdraw the authorization, I will not be allowed to continue to participate in the study.
- Any disclosure carries the potential for re-disclosure. Once UMass Memorial Medical Center releases my protected health information, it may no longer be protected by the HIPAA privacy rule.
- The entities receiving my protected health information will use it as described in the Consent Document for this study.
- I may not be allowed to review some of the research-related information in my medical record until after the study is completed. When the study is over, I will have the right to access the information again.
- I will receive a signed copy of this authorization for my personal records.

**This Authorization does not have an expiration date.**

If I have questions about the research study, I should contact: **Dr. Shalesh Kaushal, at Ph: 508 334-0687**

If I have not already received a copy of the Privacy Notice, I may request one. If I have any questions or concerns about my privacy rights, I should contact the UMass Memorial Medical Center Privacy Officer at Ph: 508-334-5551.

**I HAVE READ AND UNDERSTAND THE ABOVE STATEMENTS AND AUTHORIZE THE DISCLOSURE OF THE INFORMATION REQUESTED ABOVE.**

<table>
<thead>
<tr>
<th>Signature of Subject</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Name Printed</td>
<td>DOB</td>
</tr>
</tbody>
</table>

Use boxes below if parent or legal representative is signing for research subject

<table>
<thead>
<tr>
<th>Subject’s Legal Representative Signature</th>
<th>Relationship</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Print Name of Research Subject</td>
<td>DOB</td>
<td>SS#</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

Please explain Representative’s Relationship to Patient and include a description of Representative’s Authority to act on behalf of Patient:
__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________

Person obtaining HIPAA authorization | Date

NOTE TO PI:
Forward the original signed authorization to:

**Health Information Management – Room HB 354**  
**UMass Memorial Medical Center**  
**55 Lake Avenue North**  
**Worcester, MA. 01655**

Give a copy of the signed authorization to the research subject, and keep a copy for your study files.
**3.6.5 CLINICAL TRIAL APPLICATION**

**PROTOCOL SUMMARY SHEET**

| Today's Date: | 5/22/09 |
| P.I. Name: | Shalesh Kaushal |
| Degree: | MD PhD |
| (PI Must be UMMS Faculty Member) | |
| Faculty Title: | Chair and Assoc. Professor |
| Department: | Ophthalmology |
| Division Name: | |
| Duration of the Study: | 60 weeks |
| Phone #: | 508 334-0687 |
| Total # of subjects at UMMMC: | 45 |
| Beeper/Pager#: | |
| Total # of subjects at off-site locations: | 45 |
| Email Address: | Shalesh.kaushal@umassmemorial.org |

**Title of Study:** (type right) **Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa**

"X" below which sites will participate

| Contact Person Name | Christine Clemson, PhD |
| Pager # | |
| University: | |
| Memorial: | X |
| Identify Condition being studied: | Retinitis Pigmentosa |
| Marlborough: | |
| Shriver Center: | |
| Source of Funding: | Departmental |
| Others: | |

**DEVICE INFORMATION**

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Approved</th>
<th>Investigational</th>
<th>IDE#</th>
</tr>
</thead>
</table>

**DRUG INFORMATION**

In the table below, list all drugs being used. If the drug considered investigational by the FDA you must include the IND# assigned by the FDA. Please "X" approved or investigational.
## USE SPACE BELOW FOR COMMENTS OR ADDITIONAL DRUG INFORMATION

<table>
<thead>
<tr>
<th>Drug Name:</th>
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<th>Inves.</th>
<th>IND#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>X</td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

### DESCRIBE THE RESEARCH BY CHECKING ALL THE ITEMS “YES” OR “NO”

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>On Site at UMMS/UMMMC</td>
<td>x</td>
<td>Adults</td>
<td>x</td>
<td>Questionnaires (please provide)</td>
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<tr>
<td>x</td>
<td>Multicenter Study</td>
<td>x</td>
<td>Pregnant Women</td>
<td>x</td>
<td>Filming/video/audio</td>
</tr>
<tr>
<td>x</td>
<td>Cooperating Institutions</td>
<td>x</td>
<td>Minors (under 18)</td>
<td>x</td>
<td>Marketed drugs</td>
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<td>x</td>
<td>Research Currently Funded</td>
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<td>Teenagers (12-17)</td>
<td>x</td>
<td>Diagnostic Radiation</td>
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<tr>
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<td>Financial interest involved</td>
<td>x</td>
<td>Prisoners</td>
<td>x</td>
<td>Therapeutic Radiation</td>
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<tr>
<td>x</td>
<td>Funding applied for</td>
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<td>Randomization</td>
<td>x</td>
<td>Ultrasound</td>
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<tr>
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<td>Placebo</td>
<td>x</td>
<td>Radioisotopes</td>
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<td>Normal volunteers</td>
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<td>Investigational drugs/device</td>
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<td>Radiation involved?</td>
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<tr>
<td>x</td>
<td>Other</td>
<td>x</td>
<td>Increased hospital costs</td>
<td>x</td>
<td>Would receive radiation regardless</td>
</tr>
<tr>
<td>x</td>
<td>Males</td>
<td>x</td>
<td>Mental Impairment</td>
<td>x</td>
<td>Radiation Safety Approval Needed?</td>
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<tr>
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<td>Females</td>
<td>x</td>
<td>Data bank</td>
<td>x</td>
<td>Biosafety Review Needed?</td>
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<tr>
<td>x</td>
<td>Phase I Study</td>
<td>x</td>
<td>Phase II Study</td>
<td>x</td>
<td>Phase III Study</td>
</tr>
</tbody>
</table>

### SECTION V
DESCRIPTION OF RESEARCH PROJECT

PERSONNEL ENGAGED IN THE RESEARCH STUDY. List all personnel engaged in the study. This list must agree with that in Section VI (Delegation of roles/responsibilities).

Shalesh Kaushal, M.D. PhD. will serve as a Principal Investigator of this study providing oversight for all aspects of the design and performance of the clinical treatment. He will oversee and participate extensively in the screening of participants, and will make the ultimate determination of whether a recruit is a suitable subject. Dr. Kaushal will be involved in the baseline and ongoing follow up assessments of all participants, and will interact closely with the creation of and communication with the DSMB. Dr. Kaushal will be responsible for assessing and reporting adverse events, as well as closing monitoring the clinical and serum profiles of the second cohort on escalating dosages. Dr. Kaushal will provide pre and post test genetic counseling to participants who choose to be genotyped.

Christine Clemson, PhD. will serve as the Study Coordinator of this trial, providing oversight for all aspects of the design and performance of this project. In particular, Dr. Clemson is responsible for the pre-clinical analysis, clinical trial development and details, and all regulatory applications and reporting. Dr. Clemson is completing an intensive 2 year Masters Program in Clinical Investigation. Dr. Clemson is combining this professional development with her 15 years of experience as a cell biologist to implement a “translational” approach to this clinical trial. Her unique and broad set of skills is instrumental in the unique multi-layered study design which will allow a wealth of information on efficacy in RP patients in general and within specific mutation populations, as well as dose response and therapeutic dosing windows all within a relatively short period of time.

George Asdourian, M.D. will serve as a co-investigator. He will aid in the screening and baseline measurements of all participants, as well as help perform clinical diagnostic follow up of participants during the study. Dr. Asdourian will help provide pre and post test genetic counseling to participants who choose to be genotyped.

Judith Colbert, R.N. will serve as the study nurse coordinator for the UMMC site, performing and overseeing many diagnostic procedures. She will perform the visual acuity and color contrast sensitivity testing of all participants, and she will supervise the technicians performing the extensive ocular imaging.

Elena Filippova, MD will serve as the clinician/research technician responsible for genotyping and drug dosing analysis. She will be responsible for registering subjects with the NIH eyeGENE clinical coordinating center, collecting and coordinating NEI required participant documentation for all recruited patients; she will oversee the collection, storage and shipment of all blood samples for genotyping. Dr. Filippova will also be responsible for collecting and collating data on serum VPA levels for all patients, and for the escalating dosing in cohort 2; she will be responsible for reporting results back to principal investigators. Dr. Filippova is skilled at and will be responsible for administering many of the ophthalmic diagnostic measures.

Julie Wilson (UMMMC) will serve as one of the ophthalmic imagers and technician. Julie is highly trained on the imaging equipment that will be used during this study including static and kinetic perimetry, fundus photography, optical coherence tomography and submicrovolt ERG.

Heather Hudson (UMMMC) will serve as one of the ophthalmic imagers and technician. Julie is highly trained on the imaging equipment that will be used during this study including static and kinetic perimetry, fundus photography, optical coherence tomography and submicrovolt ERG.

Biostatistician (UMMMC) A senior biostatistician to be named later will be hired from the University of Massachusetts Medical School Quantitative Health Sciences Core Facility to consult with Dr. Clemson.

2. GENERAL STATEMENT OF PROBLEM
Purpose: Include concise hypothesis to be tested by proposed research.
**Purpose:** To investigate the safety and efficacy of valproic acid in treating retinitis pigmentosa (rod-cone dystrophy).

**Hypothesis:** Valproic acid (VPA) can reduce the rate of vision loss from RP.

### 3. BACKGROUND AND SIGNIFICANCE:

**a. Provide a summary of the facts which led to selection of the problem.**

RP is a severe neurodegenerative disease of the retina characterized initially by night blindness with progression to tunnel vision and eventual loss of central vision and total blindness. Targeted therapies for RP are complicated by the identification of more than 30 genes linked to the dominant and recessive forms of the disease. Further compounding this complexity is the rarity of this disorder: although RP is one of the most common inherited eye diseases with an incidence of ~1:3000, its prevalence is relatively rare. RP affects approximately 100,000 individuals in the U.S. which qualifies it as an orphan disease. Given the huge costs associated with the preclinical and clinical phases of drug development, pharmaceutical companies are generally reluctant to invest in developing new therapeutics for RP. While a few new approaches for RP treatment have recently been investigated including nutritional supplementation, light reduction and gene therapy (Delyfer et al., 2004; Gaby, 2008; Hartong et al., 2006), of these, vitamin A supplementation is the most promising, but its benefits are modest and side effects are problematic. Therefore, currently there is no therapy to substantially alter or reverse the progression of RP.

**b. Please describe the Investigator's previous work on the problem.**

**Scientific Rationale:**

Recently, we have demonstrated the use of retinoids and other small molecules as pharmacological chaperones to increase the yield of properly folded RP mutant rhodopsins in heterologous cell culture (Noorwez et al., 2008). We have tested whether other known small molecules can provide similar effects. We identified valproic acid (VPA) through this screen. In vitro data supports that VPA has multiple biologic properties that make it an ideal candidate for a retinal therapeutic. First, our in vitro assay shows that VPA effectively increases yields of properly folded mutant rhodopsin (Figure 1). Second, VPA protects cells from oxidative stress induced apoptosis (Figure 2), most likely through upregulation of the heat shock response (not shown). Other work demonstrates that VPA is a potent inhibitor of histone deacetylase (HDAC) (Gottlicher et al., 2001) and the inflammatory response pathway via apoptosis of microglial cells (Chen et al., 2007; Dragunow et al., 2006; Kim et al., 2007).

**Pilot Clinical Analysis:**

![Figure 1 Valproic Acid allows mutant P23H rhodopsin to properly fold to the level of wild type.](image1)

![Figure 2 VPA Rescues Retinal Pigmented Epithelium Cells from Hydroquinone (HQ) induced apoptosis.](image2)

ARPE-19 cells are protected from HQ mediated apoptosis by the presence of VPA.
Six RP patients were treated off-label with oral VPA (250 mg BID) for 2 to 6 months. Visual fields were measured using kinetic perimetry (Figure 3). Results varied from patient to patient, 2 of 6 patients experienced progression of their disease while on VPA. However, 4 of 6 patients showed no progression of their disease on VPA (Figure 4), moreover, these 4 patients experienced an increase in their visual field (e.g. Figure 3)- which no other therapeutic has previously shown. Overall, we detected an average increase in visual field of 6%/month. These results suggest that VPA has the potential to not only stop the progression but may also reverse loss of visual field.

c. What are the aspects that justify the use of human subjects, human data, or specimens as part of this research?
It is critical to emphasize that the extensive history and well established safety and tolerability profile of VPA makes it an ideal candidate for a Phase II study, which streamlines the time to treatment in humans considerably relative to new drug design. VPA was approved by the FDA for use as a broad spectrum anticonvulsant in 1978 and is also used for acute and maintenance therapy of bipolar disease, for migraine prophylaxis, and occasionally for chronic pain syndromes (Henry, 2003).

Prevention of disease progression and restoration of vision are the ultimate goals of this trial. RP is an incurable and untreatable group of heterogeneous retinal degenerative diseases that cause severe visual loss. While individual rates of vision loss can vary greatly even among siblings with the exact same mutation (Berson et al., 2002), projections from the
literature suggest that RP patients will lose an average of 15-17% of their visual field (VF) annually (Massof et al., 1990; Zeger and Liang, 1986) and 25% of RP patients will lose 20% of their VF in one year (Merin et al., 2008). There is currently no significant therapeutic that effectively slows the progression of this disease, and certainly none that can restore vision in RP patients. Our preliminary studies indicate that VPA is a remarkable retinal therapeutic that may not only stop the progression of this disease, but also reverse loss of visual field. An investigator initiated clinical trial as we propose is an important if not the only way for new therapeutics to be investigated for rare disorders such as RP.

d. Attach references as appropriate.


4. DETAILED DESCRIPTION OF RESEARCH PLAN (especially as it affects the subject)

Include a schematic representation of what the research will entail (e.g. a table with the number of visits and what will happen at each visit or flow diagram of subject's involvement over time).

This is a two-site, intervention, prospective, placebo-controlled, blinded study of 90 subjects undergoing therapy with oral VPA. The second site will be the Retina Foundation of the Southwest (RFSW). David G. Birch, Ph.D. will serve as the Principal Investigator at the RFSW. Dr. Birch is the Chief Scientific and Operating Officer of the RFSW and an adjunct Professor at the University of Texas
Southwestern Medical School. He is a highly regarded clinical trialist and his clinical team has been involved in many RP clinical trials both current and ongoing. He will be responsible for all aspects of oversight and reporting for the RFSW site. He is also highly involved in the study design and statistical analysis.

Patients will undergo clinical examinations and evaluations of retinal function and structure prior to consideration of the subject as a candidate for clinical trials. Clinical examinations will include refraction, static and kinetic perimetry, fundus photography and visual acuity. Measures of visual function will include full-field electroretinography. Optical coherence tomography will be used to measure retinal structure. Methods of these measures are detailed below. During these evaluations, medical and ophthalmic histories will be elicited from subjects and their families to ensure that there are no comorbid medical or ocular genetic conditions that may prevent study participation. While the equipment proposed for use in this trial is state of the art and as such will provide the highest level of quantitation available, the quasi-subjective nature inherent in many standard ocular tests make day-to-day variation an important confounder to our analysis. All diagnostic measures will be calibrated and standardized such that intervisit and interocular variances for each outcome measure will be quantified and included in our analysis. This will involve sequential repeated measures for the same and different patients on these machines.

**Figure 5: Study visit schedule**

Cells outlined in red represent clinic visits with full battery of outcome measures.
TABLE 1: SCHEDULED STUDY EVALUATIONS

<table>
<thead>
<tr>
<th>Time relevant to start of Oral VPA</th>
<th>Screening</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Early term.e</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>12</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week</td>
<td>-12 to -4</td>
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<td>8</td>
<td>24</td>
<td>48</td>
<td>60</td>
<td></td>
<td></td>
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<tr>
<td>Informed Consent</td>
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<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion Criteria</td>
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<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/surgical history</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmic history</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Safety Labs</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>Demographic data</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Genotyping</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmic Exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Acuity (BCVA)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Perimetry</td>
<td>x</td>
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<td></td>
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<td>Color Contrast Sensitivity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Electoretinography</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optical coherence tomography (OCT)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fundus photography (FP)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Quality of Life Questionnaire f.</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Remaining pill count for med. monitoring</td>
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<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Provide Study Meds</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA level (labs)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Adverse events assessment</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

e. If enrolled
f. Ophthalmic examinations include: slit lamp examination; tonometry, indirect ophthalmoscopy and retinal biomicroscopy.
Dose Rationale
Treatment dosages were selected based on our proof of concept preliminary studies described above and known safety and tolerability profiles of VPA. For the intervention, VPA dosage will vary by weight (Table 2) and will be ½ to ⅓ the dosage recommended for anticonvulsant therapy (Table 3).

**TABLE 2: VPA DOSAGE SCHEDULE BY WEIGHT**

<table>
<thead>
<tr>
<th>Pounds (bs)</th>
<th>Kilograms (Kg)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-87.9</td>
<td>10 – 39.9</td>
<td>Excluded from study</td>
</tr>
<tr>
<td>88 – 164.9</td>
<td>40 – 74.9</td>
<td>500</td>
</tr>
<tr>
<td>165-197.9</td>
<td>75-89.9</td>
<td>750</td>
</tr>
<tr>
<td>198-349.9</td>
<td>90-158.9</td>
<td>1000</td>
</tr>
<tr>
<td>350+</td>
<td>159+</td>
<td>Excluded from study</td>
</tr>
</tbody>
</table>

**Table 3: Recommended Starting VPA Dosage Schedule for anticonvulsant therapy . (DEPAKENE(R) oral capsules, oral syrup, 2006)**

<table>
<thead>
<tr>
<th>Pounds (bs)</th>
<th>Kilograms (Kg)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-54.9</td>
<td>10 – 24</td>
<td>250</td>
</tr>
<tr>
<td>55 – 87.9</td>
<td>25 – 39.9</td>
<td>500</td>
</tr>
<tr>
<td>88 - 131.9</td>
<td>40 – 59.9</td>
<td>750</td>
</tr>
<tr>
<td>132 -164.9</td>
<td>60 – 74.9</td>
<td>1000</td>
</tr>
<tr>
<td>165-197.9</td>
<td>75-89.9</td>
<td>1250</td>
</tr>
</tbody>
</table>

The Screening visit consists of the following examinations and procedures:
- Explanation of study and a copy of the trial Consent form (if not mailed ahead of the visit) and the genotyping consent form. (Note: eyeGENE is a separate protocol submitted to the Umass IRB – but it overlaps with this study)
- Signing of the Informed Consent for the trial
- Signing of the Informed consent for genotyping (not necessary for enrollment in study)
- Complete medical and ocular history
- Urine test for pregnancy (if of child bearing potential)
- Blood draw for hepatic and pancreatic function screen (and genotyping if enrolled).
- Visual acuity examination
- Ocular examination
- Semi-Automated Kinetic Perimetry, with static measurements in the 30° central field (in Duplicate)
- Fundus photographs

Baseline Visit
Qualified participants will be asked to return to the clinic within 30 to 120 days after the Screening Visit. Randomization will occur only after the participant is confirmed to be eligible. Participants are considered eligible if they meet all the inclusion criteria, and do not meet one or more exclusion criteria and return to the clinic within 120 days following the Screening Visit, and sign the consent form.

Participants must be re-qualified if randomization does not occur within 120 days of the Screening Visit. Re-qualification requires that the responses to each of the eligibility questions be verified and ocular exams and fundus photographs re-performed.
The UMMC coordinating center will assign bottle numbers. The master randomization list for both centers will be maintained at the UMMMC Coordinating Center.

The Baseline Visit consists of the following examinations and procedures:

Signing of the eyeGENE genotyping consent form (if not signed at the Screening Visit)- not a prerequisite for study  
(Note: eyeGENE is a separate protocol approved by the Umass IRB)

1. Urine test for pregnancy (if of child bearing potential)  
2. Semi-Automated Kinetic Perimetry, with static measurements in the 30° central field (in Duplicate)  
3. Optical Coherence Tomography (OCT)  
4. Color-Contrast Sensitivity Analysis (Chroma Test) in duplicate  
5. Full-field Electroretinogram (Spectralis) in duplicate  
6. Visual acuity examination  
7. Ocular Examination  
8. Quality of Life Questionaire (QOL)  
9. Concomittant Medications  
10. Distribution of Study Medication (or placebo) and administration directions.  
11. Assignment of Bottle Numbers

Participants who consent to participate will be contacted by telephone within 24 hours to answer questions and assure full understanding of dosing instructions and procedures.

Follow-up Visits
In-clinic follow-up visits will occur at 60, 180, and 360 days after initiating VPA treatment for evaluation of their clinical status and to assess adverse events. Participants will be asked to provide information on any side effects they are experiencing. Subjects will be followed up with phone calls after the baseline, week 1 and at month 1, 3, 4, 5, 7, 8, 9, 10, 11. The purpose of these phone calls is to assess adherence to study medication, assess adverse events, schedule additional clinic visits if needed, and clarify study procedures. In all cases, participants will be followed for a period of 3 months after the study ends.

The in-clinic follow-up visits will consist of the following examinations and procedures:

1. Safety Labs  
2. Concomitant Medications  
3. Visual acuity examination  
4. Ocular examination  
5. Adverse Event assessment  
6. Collection and re-issuance of study medication bottles  
7. Assessment of study drug adherence via self-report, VPA blood levels, and pill counting  
8. Semi-Automated Kinetic Perimetry, with static measurements in the 30° central field -in Duplicate (at month 12 follow-up visits.)  
9. Optical Coherence Tomography (OCT) in duplicate (at month 12 follow-up visit.)  
10. Color-Contrast Sensitivity Analysis (Chroma Test) in duplicate (at month 12 follow-up visit.)
11. Full-field Electroretinogram in duplicate (at month 12 follow-up visit.)
12. Quality of Life Questionaire(QOL) (at 12 month follow up visit).

b. Inclusion/Exclusion Criteria - As appropriate, explain what steps will be taken to insure that subjects meet the criteria (e.g. healthy, not pregnant, etc).

Inclusion Criteria

1. To be eligible for the study, subjects must fulfill all of the following criteria:
2. Understand and sign the IRB-approved informed consent document for the study.
3. Age ≥ 18 years.
4. Weight ≥40 Kg and ≤158.9 Kg
5. Diagnosis of Retinitis Pigmentosa including photoreceptor degeneration established by visual field constriction, night blindness, marked reduction of ERG responses, and the clinical signs of RP including waxy pallor of the optic nerve, vascular attenuation and/or the presence of intraretinal pigment on clinical examination.
6. Female adults of child bearing potential who have attained menarche must have a negative pregnancy test at study entry and commit to using an acceptable method of barrier or hormonal contraception.
7. Willingness to comply with the protocol.
8. Exclusion Criteria
9. Potential participants meeting any of the following criteria will be excluded from the study:
10. Medical problems that make consistent follow-up over the treatment period unlikely (e.g. stroke, severe MI, end stage malignancy), or in general a poor medical risk because of other systemic diseases or active uncontrolled infections.
11. Other retinal diseases: Glaucoma, retinal inflammatory disease, (Note: CME is allowable), cataract worse than +2 NS or herpes simplex virus of the eye.
12. Intact visual field of 5° or less.
13. Diabetes or cancer.
14. A hemoglobin concentration of less than 8 gm/dL a platelet count of less than 75K/mm$^3$ or an absolute neutrophil count of less than 500/mm$^3$ at study entry.
15. Liver disease determined by an alanine aminotransferase (ALT) aspartate aminotransferase (AST) or bilirubin 2.5 times greater than the upper limit of normal.
16. History of pancreatitis by clinical features and/or laboratory abnormalities in the last 12 months.
17. Renal dysfunction based on serum creatinine using the MDRD equation.
18. Patients suffering from urea cycle disorders will be excluded.
19. Patients with history of seizure disorders and/or those already receiving valproic acid or other anti-convulsants will be excluded
20. Sensitive to or have ever had an allergic reaction to Valproic Acid.
21. Pregnant or Lactating mothers who are breast feeding their babies will not be eligible.
22. RP patients involved in other clinical trials within the last 3 months are ineligible for this study.
c. Discuss the number of experimental and control subjects, and explain the statistical basis for the numbers.

Attainable recruitment goals and functional outcome data from our preliminary analysis were both used to estimate sample size for the Phase II trial. Our pilot analysis demonstrated a potential annual change of +72% in VF annually in VPA treated RP patients (Figure 4). Reports in the literature allow us to conservatively estimate a 5% reduction in VF annually in untreated RP patients (Berson et al., 2002). If we reduce our estimate of delta to boost the statistical validity of the trial, and assume a 60% difference in the rate of visual field change in Phase II, statistical significance for a two-sided test using a significance level of 0.05 and 80% power would require around 40 patients per group.

In general, RP patients are highly motivated to comply as evidenced in the similarly designed RFSW based Phase I trial of DHA where drop-out rates were 0% at year 3 and 7% at year 4. Because we will likely enroll sibling pairs into the trial, the total number of “active” participants has been increased from 80 to 90 to permit statistical compensation of these sibling pairs.

d. Does the study involve randomization?

Yes

If yes, please describe process.

Two codes will be used for the two types of capsules (placebo and VPA) provided to patients. The 250 mg VPA capsule and lactose containing placebos will be over-encapsulated (ie. put into an identical empty shell) by the research pharmacy, so their appearance is similar. All patients will be assigned to receive capsules following a computer-generated randomization performed by the UMMC research pharmacy.

The capsule code information will be kept on a password-protected computer with the password known only to the capsule coordinator.

The randomization code for the groups will consist of 2 single-letter identifiers for the two capsule types (A or B). The capsule codes are a temporary identifier of capsule bottles as the capsule coordinator (research pharmacist at UMMC) will place a label with each individual’s ID number over the capsule code. This will prevent laboratory personnel from associating the patient ID with capsule code assignment.

UMMMC will be the coordinating center and the research pharmacy will randomly assign the study intervention. Participants and investigators will be masked to the treatments. Participants will be unmasked if deemed clinically necessary by the examining physician and if the Study Chair and Data Safety and Monitoring Board (DSMB) Chair are in agreement. A written request for unmasking, after approval by the Study Chair and DSMB Chair, will be made to the Coordinating Center, who will inform the site Principal Investigator of the treatment assignment. All instances of unmasking must be reported to the IRB, the DSMB and the FDA.

e. How long will each subject be enrolled in the study?

15 months

f. Provide a brief overview of what participation in the study will mean to each participant in terms of what he/she will experience. Describe in order, each procedure, how long each procedure will take and
how often each procedure will be performed. Include doses & route of administration of any drugs and whether the procedure or drugs would always, sometimes or never be required as part of the subject's standard of care.

Please note, all of these procedures are being performed at the Department of Ophthalmology Clinical Trial Suite at Memorial Hospital and will be billed to the clinical trial. No tests, procedures or visits will be billed to the participant or their insurance company.

**Visual Field (perimetry):** 30 minutes, performed 3 times in the 15 months: at screening, baseline, and month 12. This test is sometimes administered as standard of care once a year, however these tests will be for research purposes only.
The visual field test will take about 30 minutes and will involve the participant sitting comfortably at machine that will shine lights in their eyes to determine which part of their eyes are affected by RP.

**Visual Acuity:** 5 minutes, performed 6 times, at screening, baseline, month 2, 6, 12 and 15.
This test would be administered as standard of care once a year, but is being performed here for research purposes.
This will take about 5 minutes and involves the subject sitting comfortably at a computer and answering questions about the letters that appear.

**Color Contrast Sensitivity:** 10 minutes, performed 2 times at Baseline, month 12.
This test would not be administered as standard of care
Color vision will be tested by the Chroma Test program, this involves sitting comfortably at a computer and answering questions about the colors that appear.

**Optical Coherence Tomography (OCT):** 10 minutes, performed 2 times.
This test would sometimes be administered as standard of care every 2-3 years, this test is being performed for research purposes.
The thickness of the retina will be examined by Optical Coherence Tomography (OCT). This procedure will take about 10 minutes and involves the participant sitting comfortably at a machine and looking straight ahead.

**Fundus Photography:** 10 minutes, performed 2 times, at screening and 12 month visit.
This test would sometimes be administered as standard of care every 5 years.
Photography (performed to minimize excess visible light exposure) will be performed at the screening visit and at the 12 month visit.

**Full-field Electroretinogram (ERG):** 45 minutes, performed 2 times at baseline, and month 12.
This test would sometimes be administered as standard of care every 5 years, and is being performed here for research purposes.
An ERG will be performed to determine how well the rod and cone receptors respond to light. This test takes about 45 minutes and involves having anesthetic drops placed in the eyes, causing them to become numb. The eyelids are then propped open with a speculum and an electrode is gently placed on each eye with a device very similar to a contact lens. Readings will be taken first in normal room light, then with the lights dimmed and finally readings are taken as a bright flash is directed toward the eyes.

**Quality of Life (QOL):** 15 minutes, administered 2 times at Baseline and month 12.
This test would not be administered as standard of care.
QOL will be assessed using the 25-Item National Eye Institute Visual Function Questionnaire (Mangione et al., 2001).
The questionnaire will be administered in an interview format at the baseline visit and at the 12 month visit.

**Genotyping Analysis:** blood draw – one time – at Baseline.
This test is sometimes administered as standard of care.
The genotyping test will be done as a part of the eyeGene clinical research study at the National Institutes of Health (NIH). EyeGENE informed consent for genotyping and DNA diagnostics will be included in the trial consent form and will be approved by the University of Massachusetts Institutional Review Board. These completed consent forms will be sent to the eyeGENE coordinating center and clinical criteria for each participant will be entered into the eyeGENE online database prior to shipment of blood samples. 5–10 ml of whole blood will be obtained by routine phlebotomy using plastic vacutainers containing K2 EDTA. Dr. Kaushal or Dr. Asdourian will provide pre and post-test genetic counseling to all participants.

**Safety labs: blood draw — six times — at Screening, Baseline, month 2, 6, 12 and 15 months. This test is sometimes administered as standard of care.**

**Serum VPA Assay: blood draw 4 times at month 2, 6, 12 and 15. This test would not be administered as standard of care.**

Compliance is an issue in self administered study drug clinical trials. Medication monitoring will occur at every follow up visit. Patients will be instructed to bring prescription bottles to every visit for counting. Additionally, serum VPA levels will be assayed at regular intervals for bioavailability determination as well as validation of participant compliance to protocol. Serum concentrations will be assayed by a fluorescence polarization immunoassay system (Ax-Sym analyzer; Abbott Diagnostic Division, Irving, TX).

Since the results of this test would obviously unblind any research staff, the VPA blood levels will be held by the clinical lab facility until the end of the study. Given that the VPA serum level is being used primarily for a research question, and likely does not afford useable safety information, we feel this will not compromise subject safety. If however, serious adverse events occurred, then this information would be available if a particular subject is unblinded.

**g. Is any aspect of this research study being conducted in the Medical School or a non-UMMMC facility? If yes, please explain.**

Yes, this is a two-site study performed at the Umass Memorial Campus and at the Retina Foundation of the Southwest in Dallas, Texas.

**h. Will hospitalization be required as part of this research study?**

No

If yes, how long will subjects be hospitalized?

**i. Will there be any material inducements or recruitment incentives given to research staff or research subjects as part of this research study? (e.g., direct payments, free hospitalization, care)**

Yes

**If yes, explain how much, the pay schedule, or any partial payments that will be given.**

$250 per participant for completing the 6 visit schedule. If the subject drops out before the final visit, the compensation will be prorated at $50 per visit.
DISCLOSURE OF CONFLICT OF INTEREST

Investigators should disclose any financial arrangement they may have with a company whose product figures prominently in their research or financial arrangements they may have with company making a competing product. The relationship should also be described in the informed consent documents. In the case where the only relationship is that a company is sponsoring the research study, it is sufficient to prominently identify the sponsor on the front page of the consent form and to simply state “NONE” in the consent form under Conflict of Interest.

Is there a conflict of interest?

NO

6. RELATIONSHIP TO STANDARD THERAPY.

Describe the standard therapy that patients would receive if not in the research study. Explain how this research intervention deviates from or replaces generally accepted standard therapy and justify the deviation.

While there is no known treatment to substantially alter or reverse the progression of RP, supplementation with vitamin A is currently the standard of care. The diagnostic tests proposed are state of the art optical evaluations that would be included in an advanced Ophthalmologic clinic environment.

7. DESCRIBE THE POTENTIAL BENEFITS OF THIS PROJECT.

Include hoped-for benefit to society, to the group of subjects or to individual subjects.

Based on the preclinical and preliminary clinical efficacy data, there is potential that oral VPA may provide some degree of improvement in visual function in some of the individuals participating in this study. However, the likelihood of achieving any benefit, and the degree of any benefit that may occur, is unknown.

Address the risk/benefit ratio of the study. If there are no direct subject benefits, this should be stated.

The potential benefits of this study far outweigh the potential risks. RP is a serious disorder that leads to complete blindness with no effective pharmacotherapy. Patients accepted into the study will receive close medical monitoring as well as treatment with valproic acid that has a well-documented safety profile. Patients will be screened prior to admission into the study and those at risk for adverse reactions will be excluded. The subjects selected for participation will be monitored closely for adverse effects.

8. DESCRIBE THE POTENTIAL RISKS TO SUBJECTS INCLUDE PSYCHOLOGICAL, ECONOMIC, LEGAL OR SOCIAL RISKS AS WELL AS PHYSICAL RISKS.

Include the following information:
a. Estimate likelihood of occurrence, severity, and duration. If generally accepted quantitative estimates are available based on previous data, these should be stated. Otherwise, qualitative estimates such as “rare”, “occasionally”, or “frequently” may be used. The committee needs scientific information about drug/device side effects so as to best judge the pros and cons of the study. Do not simply cut and paste the consent form “Risk” section into this part of the protocol.

VPA is well tolerated in most patients and adverse events are rare (reviewed in Peterson and Naunton, 2005). The primary concern is hepatotoxicity which is rare in low risk patients occurring in fewer than .29 in 10,000 patients (Bryant and Dreifuss, 1996). Subjects will be carefully screened for comorbid conditions and concomitant medications to ensure that only patients at the lowest risk for serious adverse events are enrolled (see Exclusion Criteria above).

In the pilot study, RP patients on similar amounts of VPA experienced minor side effects, the most common of which were stomach irritation and tiredness.

Potential risks to study subjects include the well known and characterized risks associated with administration of the therapeutic agent and with study procedures. Valproic acid can cause serious and fatal hepatotoxicity especially in individuals with liver disease, organic brain disease, serious seizure disorders, congenital metabolic disorders, those on multiple anticonvulsants and children under the age of 2. Therefore individuals with contraindicating diseases and concomitant medications as well as children under 18 will be excluded from this study. The risk of hepatotoxicity usually occurs within the first 6 months of treatment and decreases considerably in older age groups. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting.

Valproic acid can cause serious and fatal pancreatitis. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms such as abdominal pain, nausea, vomiting, and/or anorexia to death. Cases have been reported shortly after initial use as well as after several years of use.

Valproate can produce teratogenic effects such as Spina Bifida, therefore woman of child bearing potential will be screened for pregnancy prior to administration of the study agent and must maintain use of contraception during the study period.

The risks associated with ophthalmic procedures include redness, discomfort or allergic reaction to topical medications used to dilate the pupil prior to visual function tests. High blood pressure, cardiac dysrhythmias and closed angle glaucoma may be exacerbated by some of these medications and light sensitivity may be experienced when the pupil is dilated. Corneal abrasions may result from the contact lenses used in performing electroretinography testing. The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

Explain what steps will be taken to protect against its occurrence, minimizing the harm, methods for early detection of harm, and what procedures will be followed to avoid serious injury (e.g. withdraw from study or dose reduction).

In-clinic follow-up visits will occur at 60, 180, and 360 days after initiating VPA treatment for evaluation of their clinical status and to assess adverse events. Participants will be asked to provide information on any side effects they are experiencing. Subjects will be followed up with phone calls after the baseline, week 1 and at month 1, 3, 4, 5, 7, 8, 9, 10 and 11. The purpose of these phone calls is to assess adherence to study medication, assess adverse events, schedule additional clinic visits if needed, and clarify study procedures. In all cases, participants will be followed for a period of 3 months after the study ends.
In the event of a non-serious adverse effect, the drug dose may be lowered, or the participant may be counseled to take the medication with food (in the event of gastric disturbance). If that does not resolve the issue, or the adverse event is more serious, then the participant will be withdrawn from the study.

The subjects will be informed of possible consequences of the study from one of the investigators in language they can understand. They will be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. They will be asked to follow-up with necessary safety evaluations if they have received study agent prior to their desire to withdraw. They will be given full information regarding potential side effects of VPA and the procedures involved. The medical history and physical examination performed prior to study agent administration will identify patients with medical conditions that would increase the risks associated with study procedures and those subjects will be excluded from participation. The administration of the study agent and all procedures related to the study will be performed by trained and licensed medical and health professionals. They will be provided with contact numbers for any questions or concerns arising regarding the possible effects of the VPA and encouraged to call if they feel that an adverse event is occurring. In the event of an adverse event associated with the clinical trial, immediate medical care will be provided.

Patients will be followed closely, especially in the first 6 months for known adverse reactions to VPA. Safety labs regarding liver and pancreas toxicity will be drawn prior to and periodically during dosing with VPA. Results of all laboratory and safety exams performed to ensure subject eligibility and safety will be reviewed by an investigator during the study. Subjects with known risk factors such as liver disease, pancreatic conditions, metabolic disorders, organic brain diseases, seizure disorders and those on anti-convulsants will be excluded from the study. Female subjects of child bearing potential must have a negative pregnancy test at the baseline visit and prior to study agent administration. Female subjects of reproductive ability must be willing to use effective contraception for the duration of the study, one year. Lactating mothers will not be included in this study. We will not include children under 18 in this study.

The Data Safety Monitoring Board (DSMB) will be established with members who have an understanding of the disease, ethics, and biostatistics. They will review the study results and notify the PI of their findings and recommendations for study continuation or modification. The DSMB will be charged with monitoring the conduct of the trial and assessing patient safety on an ongoing basis. This group will review all safety data, including serious adverse events, adverse events, and laboratory data. Confidentiality of the subjects will be maintained in the process of review by the DSMB. The DSMB will provide committee recommendations after each review. Adverse events will be reported to the IRB, NIH, and FDA as regulated to insure the safety of subjects.

Data and Safety Monitoring Plan
The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines.

The procedures outlined in the protocol and case report forms will be carefully reviewed by the Principle Investigators and staff prior to Study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and well being of subjects.

Amendments will be submitted to the IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the Informed Consent form will be revised and if applicable, subject’s consent to continue participation will again be obtained. To ensure safety of human subjects and integrity of data in this trial, a data and safety monitoring plan will be established.

The levels of monitoring will include:

- Dr. Shalesh Kaushal, MD, PhD as Principal Investigator, will continuously monitor patient safety and be responsible for reporting serious and unexpected adverse reactions as regulated to the FDA, DSMB and IRB.
• The DSMB will provide safety oversight of the trial, to monitor the progress of the study, and to recommend modification of the trial, as appropriate. The DSMB will review safety data after two and 6 months of oral dosing. Serious and unexpected adverse reactions will be reviewed by the DSMB or subcommittee.

• Approval of the IRB will be obtained before enrolling subjects in this clinical trial. Following the beginning of enrollment, the IRB will conduct continuing reviews of the trial at intervals appropriate to the degree of risk to human subjects.

The degree of certainty with which an adverse event is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

• Known pharmacology of the drug
• Reaction of similar nature being previously observed with this drug or class of drug
• The experience having often been reported in literature for similar drugs as drug related

A detailed Data and Safety Monitoring Plan will be submitted to the IRB prior to the accrual of human subjects.

c. Explain whether or not these risks are from a procedure performed with the intent and reasonable prospect of yielding direct health related benefit to the subject.

Procedures and interventions used in this trial are performed with the intent to at the very least stop the progression of this blinding disease. The pilot study strongly suggests that VPA has the potential to reverse vision loss in RP patients who currently have no treatment options.

d. Do you, as the PI, have equipoise regarding the study? That is, are you comfortable with the risks in relationship to the knowledge gained? If the study involves randomization, do you believe in the equality of the treatment arms?

Yes. It is possible to treat patients off-label with this medication, however an investigator initiated clinical trial, such as proposed here, is the robust way to examine the efficacy of this medication for RP.

9. CONFIDENTIALITY CONSIDERATIONS: EXPLAIN STEPS THAT WILL BE TAKEN TO INSURE THE CONFIDENTIALITY OF INFORMATION THAT IS OBTAINED IN THE COURSE OF THIS RESEARCH PROJECT. INCLUDE THE FOLLOWING:

a. How will identifiers be used?

Research material obtained from identifiable living human subjects includes reports of: history and physical assessments, blood, urine, pregnancy tests, perimetry, optical coherence tomography, visual acuity measurements, color contrast sensitivity and electroretinography measurements, clinical assessments, adverse events, and autopsies. Copies of case report forms, original test results, subject medical records, signed subject informed consent, correspondence, and any other documents of the subjects, relevant to the conduct of the study will be kept on file by the principal investigator. All material or data collected as part of the study will be obtained specifically for research purposes.
The patients will be de-identified by the creation of a master list assigning a study number to each patient. The database will be protected and will include the study number with a reference to the medical record number and name during data collection phase. Then it will be de-identified by removing the name and medical record for a final analysis.

b. Where will data be stored?

Electronic sources of data will only be stored on the hospital secure server and will be deleted from storage. Any paper containing identifying data will be shredded and placed in secured disposal bins available throughout the hospital.

c. Besides the UMMS IRB and their representatives, who will have access to the research data?

Only those personnel participating in the research study from UMMMC and RFSW described above will have access to the research data. The subjects will be informed of the information stored and the review of that information by the DSMB, U Mass and RFSW IRB, and U Mass and RFSW clinical facility personnel, Data Management and Statistical personnel, research staff, and personnel performing the procedures.

d. When will the data/specimens be destroyed?

The identifiers collected during the study will be destroyed upon completion of the statistical analysis of the study data.

e. In the future, might other use be made of specimens collected as part of the research? If yes, please describe.

NO

10. ECONOMIC CONSIDERATIONS:

In the course of this research project, might the subjects experience any additional expenses as a result of study participation? This includes both out-of-pocket costs and expenses that might not be covered by medical insurance.

If yes, please explain and justify.

Yes

Patients may incur travel expenses. Many RP patients seek out clinical trials and may travel a great distance to both the UMMMC and RFSW clinics. Given the limited funding of this trial, travel expenses will not be covered.

b. Please explain potential increase in standard hospital costs if any.

N/A

11. DESCRIBE THE CHARACTERISTICS OF THE SUBJECT POPULATION.
a. The subject population includes:

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<tr>
<td>ADULTS</td>
<td>CHILDREN</td>
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b. Is the subject population restricted in respect to any of the following characteristics?

- Age Range: x
- Health Status: x
- Gender: x
- Racial/Ethnic composition: x

Please “x” those that apply

Yes  No

If you responded YES to any of the above, include a clear rationale for this restriction.

Retinitis Pigmentosa is a disease caused by a variety of mutations. This is a rare disorder that tends to run in families, so recruitment efforts will likely result in a homogenous population. Because of X-linked forms, men are affected at a slightly higher rate than woman. Women will not be excluded from this study. While most ethnic groups are affected by RP, in the United States, RP cases are predominantly Caucasian. We would not refuse anyone admission with another ethnic or racial group.

The age range for the onset of vision loss in most individuals with RP is over 18 years of age. Additionally, the risk of the study medication is significantly greater in children. Thus no children younger than 18 will be included in this study.

12. WILL THE STUDY POPULATION SPECIFICALLY INCLUDE A POPULATION OF SUBJECTS CONSIDERED “VULNERABLE”? VULNERABLE POPULATIONS ARE CHILDREN, MENTALLY IMPAIRED, PREGNANT WOMEN, PRISONERS, OR FETUSES.

No

If yes, please explain.

13. WHAT IS THE SOURCE OF THE SUBJECT POPULATION?

Retinitis Pigmentosa patients from the Greater Worcester and Dallas area and throughout the US.

14. EXPLAIN ANY STEPS TAKEN TO INSURE THAT THE SUBJECT POPULATION IS REPRESENTATIVE.
No restriction on the form or genotype of RP patients will be instituted and as such it is expected that the recruited patients will be representative of all RP patients.

15. HOW AND WHERE WILL SUBJECTS BE RECRUITED FOR THE STUDY? CONSULT THE IRB GUIDELINES FOR THE RESTRICTIONS ON RECRUITMENT OF EMPLOYEES, STUDENTS, AND INPATIENTS. ATTACH COPIES OF ALL RECRUITMENT MATERIALS TO BE USED AS PART OF THIS RESEARCH STUDY. THESE MATERIALS MUST BE APPROVED BY THE IRB BEFORE BEING USED. Recruitment guidance can be found on our website under HSC Forms.

Patients will be recruited from the Ophthalmology clinics at the University of Massachusetts Medical Center and the Retina Foundation of the Southwest as well as through the Foundation Fighting Blindness disease specific web site and email blast. This protocol will be listed in the Clinical Trials Data Bank of the NIH. The copy for all advertisements will be submitted to the IRB as an amendment for approval prior to any posting.

16. WILL PROTECTED HEALTH INFORMATION (PHI) BE USED AS PART OF THIS RESEARCH STUDY? PLEASE VISIT OUR WEBSITE FOR MORE INFORMATION ABOUT PHI OR THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA).

Yes

If yes, please answer the following questions.

How and where will the PHI be accessed (i.e. meditech, database, medical records, another site)?

Meditech, database and Medical Records

Will a subject’s PHI be accessed before the subject is enrolled in the study?

NO

Please list the PHI to be used as part of this research study (i.e. name, DOB, medical record #).

Name, DOB, address, medical record#

17. METHOD FOR OBTAINING INFORMED CONSENT

a. Are you requesting a waiver of the requirement for obtaining consent?

No

Do not complete the following questions if you are requesting a waiver of informed consent.

18. WILL VERBAL CONSENT BE OBTAINED?

Yes No x
If yes, will an unsigned “fact sheet” be given to subjects before verbal consent is obtained?

Yes  No

If yes, please provide a copy of the “fact sheet”.

19. WILL A SIGNED CONSENT FORM BE REQUIRED?

Yes

AS A GROUP, ARE THESE SUBJECTS EXPECTED TO BE COMPETENT TO GIVE CONSENT FOR THEMSELVES?

Yes

If no, please explain why and how consent will be obtained.

21. EXPLAIN THE CIRCUMSTANCES UNDER WHICH CONSENT WILL BE OBTAINED. HOW WILL YOU INSURE THAT POTENTIAL SUBJECTS HAVE ADEQUATE TIME TO CONSIDER THEIR OPTIONS, AND THAT POSSIBLE COERCION IS MINIMAL?

Consent forms will be distributed in written format which will be mailed in advance of the screening visit. Potential study patients who demonstrate an interest in participating in the study will receive an explanation of the terms, procedures, and requirements of the study from an investigator of the research team in language they can understand. They will receive a copy of the written version of the Informed Consent Form to read (or be read to) and share with family or friends. Subsequently, an investigator will answer questions and request the patient's permission to participate in the study. Volunteer participants who sign a study-specific patient informed consent form approved by the Institutional Review Board will then be scheduled for a screening evaluation to determine their eligibility.

22. IF THE SUBJECT POPULATION INCLUDES MINORS, AND SIGNED CONSENT WILL BE OBTAINED, WILL AN ASSENT FORM BE USED AS PART OF THE CONSENSING PROCESS? CONSULT IRB GUIDELINES FOR INFORMATION ABOUT CHILDREN IN RESEARCH STUDIES.

No Minors enrolled

NOTE: In general, it is expected that minors from age 8 to 15 will read and sign an assent form. Older adolescents (16 and 17) will usually read and sign the same consent form as the parents signed. The assent form template is available on our website.
23. IF YES, PLEASE EXPLAIN WHO WILL APPROACH THE MINORS AND HOW AND WHERE THE ASSENTING PROCEDURE WILL TAKE PLACE.
**SECTION VI**
CERTIFICATION OF APPROVAL
PI Name: Kaushal, Shalesh

DELEGATION OF ROLES/RESPONSIBILITIES*: Checklist/Sigature List

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<tr>
<th>Please type Name and Credentials</th>
<th>Delegation of responsibilities: Please use key** in box below to summarize your study activities and place an “x” in the appropriate column</th>
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<tr>
<td>Shalesh Kaushal, MD PhD</td>
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<td>Christine Clemson, PhD</td>
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<td>George Asdourian, MD</td>
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<td>Judith Colbert RN Coordinator, RN</td>
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<td>Julie Wilson Other Coordinator, RN</td>
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<td>Heather Hudson Other Coordinator, UMMMC</td>
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<td>Elena Filippova, MD Other</td>
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*Roles: (choose appropriate # below)
1. Sub or Co-Investigator
2. Study Nurse
3. Study Coordinator
4. Other: Ophthalmic Imager

**Delegation of Responsibility Codes:** (choose all that apply)

A. Consent Subjects
B. Take Medical History
C. Conduct Physical Exam
D. Phlebotomy
E. Monitor Vital Signs/Nursing Assessment
F. Maintain Regulatory Documents
G. CRF Completion and Query Resolution
H. SAE/AE Monitoring/Reporting
I. IRB Communications and Continuing Review
J. Other (explain): Although the Principal Investigator is ultimately responsible for every element of study activity, this form serves to clarify to whom the PI has delegated specific study activities and responsibilities.
CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

Title: Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

Principal Investigator: Shalesh Kaushal, MD, PhD
Contact Information: (508) 334-0687

Research Subject’s Name: ___________________________ Date: __________________

Invitation to Take Part and Introduction

You are invited to volunteer for a research study. You are asked to take part because you have been diagnosed with Retinitis Pigmentosa (RP). The 45 human subjects who will be included in the proposed clinical trial will be males and females who have been diagnosed with Retinitis Pigmentosa, 18 years of age and older, who do not have any diseases or conditions inconsistent with treatment using valproic acid.

Purpose of Research

The goal of this research is to determine if valproic acid (VPA) can reduce the rate of vision loss from RP.

Your Rights

It is important for you to know that:

Your participation is entirely voluntary.

You may decide not to take part or decide to quit the study at any time, without any changes in the quality of the health care you receive.

You will be told about any new information or changes in the study that might affect your willingness to participate.

Description of the Investigational Drug:
VPA is already approved by the U.S. Food and Drug Administration (FDA) for sale by prescription to treat seizure disorders. VPA is not approved by the FDA for RP but approval is currently being pursued for treatment of patients with RP.

**Randomization:** Since no one knows yet whether Valproic Acid will be effective or not, not everyone in the research study will be treated with VPA. Each volunteer in the study will get either VPA or a placebo. A placebo is an inactive substance which looks exactly like the experimental drug, but which is not expected to have any medical effects. This means you may not receive the drug being tested. The decision as to whether you receive the drug or placebo will be made by chance, like the flip of a coin, not by your doctor or based on your medical condition. Neither you nor the doctors will know whether you are getting the experimental drug or a placebo. You have 1 chance in 2 of getting the experimental drug. This way of studying medicines provides more objective information about the drugs and allows better comparisons to be made. In an emergency, a doctor can find out what you are taking by calling (508) 334-1000 and have the operator page the on-call Investigational Pharmacist.

**PROCEDURES**

**Screening:** You will be screened to determine if you are suitable for this study. The screening visit will take about 3 hours. We will go over this consent form with you and once all of your questions are answered, and you wish to be considered for this trial, you can sign it.

At the Screening visit these procedures will be performed:

1. Signing of consent forms.

2. A small sample of blood (about 5 tablespoons) will be collected from the arm vein to be sure it is safe for you to take the study medication.

3. Signing of genotyping consent forms if you wish to have genetic testing performed. This is blood test that may be able to determine which gene is causing your RP. (You do not need to be genotyped to be in this study).

4. A small sample of blood (about 1 tablespoon) will be collected from your arm if you wish to have genetic testing performed.

5. If you are capable of having children, urine will be collected to be sure you are not pregnant.
6. You will have a physical exam by a study doctor.

7. You will be asked about your medical history.

8. An eye exam will be performed by one of the study doctors and your eyesight will be tested. This involves sitting at a computer and answering questions about the letters that appear.

9. Your visual field will be measured. The visual field test will take about 30 minutes and will involve you sitting at machine that will shine lights in your eyes to determine which part of your eyes are affected by RP.

10. Fundus photography will be performed that will take about 10 minutes and involves having your eyes photographed.

11. You will be asked about any other medications you take.

12. If the study doctors determine that you are suitable for this trial, you will be contacted in a few weeks to participate in this research.

**Evaluations during the research:**
If you choose to be part of this trial, the research will last for about 15 months and you will be asked to return to the clinic 4 more times.

The **First visit** (also called the Baseline visit) will occur within 120 days of the Screening visit. At this visit you will be given a supply of either the valproic acid or the placebo, depending on which you were randomly assigned to take. This will be a pill to be taken up to 4 times a day (depending on your weight). You will be advised to take this pill with food and to slowly increase the amount you take over the course of seven days until you reach the prescribed dose.

The **Baseline clinic visit** will take about three hours and these procedures will be performed:

1. A small sample of blood (about 5 tablespoons) will be collected from the arm vein to be sure it is safe for you to take the study medication.

2. If you are capable of having children, urine will be collected to be sure you are not pregnant.
3. An eye exam will be performed by one of the study doctors and your eyesight will be tested. This involves sitting at a computer and answering questions about the letters that appear.

4. Your visual field will be measured. The visual field test will take about 30 minutes and will involve you sitting at a machine that will shine lights in your eyes to determine which part of your eyes are affected by RP.

5. The thickness of your retina will be examined by Optical Coherance Tomography (OCT). This procedure will take about 10 minutes and will involve you sitting comfortably at a machine and looking straight ahead.

6. Your color vision will be tested by the Chroma Test program, this involves sitting comfortably at a computer and answering questions about the colors you see.

7. An important test called an Electroretinogram will be performed to determine how well your eye cells respond to light. This test takes about 45 minutes and involves having anesthetic drops placed in your eyes, causing them to become numb. The eyelids are then propped open with a speculum and an electrode is gently placed on each eye with a device very similar to a contact lens. Readings will be taken first in normal room light, then with the lights dimmed and finally readings are taken as a bright flash is directed toward the eyes.

8. You will be asked to fill out a 25 question survey about how your vision affects your quality of life.

9. You will be asked about any other medications you take.

The 2 month follow up visit will occur approximately 60 days after the Baseline visit. It will take approximately 90 minutes and these procedures will be performed:

- A small sample of blood (about 5 tablespoons) will be collected from the arm vein to check for safety and levels of the study medication.
- An eye exam will be performed by one of the study doctors and your eyesight will be tested. This involves sitting at a computer and answering questions about the letters that appear.
- You will be asked about any other medications you take.
- You will be asked about any side effects you are feeling.
- Your remaining study capsules will be counted.
- You will be provided more study drug if needed.
The 6 month follow up visit will occur approximately 180 days after the Baseline visit. It will take approximately 90 minutes and these procedures will be performed:

1. A small sample of blood (about 5 tablespoons) will be collected from the arm vein to check for safety and levels of the study medication.

2. An eye exam will be performed by one of the study doctors and your eyesight will be tested. This involves sitting at a computer and answering questions about the letters that appear.

3. You will be asked about any other medications you take.

4. You will be asked about any side effects you are feeling.

5. Your remaining study capsules will be counted.

6. You will be provided more study drug if needed.

The 12 month visit will occur approximately one year after the baseline visit. It will take about three hours and these procedures will be performed:

1. A small sample of blood (about 5 tablespoons) will be collected from the arm vein to check for safety and levels of the study medication.

2. An eye exam will be performed by one of the study doctors and your eyesight will be tested. This involves sitting at a computer and answering questions about the letters that appear.

3. Your visual field will be measured. The visual field test will take about 30 minutes and will involve you sitting at a machine that will shine lights in your eyes to determine which part of your eyes are affected by RP.

4. The thickness of your retina will be examined by Optical Coherence Tomography (OCT). This procedure will take about 10 minutes and will involve you sitting comfortably at a machine and looking straight ahead.

5. Your color vision will be tested by the Chroma Test program, this involves sitting comfortably at a computer and answering questions about the colors you see.

6. An important test called an Electroretinogram will be performed to determine how well your eye cells respond to light. This test takes about 45 minutes and involves having
anesthetic drops placed in your eyes, causing them to become numb. The eyelids are then propped open with a speculum and an electrode is gently placed on each eye with a device very similar to a contact lens. Readings will be taken first in normal room light, then with the lights dimmed and finally readings are taken as a bright flash is directed toward the eyes.

7. Fundus photography will be performed that will take about 10 minutes and involves having your eyes photographed.

8. You will be asked to fill out a 25 question survey about how your vision affects your quality of life.

9. You will be asked about any other medications you take.

10. You will be asked about any side effects you are feeling.

11. Your remaining study capsules will be counted.

The 15 month follow up visit will occur approximately 90 days after the 12 month visit. It will take approximately 45 minutes and these procedures will be performed:

1. A small sample of blood (about 5 tablespoons) will be collected from the arm vein to check for safety and levels of the study medication.

2. An eye exam will be performed by one of the study doctors and your eyesight will be tested. This involves sitting at a computer and answering questions about the letters that appear.

3. You will be asked about any other medications you take.

4. You will be asked about any side effects you are feeling.
Follow up phone calls
You will be followed closely during this research for your safety. During the months that you do not have clinic visits scheduled (month 1, 3, 4, 5, 7, 8, 9, 10 and 11) a research nurse will call you at a time that is convenient for you. She will ask you about any side effects you are feeling and if you are taking the medication as prescribed. If necessary, she will arrange for you to come into the clinic for an additional visit.

CONFLICT OF INTEREST DISCLOSURE
NONE

POSSIBLE RISKS:
In patients with RP who have taken similar amounts of VPA to this study, the most common side effects were not serious and included stomach irritation and tiredness. These symptoms may be alleviated by taking the medication on a full stomach and slowly ramping up the dosage over the course of 7 days.

The risks associated with this study involve blood collection, the visual function tests and taking VPA. During the blood draw your may experience discomfort, bleeding, and/or bruising. Your may feel dizzy or faint. On a rare occasion, an infection could develop at the site where the blood was collected. Blood will be drawn by personnel experienced in blood collection.

The risks associated with ophthalmic procedures include redness, discomfort or allergic reaction to topical medications used to dilate the pupil prior to visual function tests. High blood pressure, cardiac dysrhythmias and closed angle glaucoma may be exacerbated by some of these medications and light sensitivity may be experienced when the pupil is dilated. Corneal abrasions may result from the contact lenses used in performing electroretinography testing.

The most common side effects from VPA are stomach irritation, drowsiness or dizziness, restlessness or irritability, diarrhea or constipation, trembling of hands or arms. In addition you may experience other unforeseen side effects that have not been reported before.
More serious side effects are rare (less than 1% of patients who take this medication experience these), but include: Severe weakness or dizziness, severe vomiting that doesn’t go away, unusual bleeding or bruising and yellowing of the skin or eyes. If any of these symptoms occur, contact your study doctor immediately or seek emergency care.

As with any study agent, there may be a risk of allergic reaction that could include rash, hives, itching skin, difficulty breathing, lowered blood pressure, swelling and even death. If any of these symptoms occur, contact your study doctor immediately or seek emergency care. You will be immediately treated with standard medicines used to treat such reactions.

Your condition will be watched closely during the study. If you have any serious reactions or problems, the treatment will be changed or stopped to protect your health.

**How you can help reduce some of the risks:** During your participation in this research, the study doctor will watch closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Let the investigators know if your telephone number, address or e-mail address changes.
- Follow the study doctor’s instructions.
- Take the medication with meals and slowly increase the dosage over 7 days until the prescribed dosage is reached.
- Store study capsules in a cool, secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell the study doctor before you take any new medication even if it is prescribed by another doctor for a different medical problem.

**Tell your regular doctor about participating in this research.**

What to do if you have problems: If you have problems, such as unusual symptoms or pain, at any time while participating in the research, the study doctor can recommend treatment. Please report the problem to Dr. Kaushal immediately at (508) 334-0687.
PREGNANCY and REPRODUCTION

VPA is known to be unsafe to the fetus during pregnancy and the infant during breast feeding, so women who are pregnant or nursing may not take part in this study. VPA is known to have negative effects on sperm and hormones involved in reproduction. The long term effects of VPA on reproduction are not known. If you are a woman who is able to have children, you must have a negative pregnancy test before you begin the study and you must agree to use an effective birth control, such as oral contraceptive pills, contraceptive patch (if less than 198 lbs), Depo Provera injection, or IUD during the study and up to 3 months after stopping the study drug. If you become pregnant during the study, you should inform the doctors. You and your child will need to be followed closely until the baby is born. Men involved in this study must agree to use a barrier method of birth control during the study and up to 3 months after stopping the study drug.

POSSIBLE BENEFITS:

You may not benefit directly from being in this research study, either because you are assigned to take the placebo, or because VPA does not prove effective for RP. However, your participation may help others with this condition in the future as a result of knowledge gained from the research.

REASONS YOU MIGHT BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be taken out of the research study if:
1. The investigator decides that continuing in the study would be harmful to you.
2. You need treatment not allowed on this study.
3. You fail to keep your appointments or take the medications as instructed.
4. You become pregnant.
5. The study is canceled by the company making the drug, the FDA, or the University of Massachusetts Medical School Institutional Review Board.
ALTERNATIVES
You do not have to participate in this research to receive care for your medical problem. Although VPA is not approved for RP, it is possible to receive this medication without being involved in this study. Alternative care includes nutritional supplementation with vitamin A that may slow progression of the disease. No other treatment for RP is available.

COSTS
There will be no additional cost to you or your insurance company from being in this research study. All the clinic visits, medicine and tests are done for research purposes and will be free.

COMPENSATION
You will be paid $250 for completing the six visits required to reimburse you for your time, travel and other expenses associated with this research study. If you do not complete the entire study you will be reimbursed $50 per visit completed.

CONFIDENTIALITY
Your privacy is important to us. Your research records will be confidential to the extent possible. In all records, you will be identified by a code number and your name will be known only to the researchers. Your name will not be used in any reports or publications of this study. However, the U.S. Food and Drug Administration (FDA), and the UMMS Institutional Review Board and/or their representatives may inspect your medical records that pertain to this research study. We will not allow them to copy down any parts of your identifiable information (e.g. your name) or take any of your identifiable information from our offices.

YOUR PARTICIPATION IN THIS PROJECT IS ENTIRELY VOLUNTARY. YOU MAY WITHDRAW FROM THE STUDY AT ANY TIME.

THE QUALITY OF CARE YOU RECEIVE AT THIS HOSPITAL WILL NOT BE AFFECTED IN ANY WAY IF YOU DECIDE NOT TO PARTICIPATE OR IF YOU WITHDRAW FROM THE STUDY.

CONSEQUENCES OF WITHDRAWAL
If you, the study doctor, or the Monitoring Board stops your participation in the research it is your responsibility to do the following:

- Let the study doctor know immediately that your wish is to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Return any unused study materials, including empty containers.
- Discuss your future medical care with the study doctor and your regular doctor.

**RESEARCH INJURY COMPENSATION**

If you are injured or have any harmful effects as a direct result of your being in this research, treatment will be made available to you at UMass Memorial Medical Center (UMMMC). You will not have to pay any charges resulting from the harmful effect or injury of a study drug (or device) or procedure that would not have otherwise been done as part of your regular care.

**QUESTIONS**

Before you sign this consent form, please feel free to ask any questions you may have about the study or about your rights as a research subject. If other questions occur to you later, you may ask Dr. Kaushal at (508) 334-0687, the Principal Investigator. You may take as much time as needed to think this over. If at any time during or after the study, you would like to discuss the study or your research rights with someone who is not associated with the research study, you may contact the Administrative Coordinator for the Committee for the Protection of Human Subjects in Research at UMMS. The telephone number is (508) 856-4261.
CONSENT TO PARTICIPATE IN THE RESEARCH PROJECT

Title: Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

P.I. Name: Shalesh Kaushal, MD PhD

Subject’s Name:

I understand the purpose and procedures of this research project and the predictable discomfort, risks, and benefits that might result. I have been told that unforeseen events may occur. I have had an opportunity to discuss the risks and benefits of this research with the investigator and all of my questions have been answered. I agree to participate as a volunteer in this research project. I understand that I may end my participation at any time. I have been given a copy of this consent form.

_________________________________________ Date:______________

Subject’s signature

STATEMENT OF PERSON OBTAINING CONSENT

I, the undersigned, have fully explained the details of this clinical study as described in the consent form to the subject named above.

_________________________________________ Date: ______________

Signature of person obtaining consent

INVESTIGATOR’S DECLARATION

As the principal investigator or co-investigator on this study, I attest to the following:

- the nature and purpose of the study and study procedures, as well as the foreseeable risks, discomforts and benefits have been explained to the above-named subject
- this subject has been given the opportunity to ask questions and to have those questions answered by knowledgeable research staff
- this subject meets the inclusion/exclusion criteria for this study

I have considered and rejected alternative procedures for answering this research question.

____________________  ______________
PI Signature                   Date

3.6.7 CLINICAL TRIAL HIPPA RELEASE
The privacy law, Health Insurance Portability & Accountability Act (HIPAA), protects my individually identifiable health information (protected health information). The privacy law requires me to sign an authorization (or agreement) in order for researchers to be able to use or disclose my protected health information for research purposes in the study entitled: Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

I authorize UMass Memorial Medical Center to disclose my protected health information to:

UMass Medical School including the researcher Dr. Shalesh Kaushal and his/her research staff
Federal and State authorities that oversee research

Protected health information (PHI) that may be disclosed includes all “x” boxes, and PHI which is listed in the sections titled “other” below.

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<td>Other (specify):</td>
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My protected health information will be disclosed as listed above for the following reasons:

The purpose of this research is to investigate whether valproic acid is safe and effective for treating retinitis pigmentosa (rod-cone dystrophy).

I do not have to sign this Authorization. If I decide not to sign the Authorization:

- It will not affect my treatment, payment or enrollment in any health plans, or affect my eligibility for benefits.
- I will not be allowed to participate in the research study.
If I sign the Authorization, I understand that:

- I have the right to withdraw, or revoke, the Authorization.
- If I revoke the Authorization, I will send a written letter to: Dr. Shalesh Kaushal, Dept of Ophthalmology, Rm S6-410; UMMS, 55 Lake Ave. N, Worcester, MA 01605 to inform him of my decision.
- If I revoke this Authorization, researchers may only use the protected health information already collected for this research study.
- If I revoke this Authorization my protected health information may still be used and disclosed should I have an adverse event (a bad effect).
- If I change my mind and withdraw the authorization, I will not be allowed to continue to participate in the study.
- Any disclosure carries the potential for re-disclosure. Once UMass Memorial Medical Center releases my protected health information, it may no longer be protected by the HIPAA privacy rule.
- The entities receiving my protected health information will use it as described in the Consent Document for this study.
- I may not be allowed to review some of the research-related information in my medical record until after the study is completed. When the study is over, I will have the right to access the information again.
- I will receive a signed copy of this authorization for my personal records.

This Authorization does not have an expiration date.

If I have questions about the research study, I should contact: Dr. Shalesh Kaushal, at Ph: 508 334-0687

If I have not already received a copy of the Privacy Notice, I may request one. If I have any questions or concerns about my privacy rights, I should contact the UMass Memorial Medical Center Privacy Officer at Ph: 508-334-5551.

I HAVE READ AND UNDERSTAND THE ABOVE STATEMENTS AND AUTHORIZE THE DISCLOSURE OF THE INFORMATION REQUESTED ABOVE.

<table>
<thead>
<tr>
<th>Signature of Subject</th>
<th>Date</th>
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| Subjects Name Printed | DOB | SS# |

Use boxes below if parent or legal representative is signing for research subject

| Subject’s Legal Representative Signature | Relationship | Date |
Please explain Representative’s Relationship to Patient and include a description of Representative’s Authority to act on behalf of Patient:

__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________

Person obtaining HIPAA authorization

Date
3.6.8 Research Pharmacy
CHAPTER 4: APPLICATIONS FOR FUNDING

4.1 INTRODUCTION

Funding mechanisms for investigator initiated clinical trials are limited at best. NIH initiatives tend to be for large, collaborative, extremely expensive studies or small proof of concept studies. The NEI is one of the smaller NIH institutes and their funding opportunities for clinical trials appear to be limited to one large U-type grant opportunity. In fact, many of their RFPs specifically exclude clinical trials.

The primary pathway we initially pursued for funding this trial was through private foundations. We were in early discussions with the Foundation Fighting Blindness (FFB) when the stimulus funding was announced and I discovered a potential challenge grant opportunity (15-OD(ORDR)-101* Pilot Projects for prevention, early detection and treatment of rare diseases.) While the description of this RFA only mentioned clinical trials briefly, we felt that the contained nature of the trial would make it ideal for the 2 year Challenge grant mechanism. Dr. Kaushal and I spoke directly to the contact at NEI who administered this specific RFA and he informed us that it was likely written specifically for an existing consortium, but our proposal sounded promising so we should submit an application.

We tandemly pursued funding through Dr. Kaushal”s contacts with the FFB. The lack of formalized process by the FFB is reflected in the fact that the only document they officially requested is the budget I produced. This does not accurately reflect the major amount of time on the phone, in email correspondence and meetings that was spent pursuing this opportunity.

4.2 THE PROCESS

4.2.1 CHALLENGE GRANT APPLICATION

Although I had been involved in many NIH submissions before, I had never independently written and submitted a grant. Fortunately, there are a host of UMMC resources to aid in submission of funding applications. The Research Office helped me to set up the ERA Commons (the NIH electronic submission tool) and Cayuse accounts and I quickly taught myself to use these systems to prepare and assemble the application. The Research Office was always available, even in the midst of an overwhelming number of Challenge grant submissions, and their help was invaluable.

Writing the research plan for the Challenge grant while designing the study was very helpful as I was able to more thoroughly define the processes and procedures proposed in the trial. Additionally, the sections required for NIH proposals proposing human subjects testing (page 201) served as the framework for many aspects of the protocol. Preparing the NIH budget was perhaps the most daunting aspect of the Challenge grant proposal. Clinical trials are not typically included in NIH research proposals from the UMMC community. Complicating this was the newness of Dr. Kaushal”s clinical trial facility at the Memorial campus and the uncertainty of how to bill the procedures. I ended up preparing two budgets – one procedure-based and a more professional services-based budget. Ultimately, the professional services-based budget was used as the template for the final NIH budget (page 210).

4.2.2 FOUNDATION FIGHTING BLINDNESS
To begin discussions regarding the funding of the trial by the FFB, Dr. Kaushal hosted a meeting at our campus with the director of the FFB and another board member. Dr. Noorwez from Dr. Kaushal’s lab presented the in vitro studies on VPA and I presented some early data from the few subjects I had access to as well as my current study design. We were extremely encouraged by the positive feedback from the FFB and pointed requests by the director for us to pursue funding with the FFB.

There was no real formal process for applying for funding from the FFB, and the process was punctuated by periodic phone calls from the director making assertions such as “I can write you a check for the trial right now” and other conflicting communiqués suggesting the FFB was in a funding crisis. The lack of FFB process was a huge disadvantage as I had no visibility into what was required, and despite my attempts to annotate the process, it can be described summarily as – whenever anyone at the FFB, from the director to a board member, thought up something new they wanted to see- we were required to produce it immediately. On one occasion they requested the protocol before it was completed, another time they asked for a complete literature review on the safety of VPA on long term reproduction, another time they requested all the raw visual fields we had collected to date on patients. Compounding the frustrating nature of the interactions was the very real lack of confidentiality maintained by everyone at the FFB.

The culmination of our funding request was a meeting of the FFB board to decide whether to commit the funds for this trial. In addition to responding to the many whims of the board member weeks before this meeting, I prepared an entirely procedure-based budget for this proposal (page 213). It was in the process of sending materials in anticipation of this meeting that Dr. Kaushal learned of several egregious instances whereby the director of the FFB and board members violated confidentiality agreements with us and we summarily severed ties with the FFB.

4.3 ISSUES AND RECOMMENDATIONS

The Research Office and Sheila Noone were incredibly helpful in guiding me through the budget process for both the NIH and FFB proposals. It is clear that the UMMC infrastructure in this area is established and expertly staffed. One area of clinical trial budgeting that could be improved upon is in defining the procedure and drug costs that the investigator will incur during the trial. There is no online standardized list of costs for services like CBCs; this information can be obtained by calling the laboratory directly or consulting the clinical research office to determine the negotiated costs. Additionally, the costs for more complicated diagnostics are not well defined. Working with the Ophthalmology clinic billing staff I was able to estimate various costs, but a formalized system of relating clinic procedures to actual investigator costs would allow more accurate accounting for these kinds of budgets.

Additionally, it will be important to centralize all the resources for clinical trial budgeting and sponsor negotiations through the UMCCTS website. Currently these documents are buried and difficult to locate among the Office of Research portal.

4.4 OUTCOMES

The Challenge grant application was reviewed but not given a priority score. The reviewer feedback was quite variable with one reviewer scoring it high in every aspect, and one reviewer giving it poor
scores for each area. The other two reviewers scored the application in the mid-range over all. The critiques ranged from my newness as a clinical researcher (which is actually supposed to be considered positively since we submitted under the “New Investigator” initiative), to the lack of evidence supporting VPA as a retinal therapeutic. Ultimately the comments will be used to strengthen the application as we plan to submit an R01 to NINDS in the spring.

Needless to say, after almost an entire year of pursuing funding of this trial by the FFB, we are no longer in contact with this organization. Nevertheless, I learned quite a bit about sponsored trials from this process.
4.5 NIH CHALLENGE GRANT SUBMISSION

Project Summary/Abstract

This application addresses broad Challenge Area (15) Translational Science, and the specific challenge area 15-OD(ORDR)-101* Pilot Projects for prevention, early detection and treatment of rare diseases.

Retinitis Pigmentosa (RP) is a rare (orphan) disease affecting approximately 100,000 people in US, with an incidence of about 1 in 3000 in the general population. This catastrophic disease is characterized by progressive loss of visual field (VF) until complete blindness. There is no treatment currently available. Investigator initiated clinical trials are an important avenue for efficacy studies in orphan diseases such as RP given the perceived lack of financial return on investment by industry. We have recently focused our efforts to couple our in-depth knowledge of the cellular basis of RP with the biological action of already approved drugs. The significantly shortened time to treatment inherent in new indications for existing medications allows for more rapid introduction of new treatments. This is appealing to independent investigators, which means more rapid translation of basic science discoveries to the clinic. We initially identified valproic acid (VPA) as a potential target for RP therapy utilizing a screen to examine small molecules for enhanced mutant rhodopsin folding. Other work by our lab has shown that this small molecule is a potent inhibitor of retinal cell apoptosis which is also important in the pathogenesis of RP. We performed a preliminary clinical analysis by treating 6 RP patients off label with oral VPA. This preliminary clinical data suggests that VPA has the potential to not only stop the progressive loss of VF in RP patients, but can also restore VF. Here, we propose to conduct a 12 month Phase II clinical trial to test the efficacy of VPA for treatment of RP. Using the pilot data, we have designed a unique one-armed self-controlled study. We propose to assess primary outcomes during a defined period just prior to start of study medication; in this manner we can predict personalized rates of vision loss that would have occurred during the 12 months of treatment. The study protocol includes screening, baseline and monthly ophthalmologic measures including perimetry, color contrast sensitivity (CCS) and visual acuity (VA). Furthermore, we propose to correlate genotyping information with efficacy to investigate whether VPA is selective for a sub-population of RP patients. Finally, we propose to perform an initial therapeutic dosing analysis in a standardized subgroup of subjects.

This clinical trial is appropriate for the 2 year timeline for the following reasons: 1) VPA’s prior FDA approval allows for an expedited approval process; 2) we have been in close contact with FDA and are in the process of submitting both the IND and the IRB application supporting our ability to begin recruitment in September 2009; 3) an established population of RP patients in our clinic combines with the absence of any standard therapy to allow for an efficient and curtailed recruitment period; 4) our new, state-of-the-art clinic is already equipped with all the necessary diagnostic equipment and 5) the study design and proposed recruitment and follow up fit within the 24 month timeline.
Specific Aims

Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

We present here a unique combination of preclinical data combined with preliminary clinical evidence suggesting that valproic acid (VPA) is an effective therapeutic agent for Retinitis Pigmentosa (RP), a devastating and serious orphan disease that currently has no effective treatment. VPA is already approved by the FDA for other indications, allowing for an expedited human study. VPA is off patent protection, and is widely used off-label for a variety of indications, making this initial efficacy study an unattractive candidate for pharmaceutical companies. Investigator initiated clinical trials, such as we propose here, are often the primary source of new therapeutics for rare diseases.

This proposal for phase II clinical trial of oral (VPA) administration to subjects with RP associated retinal disease stems from both the lack of treatment for this severe blinding disease and our proof-of-concept studies. Preliminary clinical data suggests that VPA, at doses that have not shown toxicity in humans, results in improvement in visual fields. The primary endpoints in this trial will be visual function as assessed by perimetry, standard acuity assessments, color contrast sensitivity, optical coherence tomography and electroretinograms. Safety will also be assessed by systemic clinical examinations and measurements of hepatic and pancreatic function as assessed by hematology and serum chemistries and reported subject history of any symptoms and adverse events.

Specific Aim 1: Perform a phase II clinical trial of 12 month treatment with oral VPA, 250 mg BID, in subjects 18 years and older with Retinitis Pigmentosa.

To assess the efficacy of oral administration of VPA in RP patients, we will perform an open-label, standard-dose per patient, phase II clinical trial in a cohort of 45 patients. The planned dose of VPA that will be administered to human subjects is approximately half of the recommended dose for anti-convulsant therapy and has been well demonstrated to be safe in humans. Patients will provide their own historical control as primary outcome measures will be determined from one to 3 months prior to the start of the study and again at baseline. These control measurements will provide estimated rates of vision loss that would occur during the course of the study.

Specific Aim 2: Perform a genotype analysis of enrolled subjects in order to determine both the generalizability of this medication to all RP mutant types and to collect data on the possible mechanistic action of VPA.

Preliminary studies in vitro and in vivo suggest that VPA may work at multiple levels as a retinal therapeutic. We have in vitro data to suggest that it works at the level of rhodopsin folding, which would indicate that only those patients with protein folding associated RP would benefit from this medication. However, other evidence suggests that VPA may work at the level of cell death protection or inflammatory mediation to exact its affect. Our other preliminary clinical data suggests that VPA may be beneficial to other ocular diseases that aren’t known to have protein folding pathway deficiencies, also supporting that VPA is working either on multiple pathways or in a protein folding independent pathway. To examine this in more detail, we propose to genotype the mutations associated with enrolled subjects. We will correlate primary and secondary outcome measures with each known mutation to determine if VPA has a general benefit to all patients with RP or if its effect is specific for sub populations of patients.

Specific Aim 3: In a cohort of selected patients with similar disease progression and/or mutation profile (e.g. RHO p23H), perform an escalating dose trial.

Our preliminary clinical analysis suggests that RP patients receive an almost immediate therapeutic benefit to VPA. A critical question will be the effective dose range for RP patients. Utilizing the genotyping information from Aim 2, and/or the projected rate of vision loss from the screening period coupled with outcome measures from the initial intervention phase (the first 6 months), we can identify a standardized cohort of patients. In this cohort (cohort 2), we will escalate the dose of VPA from 250 mg BID to 250 mg QID over the course of 6 months (this is still well within the known safety and tolerability profile of this medication). Primary outcome measures will be assessed to determine therapeutic dosing windows and dose response relationships.

This data from the above Specific Aims will be used, in collaboration with the NIH and potential pharmaceutical companies, for planning the Phase III clinical trial.
Research Design and Methods

Phase II Clinical Trial of Valproic Acid for Retinitis Pigmentosa

Challenge Area and Specific Challenge Topic

This application addresses broad Challenge Area (15) Translational Science, and the specific challenge area 15-OD(ORDR)-101* Pilot Projects for prevention, early detection and treatment of rare diseases.

The Challenge and Potential Impact:  

The Challenge

RP is a severe neurodegenerative disease of the retina characterized initially by night blindness with progression to tunnel vision and eventual loss of central vision and total blindness. Targeted therapies for RP are complicated by the identification of more than 30 genes linked to the dominant and recessive forms of the disease. Further compounding this complexity is the rarity of this disorder: although RP is one of the most common inherited eye diseases with an incidence of \(~1\)3000, its prevalence is relatively rare. RP affects approximately 100,000 individuals in the U.S. which qualifies it as an orphan disease. Given the huge costs associated with the preclinical and clinical phases of drug development, pharmaceutical companies are generally reluctant to invest in developing new therapeutics for RP. While a few new approaches for RP treatment have recently been investigated including nutritional supplementation, light reduction and gene therapy (Delyfer et al., 2004; Gaby, 2008; Hartong et al., 2006), of these, vitamin A supplementation is the most promising, but its benefits are modest and side effects are problematic. Therefore, currently there is no significant cure for RP.

We present here a new treatment for RP which is based upon our strategic initiative to combine understanding of the pathophysiology of the disease with the known biological properties of existing therapeutics. There are several major advantages to this approach. First, since the bulk of the pre-clinical, pharmacokinetic, manufacturing, safety and tolerability analysis is complete, clinical trials can generally begin along the Phase II spectrum. In this manner, the huge costs associated with discovering and testing new medications is avoided, effectively allowing translation of basic science discovery via investigator initiated studies. Second, the time to treatment in humans is expedited, fostering delivery of effective medications in a shortened time frame. Third, the relatively inexpensive cost of “relabeling” existing formulations for new indications may motivate pharmaceutical companies to invest in therapies for less common diseases. Recently, we have demonstrated the use of retinoids and other small molecules as pharmacological chaperones to increase the yield of properly folded RP mutant rhodopsins in heterologous cell culture (Noorwez et al., 2008). We have tested whether other known small molecules can provide similar effects. We identified valproic acid (VPA) through this screen. In vitro data supports that VPA has multiple biologic properties that make it an ideal candidate for a retinal therapeutic. First, our in vitro assay shows that VPA effectively increases yields of properly folded mutant rhodopsin (Figure 1); such a dramatic impact on mutant rhodopsin folding has never been demonstrated in a potential therapeutic. Second, VPA protects cells from oxidative stress induced apoptosis (Figure 2), most likely through upregulation of the heat shock response (not shown). This result has implications for RP but also for many other ocular disorders which are mediated through cell death. Other work demonstrates that VPA is a potent inhibitor of histone deacetylase (HDAC) (Gottlicher et al., 2001) and the inflammatory response pathway via apoptosis of microglial cells (Chen et al., 2007; Dragunow et al., 2006; Kim et al., 2007). Collectively, this body of evidence suggests that VPA is an appropriate therapeutic for patients with retinal dystrophies.

Figure 1 Valproic Acid allows mutant P23H rhodopsin to properly fold to the level of wild type. HEK293 cells stably expressing an inducible mutant P23H rhodopsin expression vector were grown to confluence and tetracycline was added to induce opsin expression. 3mM VPA was added for 48h. Rhodopsin was purified by immunoaffinity methods. Yields of folded p23H opsin were quantified by spectrophotometry. In the presence of 11-cis retinal, folded mutant rhodopsin levels (red) increase from baseline (blue) to that of wild type (green).
It is critical to emphasize that the extensive history and well established safety and tolerability profile of VPA makes it an ideal candidate for a Phase II study, which streamlines the time to treatment in humans considerably relative to new drug design. VPA was approved by the FDA for use as a broad spectrum anticonvulsant in 1978 and is also used for acute and maintenance therapy of bipolar disease, for migraine prophylaxis, and occasionally for chronic pain syndromes (Henry, 2003).

The unusual and dramatic set of pre-clinical and pilot human data that we present here with a FDA approved drug uniquely positions us to complete the clinical trial outlined in the Specific Aims in the NIH Challenge Grant funding window of 2 years.

Potential Impact
Prevention of disease progression and restoration of vision are the ultimate goals of this proposal. RP is an incurable and untreatable group of heterogeneous retinal degenerative diseases that cause severe visual loss. While individual rates of vision loss can vary greatly even among siblings with the exact same mutation (Berson et al., 2002), projections from the literature suggest that RP patients will lose an average of 15-17% of their visual field (VF) annually (Massof et al., 1990; Zeger and Liang, 1986) and 25% of RP patients will lose 20% of their VF in one year (Merin et al., 2008). There is currently no significant therapeutic that effectively slows the progression of this disease, and certainly none that can restore vision in RP patients. Our preliminary studies indicate that VPA is a remarkable retinal therapeutic that may not only stop the progression of this disease, but also reverse loss of visual field. An investigator initiated clinical trial as we propose is an important if not the only way for new therapeutics to be investigated for rare disorders such as RP.

Our comprehensive study design includes novel methodologies that address several issues inherent in diseases with wide ranging progression patterns. The individual projected rates of vision loss determined from the baseline and screening analysis described in Specific Aim 1 and the genotyping and therapeutic dosing studies proposed in Specific Aims 2 and 3 provide mechanisms to relate therapeutic benefit to specific rates of disease progression, mutations and broad groups of disease classification. Dr. Robert Brown, an internationally lauded clinical trialist in the field of amyotrophic lateral sclerosis (ALS), has reviewed and endorsed this trial, and feels that it provides methodology that can advance the science of investigating neuro-degenerative disorders in general (see Letter of Support).

The Approach:
Aim 1: Perform a phase II clinical trial of 12 month treatment with oral VPA, 250 mg BID in subjects with retinopathy due to Retinitis Pigmentosa.
To assess the efficacy of oral administration of VPA in RP patients, we will perform an open-label, phase II clinical trial in a cohort of 45 patients. The planned dose of VPA that will be administered to human subjects is approximately 1/2 of the recommended dose for anti-convulsant therapy (see Table 2) and has been well demonstrated to be safe in humans. Patients will provide their own historical control as primary outcome measures will be determined from one to 3 months prior to the start of the study and again at baseline. These control measurements will provide estimated rates of vision loss that would occur during the course of the study.

Pilot Clinical Analysis
A unique and robust aspect to our proposal is the inclusion of preliminary clinical data which informed our trial design. Six RP

Figure 2 VPA Rescues Retinal Pigmented Epithelium Cells from Hydroquinone (HQ) induced apoptosis. ARPE-19 cells are protected from HQ mediated apoptosis by the presence of VPA.

Figure 3 Perimetry Tracing of a Patient treated with VPA Goldmann Kinetic Perimetry tracings (using V4e isopter) of Patient One before and after treatment with VPA 250 mg twice daily.

Figure 4 Visual Field Areas of Patients Treated off-label with VPA. Goldmann Kinetic Perimetry tracings (isopter V4e) from each eye (e.g. Figure 3) were digitized and areas were automatically calculated. The 6 patients were treated with VPA for varying lengths of time so the percent change per month from baseline was calculated for each eye and average values are presented.
patients were treated off-label with oral VPA (250 mg BID) for 2 to 6 months. Visual fields were measured using kinetic perimetry (Figure 3). Results varied from patient to patient; 2 of 6 patients experienced progression of their disease while on VPA. However, 4 of 6 patients showed no progression of their disease on VPA (Figure 4), moreover, these 4 patients experienced an increase in their visual field (e.g. Figure 3) - which no other therapeutic has previously shown.

Overall, we detected an average increase in visual field of 6%/month. These results suggest that VPA has the potential to not only stop the progression but may also reverse loss of visual field. No adverse affect of VPA was seen in these patients as assessed by clinical analysis, hematology and serum chemistry or by patient reports.

While this preliminary clinical analysis combines with the in vitro data above to suggest that VPA may be an effective retinal therapeutic, the number of patients and length of treatment was short. Moreover, several factors likely contributed to the within-patient variability. Individual historical information was not available to calculate expected rates of vision loss. Secondly, the rigorous standardization of ophthalmologic diagnostic measures that we propose here were not instituted in the off label treatment of these few patients. We propose to address these issues carefully in our study design below. Additionally, the between-patient variability potentially suggests that certain patient populations may preferentially benefit from this medication (this will be examined in detail in Specific Aim 2).

Clinical Trial Design
A variety of factors were considered for the overall study design. While crossover, futility and delayed start type studies were initially considered, the length of time needed to detect a change in outcome combined with the potential for short term symptomatic versus therapeutic benefit suggested that these designs were not appropriate. A randomized placebo controlled trial was considered, but for the RP population with drastically different presentation and progression, it is difficult if not impossible to ensure that controls represent the treated subjects. The additional costs and difficulty in recruiting twice the number of patients in an orphan disease population were also significant concerns. A novel aspect to our trial design is that it is self controlled; individual patients provide current rates of vision loss. We designed the trial and protocol in close communication and consultation with Wiley Chambers, M.D., deputy director of the FDA's Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Product and multiple experts in the field of neurovision research including (see letters of support): Stephen Rose, Ph.D, the Research Director for the Foundation Fighting Blindness (FFB); Robert Brown, MD, PhD, the Chair and Professor of Neurology at the University of Massachusetts Medical Center (UMMMC), a renowned and experienced clinical trialist in neurodegenerative disorders similar to RP; and Gerald Cagle, Ph.D; a trustee for the National Neurovision Research Institute (NNRI) who recently retired as the senior vice president of Research and Development and Chief Scientific Officer for Alcon. Additionally, we have consulted colleagues at Ora, a retinal clinical trial contract research organization, and institutional biostatisticians.

Using a one sample t-test calculation, informed by our pilot analysis and historical control data, we estimate a treatment effect (delta) of 50% change in VF annually in untreated versus VPA treated RP patients. This estimate of delta assumes that participants would lose no VF in a year if left untreated (a conservative assumption given the natural course of this disease (Berson et al., 2002; Massof et al., 1990; Merin et al., 2008)). An enrollment of about 40 patients provides 90% power for a significance level of p<.05 (Figure 5). Due to the fact that related family members will likely co-enroll in our study (see Recruitment section), the relatively short nature of this trial and the motivation associated with this devastating disease, we conservatively estimate attrition of about 10%, leading to a projected recruitment target of 45 participants. In our novel design, assessments of primary outcomes will be performed from 1 to 3 months and immediately prior to the start of the study agent to calculate individualized (linked) loss of vision rates for each subject (Figure 6). This contemporary historical information will be used to predict the loss of vision that would have occurred in the 12 months of the study.

Study Medication, Route of Administration and Dosage

Figure 5 Sample Size and Power calculations. Sample size estimates using pilot data (Figure 4). A one sample t-test calculation assuming no loss of VF in untreated RP patients (U0=0%) and an estimated VF yearly gain of U1= 50%, (SD=96%) on VPA provides an estimate of around 40 patients with 90% power and statistical significance of p<.05.
VPA is well tolerated in most patients and adverse events are rare (reviewed in Peterson and Naunton, 2005). The primary concern is hepatoxicity which is rare in low risk patients occurring in fewer than .29 in 10,000 patients (Bryant and Dreifuss, 1996). Subjects will be carefully screened for comorbid conditions and concomitant medications to ensure that only patients at the lowest risk for serious adverse events are enrolled (see Exclusion Criteria in Protection of Human Subjects Section).

VPA will be administered orally by ingestion of 250 mg capsules. Cohort 1 will receive 250 mg BID (for a total daily dose of 500 mg) for the entire 12 months of the study, while subjects in cohort 2 will receive a dose of 250 mg BID for the first six months and receive a dose of 250 mg TID (for a total daily dose of 750 mg) from month 6-9 and 250 mg QID (for a total daily dose of 1000 mg) from month 9-12 – see Specific Aim 3. In order to avoid gastrointestinal side-effects all patients will be instructed to take the medication with food and to gradually increase the dosage of VPA to achieve targeted dosing in 7 days.

Study Design and Execution

Patients will undergo clinical examinations and evaluations of retinal function and structure prior to consideration of the subject as a candidate for clinical trials. Clinical examinations will include refraction, static and kinetic perimetry, fundus photography and visual acuity. Measures of visual function will include full-field electroretinography. Optical coherence tomography will be used to measure retinal structure. Methods of these measures are detailed below. During these evaluations, medical and ophthalmic histories will be elicited from subjects and their families to ensure that there are no comorbid medical or ocular genetic conditions that may prevent study participation. While the equipment proposed for use in this trial is state of the art and as such will provide the highest level of quantitation available, the quasi-subjective nature inherent in many standard ocular tests make day-to-day variation an important confounder to our analysis. All diagnostic measures will be calibrated and standardized such that intervisit and interocular variances for each outcome measure will be quantified and included in our analysis. This will involve sequential repeated measures for the same and different patients on these machines from a representative sample of our recruited patients.

Recruitment

Primary recruitment would be from the greater Worcester area from the UMMMC Department of Ophthalmology. Additional recruitment support will be provided by the Foundation Fighting Blindness (see letter of support). Given the debilitating nature of this disease, established number of clinically well characterized RP patients and family groups and lack of any available treatment combined with the overwhelming expressed interest of our established patients, recruitment will be swift. At present, 20 patients in Dr. Kaushal’s rapidly growing practice are likely recruitments. We anticipate that we can begin screening the first patients in September 2009, with baseline screening of the last patient in June, 2010 (see Timeline and Milestones). Given our access to the extensive histories of most of those recruited, we anticipate that most screened participants will be suitable for enrollment, hence an estimate of 50 screened subjects to achieve the target of 45 enrolled patients.

Study Visit Schedule (see Table 1)

All screening determinations will be performed between 4 and 12 weeks prior to the baseline visit. Baseline determination will be considered time 0 and study medication will commence on that day. Screening and baseline determinations will be used as individual control information for each patient. Most participants will take oral VPA 250 mg BID for the entire study period, while a small cohort in the second half of the study will take escalating doses as described below. All participants will return to the clinic 7, 21, 60, 120, 180, 270 and 360 days after initiating VPA treatment for evaluation of their clinical status and to assess adverse events. Participants will be asked to provide information on any side effects they are experiencing. Subjects will be followed up with phone calls after the baseline, week 1 and 6 and 9 month visit. In all cases, participants will be followed for a period of 3 months after the study ends. In the latter 6 month phase of the trial, cohort 2 patients will be followed closely during the escalation phase of their dosing. Additional visits may be scheduled as clinically required.
**Evaluation of Primary Endpoint- Visual Function and Retinal Anatomy Changes**

Visual function will be quantified for the months prior to and after start of study medication in order to determine whether VPA administration affects visual/retinal function. The main measure of visual function will be visual fields as measured by kinetic and static perimetry. Other measures of visual function will include best corrected ETDRS visual acuity; color contrast sensitivity as measured by the Chroma Test; retinal anatomy as measured by Optical Coherance Tomography (OCT) and rod and cone responses as analyzed by electroretinography (ERG). Primary outcomes for efficacy for both eyes will be determined.

Secondary outcomes will include: fundus photography; the 25 item National Eye Institute Visual Function questionnaire to assess quality of life (QOL); efficacy as predicted by specific mutation; the dose response profile of VPA as measured by serum VPA levels and the toxicity and safety profile of VPA in RP patients.

**Follow-Up**

We have been in close contact with Wiley Chambers, M.D., deputy director of the FDA’s Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products throughout the development of this protocol. Although we were advised that no additional follow up of these subjects after the 12 month treatment is necessary, we intend to follow these patients for an additional 3 months after the end of the study. Additionally, if the VPA treatment appears to be efficacious and the DSMB concurs, interested participants will continue to be provided prescriptions for VPA and standard follow up care, at their own incurred expense.

### Table 1: Schedule of Study Evaluations.

<table>
<thead>
<tr>
<th>Time relevant to start of Oral VPA</th>
<th>Screening</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Early term. 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>Visit 1</td>
<td>Visit 2</td>
<td>Visit 3</td>
<td>Visit 4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Visit 5</td>
<td>Visit 6</td>
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<tr>
<td></td>
<td>Visit 7</td>
<td>Visit 8</td>
<td>Visit 9</td>
<td>Visit 10</td>
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<tr>
<td>Week</td>
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<td>0</td>
<td>1</td>
<td>2</td>
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<td>15</td>
<td>15</td>
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</table>

| Informed Consent                  | x         | x        | x         | x           |
| Inclusion/exclusion Criteria      | x         | x        | x         | x           |
| Medical/surgical history         | x         |          | x         | x           |
| Physical examination             | x         |          | x         | x           |
| Ophthalmic history               | x         |          | x         | x           |
| Safety Labs                      | x         | x        | x         | x           |
| Demographic data                 | x         |          | x         | x           |
| Molecular Genotyping             | x         |          |           |             |
| Ophthalmic Exam                  | x         | x        | x         | x           |
| Urine pregnancy test             | x         |          | x         | x           |
| Visual Acuity (BCVA)             | x         | x        | x         | x           |
| Perimetry                        | x         | x        | x         | x           |
| Color Contrast Sensitivity       | x         | x        | x         | x           |
| Electoretinography              | x         |          | x         | x           |
| Optical coherence tomography (OCT)| x       |          | x         | x           |
| Fundus photography (FP)          | x         |          | x         | x           |
| Quality of Life Questionnaire    | x         |          | x         | x           |
| Remaining pill count for med. monitoring | x | x | x | x |
| VPA prescribed                   | x         | x        | x         | x           |
| VPA level (labs)                 | x         | x        | x         | x           |
| Increase VPA dose (cohort 2)     | x         | x        | x         | x           |
| Concomitant medications          | x         | x        | x         | x           |
| Adverse events assessment        | x         | x        | x         | x           |
| 24 hours follow-up phone call    | x         | x        | x         | x           |

i. If enrolled
j. Ophthalmic examinations include: slit lamp examination; tonometry, indirect ophthalmoscopy and retinal biomicroscopy.
k. Quality of Life Assessed using the 25-Item NEI Visual Function Questionnaire
l. For subjects that withdraw from the study at any time before visit 9.

**Statistical Methods**
Sample size calculations were based on the pilot study as described in detail above and in Figure 5. Briefly, the null hypothesis being tested in this trial is that there will be no change in measures of visual field upon treatment. An effect of 50% positive increase in VF annually will provide 90% power for a significance level of $p<.05$. Data will be analyzed using student t tests (paired and unpaired). Multiple predictor regression models will be created using exponential change (to better approximate normality) in VF area, visual acuity, color contrast sensitivity, ERG amplitude and central foveal thickness as outcomes. Predictor covariates will be age, age at presentation, VF area at baseline, genotype, inheritance pattern, current rate of annual VF loss (predicted from baseline and screening visits), average serum VPA value and dose of VPA. Analysis will be performed based on an intention to treat analysis.

The relationship between VPA dosing and efficacy as measured by change in VF from baseline will be assessed in cohort 2 at total daily dose levels of 500 mg; 750 mg and 1000 mg via AUC analysis. A secondary objective will be to investigate the relationship between serum VPA concentrations and efficacy in the entire study group.

**Premature Discontinuation**

Subjects who do not complete the full schedule of evaluations will be considered to have prematurely discontinued the clinical trial. The reasons for premature discontinuation will be documented. Subjects who elect to prematurely discontinue participation may be considered for re-entry into the study at their request. Potential reasons for premature discontinuation include: grade 3 or 4 toxicity judged to be possibly or probably related to study therapy, or the development of other unexpected, life-threatening complication not described; patient noncompliance with study procedures; voluntary withdrawal; termination of the study by a Principal Investigator, the Data Safety Monitoring Board, or the Food and Drug Administration. Subjects may voluntarily discontinue their participation prematurely without prejudice. Subjects who withdraw from the study will be asked to return to the study center to complete an early withdrawal visit.

**Detailed Methods for Visual Function:**

**Visual Field**

Visual field measurements will be made as described for patients with severe vision loss (Nowomiejska et al., 2005; Nowomiejska et al., 2008) using the Octopus 101 (Haag-Streit International) with the semiautomatic kinetic perimetry (SKP) module. Stimuli of selected size and luminance according to the Goldmann classification are moved along user-defined vectors having a constant angular velocity of 3° per second. Vectors are drawn manually using an electronic pen. The stimulus is moved almost perpendicularly towards the presumed scotoma border from nonseeing towards seeing areas of the VF. Fixation is monitored by a digital infrared camera, which provides a highly magnified image of the tested eye. The stimulus movement along each vector is terminated by the response of the patient, who is instructed to look straight ahead at the fixation point (green cross) and press a button as soon as the stimulus is perceived. The respective stimulus location is marked on the screen automatically by the software with a size- and intensity-specific symbol, and after several repetitions with different vectors, the symbols are connected, and enabling isopters are drawn in selectable color. The area enclosed by an isopter is automatically quantified by the software using triangulation in square degrees of eccentricity.

**Visual Acuity**

Although patients in this clinical trial may have severe loss of visual function, an attempt will nevertheless be made at measuring a best-corrected visual acuity. Testing in each eye will use standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. If the patient cannot read at least three of the letters of the first line correctly, the chart distance will be progressively halved from the standard 4 m until either the first line is correctly read or the shortest distance of 0.5 m is reached. The measurable range of visual acuity will be 20/20 or better to 20/1600. Patients who are unable to read any letters on the chart will be tested for light perception and if they can perceive light they will be assigned the acuity score equivalent of 20/3200.

**Color Contrast Sensitivity**

The ChromaTest psychophysical vision testing system (CH Electronics) will be used to measure color contrast sensitivity. For this test the subject is seated at a fixed distance from a large format standardized and calibrated NEC Spectraview LCD monitor. Alphabetical letters displayed on a background of equiluminance at a constant angle and size create an image that tests the central 6.5 degrees of the retina. The computer finds the endpoint of the test by a Modified Binary Search method; if response is correct, on the next presentation the color difference between letter and background is halved. If response is incorrect, the color contrast is doubled. Incorrect responses prolong the test, but do not influence the final threshold. This method of determining thresholds leads to finite steps which reach a plateau at the color contrast sensitivity threshold at a test sensitivity of 1% (Wong et al., 2008).

**Optical Coherence Tomography (OCT)**
Spectral –domain OCT (Spectralis –Heidelberg Engineering) will be used to estimate the existence and the extent of retained photoreceptors. In patients with stable fixation, the OCT studies will involve groups of raster scans to sample the retinal region of interest. The distance between the parallel scans (and thus the lateral resolution) will be 0.3 mm (~1 degree) and will cover a 18x12 mm² region of the retina centered on the fovea.

**Fundus Photography**

Photography (performed to minimize excess visible light exposure) will be performed at the screening visit and at the 12 month visit.

**Full-field Electroretinogram (ERG)**

Multi-focal full field ERGs (Veris, Electro-diagnostics Imaging Co.) will be performed. Special protocols for the recording of “submicrovolt” ERGs have already been used in two clinical trials that included patients with relatively severe forms of retinitis pigmentosa (RP). For this proposal, methods of recording submicrovolt ERGs will be similar to those previously used in very severe retinal degenerative diseases (Jacobson et al., 1998). Full-field 29 Hz flicker will be presented with the standard stimulus on the 7 cd.m⁻² white background and 100 sets of flicker trains consisting of three consecutive responses will be recorded. These sets will be repeated five times to obtain a measure of reproducibility.

**Quality of Life (QOL)**

QOL will be assessed using the 25-Item National Eye Institute Visual Function Questionnaire (Mangione et al., 2001). The questionnaire will be administered in an interview format at the baseline visit and at the 12 month visit.

**Genotyping Analysis**

The genotyping test will be done as a part of the eyeGene clinical research study at the National Institutes of Health (NIH). EyeGENE informed consent for genotyping and DNA diagnostics will be included in the trial consent form and will be approved by the University of Massachusetts Institutional Review Board. These completed consent forms will be sent to the eyeGENE coordinating center and clinical criteria for each participant will be entered into the eyeGENE online database prior to shipment of blood samples. 5–10 ml of whole blood will be obtained by routine phlebotomy using plastic vacutainers containing K2 EDTA. All samples will be stored exclusively at room temperature with overnight shipping. Participants will be screened for the most common RP mutations including: ABCA4, RHO, RDS, IMPDH1, PRPF31, PRPF3, RP1, PRPF8, NR2E3, TOPORS, RPGR, RP2, CNGA1, CRB1, C1QTNF5/CTRPS5, MERTK, PDE6A, PDE6B, RGR, RLBP1, RPE65, TULP1, CA4. Dr. Kaushal or Dr. Asdourian will provide pre and post-test genetic counseling to all participants.

**Serum VPA Assay**

Compliance is an issue in self administered study drug clinical trials. Medication monitoring will occur at every follow up visit. Patients will be instructed to bring prescription bottles to every visit for counting. Additionally, serum VPA levels will be assayed at regular intervals for bioavailability determination as well as validation of participant compliance to protocol. Serum concentrations will be assayed by a fluorescence polarization immunoassay system (Ax-Sym analyzer; Abbott Diagnostic Division, Irving, TX).

**Specific Aim 2**: Perform a genotype analysis of enrolled subjects in order to determine both the generalizability of this medication to all RP mutant types and to collect data on the possible mechanistic action of VPA

Retinitis Pigmentosa is technically a group of retinal dystrophic disorders characterized by multiple mutations in proteins such as rhodopsin, retinal pigment epithelium protein, GTPase regulator; ATP binding cassettes; carbonic anhydrase, an oxygen-regulated photoreceptor protein. The mutations are inherited in either an autosomal dominant, autosomal recessive or X-linked recessive fashion. The heterogenic nature of RP mutations makes correlating progression of disease with therapeutic benefit difficult. Recent clinical trials for RP generally classify patients according to gross class of disease without identifying or correlating treatment benefit with specific mutations involved (e.g. Bahrami et al., 2006; Merin et al., 2008; Radtke et al., 2008; Vingolo et al., 2008). It is likely given the vastly different nature of the proteins involved in this disorder, that certain therapies will have varying beneficial effects on patients with different mutations. Indeed our preliminary clinical analysis suggests a varied response to VPA among the 6 RP patients treated (Figure 4), and indicates that certain individual or patient populations may preferentially respond to this medication.

Our preliminary studies in vitro and in vivo also suggest that VPA may work at multiple levels as a retinal therapeutic. We have in vitro data to suggest that it works at the level of rhodopsin folding (Figure 1), which would indicate that only those patients with protein folding associated RP would benefit from this medication. However, other preclinical evidence suggests that VPA may work at the level of cell death protection (Figure 2) or inflammatory mediation (Chen et al., 2007; Dragunow et al., 2006; Kim et al., 2007) to exact its affect. Preliminary clinical data on patients with age related macular degeneration suggests that VPA may be beneficial to other ocular diseases that aren’t known to have protein folding pathway deficiencies (not shown), also supporting that VPA can work either on multiple pathways or in a protein folding
independent pathway. Patients included in our preliminary clinical analysis described above (Figure 4), were not well characterized in regards to their RP genotype. To examine this in more detail, we propose to perform molecular genotype analysis on each enrolled patient. Performing stepwise regression analysis adjusting for each mutation, we will correlate primary and secondary outcome measures with genotype to determine if VPA has a general benefit to all patients or if it effect is specific for certain populations of RP patients.

The genotyping test will be done as a part of the eyeGene clinical research study at the National Institutes of Health (NIH). After informed consent, blood samples will be collected from enrolled patients and mailed to the eyeGENE coordinating center where it will be screened for the most common RP mutations (see Detailed Methods). Due to the rarity and sporadic nature of the many mutations associate with RP, it is likely that specific mutation information will not be identified for over half of our enrolled patients, (Daiger et al., 2007; Daiger et al., 2008; Sullivan et al., 2006); however, the additional information gained from the patients that can be genotyped will be valuable in understanding the potential mode of VPA action and targeted effectiveness of therapy. Additionally, this information will be used to inform our escalating dose study in Aim 3.

Specific Aim 3: Perform an escalating dose trial in a sub cohort of selected patients with similar rates of vision loss and/or mutation profile.

If VPA proves to be an effective medication for ocular therapy, it will be important to establish effective therapeutic dosing windows. The myriad of proteins and mutations that give rise to RP lead to an inherent heterogeneity in patients in both presentation and progression, which can compound attempts to narrowly define therapeutic dosing windows. Utilizing the genotyping information from Aim 2, and/or the rate of vision function loss determined in the baseline screening, we can identify a standardized cohort of patients. In this cohort (cohort 2 – see Figure 7), we propose to perform a pilot analysis to define both dose response relationships and to identify effective dosing windows.

While over 25 genes have been associated with RP, by far the most studied is rhodopsin (RHO). Over 120 point mutations in RHO have now been identified. Although some of these mutations cause recessive RP and congenital stationary night blindness (CSNB), the vast majority cause autosomal-dominant RP (ADRP). ADRP is estimated to account for between 20 and 40% of all RP cases in the US. The most common ADRP mutations (about 26%), are characterized by mutations in the intradiscal, transmembrane and cytoplasmic domains of RHO, which result in misfolding of the protein, defined by the inability to form a functional chromophore with 11-cis-retinal. Published estimates (Daiger et al., 2007), and patient profiles from the primary recruiting site (UMMMC Ophthalmology clinic), coupled with the tendency for family groups to co-enroll in these kinds of trials, we estimate that we will enroll approximately 10 patients with RHO associated ADRP. Since these patients are likely to define the largest majority of patients enrolled in our study, we project that patients with RHO associated ADRP mutations will be enrolled in the escalating dose phase as cohort 2.

However, there are several scenarios that could occur that may make it unlikely for us to form the second cohort based on mutational analysis alone. We may not get adequate genotyping information on enough of the enrolled participants (if for example many of our enrolled patients have rare or as of yet unidentified mutations), alternatively and additionally, the enrolled patient population that can be genotyped may have a wide mix of mutations. Finally, it has been shown previously the rates of vision function loss for RP patients with similar or even identical mutations may vary considerably (Berson et al., 2002). If initial results disallow a second cohort to be formed based on common mutations, then we will form the second cohort based on similar disease progression as determined by the linked historical control analysis performed prior to the start of study medication. In this manner, we hope to assure a standard population of participants in which to perform the dosing analysis.

### Table 2: Recommended Starting VPA Dosage Schedule for anti-convulsant therapy.

<table>
<thead>
<tr>
<th>Pounds (lbs)</th>
<th>Kilograms (Kg)</th>
<th>Total Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 - 54.9</td>
<td>10 - 24</td>
<td>250</td>
</tr>
<tr>
<td>55 - 87.9</td>
<td>25 - 39.9</td>
<td>500</td>
</tr>
<tr>
<td>88 - 131.9</td>
<td>40 - 59.9</td>
<td>750</td>
</tr>
<tr>
<td>132 - 164.9</td>
<td>60 - 74.9</td>
<td>1000</td>
</tr>
<tr>
<td>165 - 197.9</td>
<td>75 - 89.9</td>
<td>1250</td>
</tr>
</tbody>
</table>
Providing there were no serious adverse events at the initial dose and DSMB approval, cohort 2 will receive a dose of 250 mg VPA TID during month 6-9 of the study; if the safety and tolerability profile at this dose remains favorable and DSMB approves, this dose will then be escalated to 250 mg QID for months 6-9 (Figure 7). This is still within and likely below the drug dosing guidelines for this medication (Table 2). Serum VPA and safety measures in our standardized population of cohort 2 will be monitored closely (see Table 1).

While there is no established relationship between mean VPA plasma concentration and clinical response for anticonvulsant therapy (Gram et al., 1979), it is possible that for this indication of retinal therapy, such a relationship can be established. Serum VPA levels will be collected from all enrolled patients (cohort 1 and 2) at all visits starting at week 3. These levels will be correlated with primary outcome measures to determine therapeutic dosing windows and dose response relationships.

**Timeline and Milestones:**
We have been extremely rigorous in our estimation of the timeline for this study. This estimated timeline is based on Dr. Kaushal’s extensive prior experience in vision based clinical trials and our consultation with relevant and appropriate officials and researchers as described above. Dr. Robert Brown in particular has scrutinized this study in regards to the proposed timeline and feels that it fits well within this funding window (see Letter of Support). However, in the event that the timeline for this proposed study extends beyond the 2 year funding window, we have already lined up the FFB as a source of funds to complete the trial (see Letter of Support). If, as we fully expect, this trial is completed by September 2011, then the FFB has expressed interest in funding a new protocol for continued long term follow up of these participants.

**Timeline – Current and Projected Ongoing Milestones**

<table>
<thead>
<tr>
<th>Pre-Clinical and Preliminary Clinical Evaluation</th>
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<tbody>
<tr>
<td>Pre-clinical assessment of VPA’s effect on cellular rhodopsin folding</td>
<td>January 2008- January, 2009</td>
</tr>
<tr>
<td>Pre-clinical assessment of VPA’s protection of cells from apoptosis</td>
<td>February, 2008 – January, 2009</td>
</tr>
<tr>
<td>Dr. Kaushal treats several RP patients off label with VPA at the University of Florida</td>
<td>January 2008-December 2009</td>
</tr>
<tr>
<td>University of Massachusetts IRB approval for retrospective chart review of RP patients treated with VPA</td>
<td>February, 2009</td>
</tr>
<tr>
<td>Abstraction of pilot data on Visual Field measures and statistical analysis for study design</td>
<td>February -April, 2009</td>
</tr>
</tbody>
</table>

**Institutional Regulatory Requirements**

| Dr. Clemson communicates with Brian O’Sullivan, MD chair of University of Massachusetts Medical Center IRB to discuss specifics of clinical trial | February, 2009 |
| Drs. Kaushal and Clemson submit full proposal to UMMMC IRB | June, 2009 |
| IRB Approval of Phase II Clinical Trial | August, 2009 |
| Data, Safety and Monitoring Board Convened | December, 2009 |

**CDER/FDA Interactions**

| Pre-IND teleconferences with Wiley Chambers, M.D., deputy | January, February, March and April, May, June, 2009 |
Drs. Kaushal and Clemson submit expedited IRB proposal to the FDA  | July, 2009

FDA approval for Phase II Clinical Trial  | August, 2009

**Subject Recruitment**

Dr. Kaushal currently has about 20 RP patients who would be appropriate for this trial, and receives weekly calls from RP patients seeking new treatment options.  | Ongoing

Meeting with Steve Rose, PhD Chief Research Officer, Foundation For Fighting Blindness to discuss recruitment support (see Letter of Support)  | March 30, 2009

Advertise at UMMMC, and the Foundation for Fighting Blindness website and email list and the Research to Prevent Blindness website  | September, 2009

List trial in Clinicaltrials.gov  | September, 2009

Begin Screening of potential subjects  | September, 2009

Enroll first patients  | October, 2009

Screening of potential Subjects (we estimate need to screen total of 50 patients)  | September, 2009 - April, 2010

Final Patient Enrolled (enroll 45 patients assuming 10% loss to follow up)  | May, 2010

**Baseline Evaluation**

Enrolled patients receive baseline evaluations  | October, 2009 – June, 2010

Last patient in receives baseline evaluation  | June, 2010

**Therapeutic Intervention/Outcome Measures**

First Enrolled patients begin oral VPA  | January, 2010

Last Enrolled patients begin oral VPA  | May, 2010

Patients return for periodic follow up/clinical assessments according to schedule (see Table 1)  | January 2010 – May, 2011

**Genotype Profiling and Analysis**

Serum samples sent to EyeGene for mutational analysis  | October, 2009 – May, 2010

Expected results returned from genotyping  | February 2010 – November 2010

**Dose Escalation Analysis**

A standardized cohort of already enrolled subjects with similar mutation profiles and/or progression patterns is  | July – Nov 2010
<table>
<thead>
<tr>
<th>defined as cohort 2</th>
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<tbody>
<tr>
<td>Cohort 2 dosing increased to 250 mg TID</td>
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<tr>
<td>Cohort 2 dosing increased to 250 mg QID</td>
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<table>
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<th><strong>Safety Assessments</strong></th>
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<tr>
<td>Patients routinely screened for adverse events with follow up phone calls, safety labs and clinical assessment (see Table I)</td>
</tr>
<tr>
<td>DSMB reviews patient records and clinical outcomes for first dose escalation proposed cohort 2</td>
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<tr>
<td>DSMB reviews patient records and clinical outcomes for second dose escalation cohort 2</td>
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<tr>
<td>DSMB reviews patient records and clinical outcomes for second dose escalation cohort 2</td>
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<table>
<thead>
<tr>
<th><strong>Statistical and Data Analysis</strong></th>
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<tr>
<td>Dr. Clemson consults with institutional biostatisticians; Dr. Gerald Cagle at the National Neurovision Research Institute and Dr. David Birch of the Retinal Foundation of the Southeast on study design</td>
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<tr>
<td>Dr. Clemson utilizes preliminary clinical data to finalize clinical trial design</td>
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<tr>
<td>Baseline and Screening Control Data assessed for cohort 2 definition</td>
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<tr>
<td>Analysis of 6 month primary outcome measures as predicted by RP mutation for definition of cohort 2</td>
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<tr>
<td>15 month follow up visit and safety assessment</td>
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<tr>
<td>Data analysis</td>
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</table>
References


**Protection of Human Subjects**

**Human Subjects Research** Yes  
**Exemption** No  
**Clinical Trial** Yes  
**NIH-Defined Phase III Clinical Trial** No

Protection of Human Subjects  
This Human Subjects Research meets the definition of a clinical trial.

**Inclusion of Women and Minorities**  
Retinitis Pigmentosa is a disease caused by a variety of mutations. This is a rare disorder that tends to run in families, so recruitment efforts will likely result in a homogenous population. Because of X-linked forms, men are affected at a slightly higher rate than woman. Women will not be excluded from this study. We anticipate enrolling women who are not pregnant or lactating, and will agree to contraception if of childbearing capacity. While most ethnic groups are affected by RP, in the United States, RP cases are predominantly Caucasian. We would not refuse anyone admission with another ethnic or racial group.

**Targeted/Planned Enrollment Table**

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<th>TARGETED/PLANNED ENROLLMENT: 45</th>
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<tr>
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</tr>
<tr>
<td>Ethnic Category Total of All Subjects*</td>
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</table>

| Racial Categories |
### Participation of Children
The age range for the onset of vision loss in most individuals with RP is over 18 years of age. Additionally, the risk of the study medication is significantly greater in children. Thus no attempt will be made to include children younger than 18 in this study.

### Protection of Human Subjects

#### Risks to Human Subjects

a. Human Subjects Involvement and Characteristics
The proposed clinical trial is open-label, single and escalating dose oral VPA treatment. The Phase II clinical trial using VPA will assess efficacy and safety measures. VPA has a well documented and established safety profile given that it has been used for other indications for over 30 years. The 45 human subjects who will be included in the proposed clinical trial will be males and females who have been diagnosed with RP, 18 years of age and older, who do not have any diseases or conditions contraindicated for VPA administration.

#### Inclusion Criteria:
- Understand and sign the IRB-approved informed consent document for the study.
- Age ≥ 18 years.
- Diagnosis of Retinitis Pigmentosa including photoreceptor degeneration established by reduced visual acuity, visual field constriction, night blindness, marked reduction of rod and cone ERG responses, and presence of intraretinal “bone-spicule” pigment on clinical examination.
- Willingness to comply with the protocol.

#### Exclusion Criteria:
- Medical problems that make consistent follow-up over the treatment period unlikely (e.g. stroke, severe MI, end stage malignancy), or in general a poor medical risk because of other systemic diseases or active uncontrolled infections.
- Other retinal diseases: Glaucoma, retinal inflammatory disease, macular edema, cataract or herpes simplex virus of the eye.
- Diabetes or cancer.
- A hemoglobin concentration of less than 8 gm/dL a platelet count of less than 75K/mm(3) or an absolute neutrophil count of less than 500/mm(3) at study entry.
- Liver disease determined by an alanine aminotransferase (ALT) aspartate aminotransferase (AST) or bilirubin 2.5 times greater than the upper limit of normal.
- History of pancreatitis by clinical features and/or laboratory abnormalities in the last 12 months.

### Table: Racial Categories: Total of All Subjects

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<td><strong>Racial Categories: Total of All Subjects</strong></td>
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<td>45</td>
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</table>
• Renal dysfunction determined by a calculated urine creatinine clearance of less than 60 mL/min in adults or using the Schwartz formula or Levy formula based on serum creatinine.
• Patients clinically suspected of suffering from urea cycle disorders will be excluded.
• Patients with history of seizure disorders and/or those already receiving valproic acid or other anti-convulsants will be excluded.
• Sensitive to or have ever had an allergic reaction to Valproic Acid.
• Female adults who have attained menarche must have a negative pregnancy test at study entry and commit to using an acceptable method of barrier or hormonal contraception.
• Lactating mothers who are breast feeding their babies will not be eligible.
• RP patients involved in other clinical trials within the last 3 months are ineligible for this study.

**Adequacy of Protection Against Risks**

*a. Recruitment and Informed Consent*

Patients will be recruited from the Department of Ophthalmology at the University of Massachusetts Medical Center and through the Foundation Fighting Blindness disease specific web site and email blast. This protocol will be listed in the Clinical Trials Data Bank of the NIH. Potential study patients who demonstrate an interest in participating in the study will receive an explanation of the terms, procedures, and requirements of the study from an investigator of the research team in language they can understand. They will receive a copy of the Informed Consent Form to read and share with family or friends. Subsequently, an investigator will answer questions and request the patient's permission to participate in the study. Volunteer participants who sign a study-specific patient informed consent form approved by the Institutional Review Board will then be scheduled for a screening evaluation to determine their eligibility. Children under 18 are not included in this study.

*b. Protections Against Risk*

The subjects will be informed of possible consequences of the study from one of the investigators in language they can understand. They will be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. They will be asked to follow-up with necessary safety evaluations if they have received study agent prior to their desire to withdraw. They will be given full information regarding potential side effects of VPA and the procedures involved. The medical history and physical examination performed prior to study agent administration will identify patients with medical conditions that would increase the risks associated with study procedures and those subjects will be excluded from participation. The administration of the study agent and all procedures related to the study will be performed by trained and licensed medical and health professionals. They will be provided with contact numbers for any questions or concerns arising regarding the possible effects of the VPA and encouraged to call if they feel that an adverse event is occurring. In the event of an adverse event associated with the clinical trial, immediate medical care will be provided.

Patients will be followed closely, especially in the first 6 months for known adverse reactions to VPA. Safety labs regarding liver and pancreas toxicity will be drawn prior to and periodically during dosing with VPA. Results of all laboratory and safety exams performed to ensure subject eligibility and safety will be reviewed by an investigator during the study. Subjects with known risk factors such as liver disease, pancreatic conditions, metabolic disorders, organic brain diseases, seizure disorders and those on anti-convulsants will be excluded from the study. Female subjects of child bearing potential must have a negative pregnancy test at
the baseline visit and prior to study agent administration. Female subjects of reproductive ability must be willing to use effective contraception for the duration of the study, one year. Lactating mothers will not be included in this study. We will not include children under 18 in this study.

Confidentiality will be assured by limiting access to the subject database to key research personnel. Individual identifiers will be stored in the computerized database and will also be the only identifier on analyzed and stored subject specimens. Access to the database will be controlled by a user code. The log identifying the subject names with the subject numbers, as well as Case Report Forms, Informed Consent Forms, laboratory study reports, and demographic profiles will be kept locked in an investigator’s office. The subjects will be informed of the information stored and the review of that information by the DSMB, U Mass IRB, and U Mass clinical facility personnel, Data Management and Statistical personnel, research staff, and personnel performing the procedures.

The Data Safety Monitoring Board (DSMB) will be established with members who have an understanding of the disease, ethics, and biostatistics. They will review the study results and notify the PI of their findings and recommendations for study continuation or modification. The DSMB will be charged with monitoring the conduct of the trial and assessing patient safety on an ongoing basis. This group will review all safety data, including serious adverse events, adverse events, and laboratory data. Confidentiality of the subjects will be maintained in the process of review by the DSMB. The DSMB will provide committee recommendations after each review. Adverse events will be reported to the IRB, NIH, and FDA as regulated to insure the safety of subjects.

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines.

Potential Benefits of the Proposed Research to Human Subjects and Others
There is no currently available treatment for RP. Based on the preclinical and preliminary clinical efficacy data, there is potential that oral VPA may provide some degree of improvement in visual function in some of the individuals participating in this study. However, the likelihood of achieving any benefit, and the degree of any benefit that may occur, is unknown.

Importance of the Knowledge to be Gained
Currently there is no cure for the retinal degeneration that occurs in RP. Determining the efficacy of oral VPA has the potential for improving vision in RP patients who are most certainly going blind.

Data and Safety Monitoring Plan
The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines.

The procedures outlined in the protocol and case report forms will be carefully reviewed by the Principle Investigators and staff prior to Study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and well being of subjects.

Amendments will be submitted to the IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject,
the Informed Consent form will be revised and if applicable, subject’s consent to continue participation will again be obtained.

To ensure safety of human subjects and integrity of data in this trial, a data and safety monitoring plan will be established. The levels of monitoring will include:

Dr. Shalesh Kaushal, MD, PhD as Principal Investigator, will continuously monitor patient safety and be responsible for reporting serious and unexpected adverse reactions as regulated to the FDA, DSMB and IRB. The DSMB will provide safety oversight of the trial, to monitor the progress of the study, and to recommend modification of the trial, as appropriate. The DSMB will review safety data after the first month of oral dosing and at regular intervals. Serious and unexpected adverse reactions will be reviewed by the DSMB or subcommittee.

Approval of the IRB will be obtained before enrolling subjects in this clinical trial. Following the beginning of enrollment, the IRB will conduct continuing reviews of the trial at intervals appropriate to the degree of risk to human subjects.

The degree of certainty with which an adverse event is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drugs as drug related

A detailed Data and Safety Monitoring Plan will be submitted to the IRB prior to the accrual of human subjects.

ClinicalTrials.gov Requirements
The application includes a trial which requires registration in ClinicalTrials.gov. The clinical trial will be registered in ClinicalTrials.gov when IRB approval has been received.

Inclusion of Women and Minorities
A section heading entitled "Inclusion of Women and Minorities" has been placed immediately following the "Protection of Human Subjects" section.

b. Sources of Materials
Research material obtained from identifiable living human subjects includes reports of: history and physical assessments, blood, urine, pregnancy tests, perimetry, optical coherence tomography, visual acuity measurements, color contrast sensitivity and electroretinography measurements, clinical assessments, adverse events, and autopsies. Copies of case report forms, original test results, subject medical records, signed subject informed consent, correspondence, and any other documents of the subjects, relevant to the conduct of the study will be kept on file by the principal investigator. All material or data collected as part of the study will be obtained specifically for research purposes.

c. Potential Risks
Potential risks to study subjects include the well known and characterized risks associated with administration of the therapeutic agent and with study procedures.

Valproic acid can cause serious and fatal hepatotoxicity especially in individuals with liver disease, organic brain disease, serious seizure disorders, congenital metabolic disorders, those on multiple anticonvulsants and children under the age of 2. Therefore individuals with contraindicating diseases and concomitant medications as well as children under 18 will be excluded from this study. The risk of hepatotoxicity usually occurs within the first 6 months of treatment and decreases considerably in older age groups. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting.

Valproic acid can cause serious and fatal pancreatitis. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms such as abdominal pain, nausea, vomiting, and/or anorexia to death. Cases have been reported shortly after initial use as well as after several years of use.

Valproate can produce teratogenic effects such as Spina Bifida, therefore woman of child bearing potential will be screened for pregnancy prior to administration of the study agent and must maintain use of contraception during the study period.

The risks associated with ophthalmic procedures include redness, discomfort or allergic reaction to topical medications used to dilate the pupil prior to visual function tests. High blood pressure, cardiac dysrhythmias and closed angle glaucoma may be exacerbated by some of these medications and light sensitivity may be experienced when the pupil is dilated. Corneal abrasions may result from the contact lenses used in performing electroretinography testing. The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.
Multiple PI Leadership Plan

Shalesh Kaushal, MD/PhD is the surgeon in the currently NIH funded (National Eye Institute) study entitled “Clinical Trials of Gene Therapy for Leber Congenital Amaurosis”, and is the first investigator to use complement inhibitor molecules to treat patients. He is an internationally known clinician and researcher and will be responsible for all clinical aspects of this project. He will oversee the screening, treatment and follow up of the subjects. Dr. Kaushal will be responsible for supervision of clinical personnel. Dr. Kaushal will be responsible for adverse event assessment and reporting. He will form and report to the Data, Safety and Monitoring Board (DSMB). Dr. Kaushal will serve as the contact PI.

Christine Clemson, PhD is also uniquely poised to be a new investigator with PI responsibilities. She is an established and highly regarded Cell Biologist. She is currently part of an elite group of professionals being trained to run clinical studies in the Master of Science in Clinical Investigation Program at the University of Massachusetts Medical School. The purpose of this program is to train promising researchers to translate basic science findings to the clinic. This program is a direct result of the NIH’s strategic direction towards this goal. This application is an important benchmark in Dr. Clemson’s transition to an independent investigator. Dr. Clemson will be responsible for all aspects of experimental design, data analysis, and all project management and administrative responsibilities. Dr. Clemson will be responsible for supervision of personnel related to these roles. She will be responsible for overseeing recruitment outreach and milestone monitoring. Dr. Clemson will be responsible for submission of progress reports and all communication with the NIH, FDA, and IRB.

Dr’s. Clemson and Kaushal will be jointly responsible for project direction and progress, and they will communicate daily by phone, email or in person. They will work together on any proposed changes in research direction and redirection of funds necessary. They will each share their results with each other and key personnel. They will jointly publish results from this study.
Budget Justification

Personnel

Shalesh Kaushal, M.D. PhD. (30% effort, 3.6 cal. mos.) will serve as a Principal Investigator of this study providing oversight for all aspects of the design and performance of the clinical treatment. He will oversee and participate extensively in the screening of participants, and will make the ultimate determination of whether a recruit is a suitable subject. Dr. Kaushal will be involved in the baseline and ongoing follow up assessments of all participants, and will interact closely with the creation of and communication with the DSMB. Dr. Kaushal will be responsible for assessing and reporting adverse events, as well as closing monitoring the clinical and serum profiles of the second cohort on escalating dosages. Dr. Kaushal will provide pre and post test genetic counseling to participants who choose to be genotyped. Dr. Kaushal has had extensive experience in ocular clinical research and treated the patients in the preliminary clinical phase. Dr. Kaushal is the surgeon in the currently NIH funded (National Eye Institute) study entitled “Clinical Trials of Gene Therapy for Leber Congenital Amaurosis”, and is the first investigator to use complement inhibitor molecules to treat patients. *The actual institutional base salary for Dr. Shalesh Kaushal exceeds the current NIH rate allowed, however the salary requested is within the rate authorized by the NIH.

Christine Clemson, PhD. (50% effort, 6 cal mos.) will serve as a Principal Investigator of this trial, providing oversight for all aspects of the design and performance of this project. In particular, Dr. Clemson is responsible for the pre-clinical analysis, clinical trial development and details, and all regulatory applications and reporting. Dr. Clemson is completing an intensive 2 year Masters Program in Clinical Investigation. Dr. Clemson is combining this professional development with her 15 years of experience as a cell biologist to implement a “translational” approach to this clinical trial. Her unique and broad set of skills is instrumental in the unique multi-layered study design which will allow a wealth of information on efficacy in RP patients in general and within specific mutation populations, as well as dose response and therapeutic dosing windows all within a relatively short period of time.

She will also serve as the primary data analyst and will carry out the quantification of the diagnostic tests including visual field perimetry, visual acuity, Color Contrast Sensitivity, ERG and QOL. The unique design and compressed timeline of this clinical trial allows much information to be extracted in a short period of time, so the success of this design hinges on rapid acquisition and analysis of the data.

*The actual institutional base salary ($51,200) for Dr. Christine Clemson reflects her current status as a graduate student. Dr Kaushal, as Chair of the Ophthalmology department, has begun the process of promoting her to Asst. Professor, a position commensurate with her multiple degrees and length of experience. The $98,000 salary requested reflects this impending promotion and is within the rate authorized by the NIH for this position.

George Asdourian, M.D. (20% effort, 2.4 cal mos.) as a co-investigator, will aid in the screening and baseline measurements of all participants, as well as help perform clinical diagnostic follow up of participants during the study. Dr. Asdourian will help provide pre and post test genetic counseling to participants who choose to be genotyped. Dr. Asdourian has been a practicing ophthalmologist for 30 years, and has been the Director of Retina Service in the Ophthalmology program at UMMC for over 20 years, as such he has extensive experience as a clinician.
*The actual institutional base salary for Dr. Asdourian exceeds the current NIH rate allowed, however the salary requested is within the rate authorized by the NIH.

Margaret Humphries, R.N. (20% effort, 2.4 cal mos.) will serve as the nurse/coordinator, working with the Principal Investigators, in the design of the clinical trial, case report forms, standard operating procedures, interacting with and reporting to NIH, DSMB, IRB and FDA. She will be training personnel involved in the clinical trial, arranging parts of the study visits, organizing and assisting with procedures, reporting data, and interacting with Judith Colbert, the trial administrator. Margaret has extensive experience in this capacity and is currently the senior research nurse on the NIH funded (National Eye Institute) study entitled “Clinical Trials of Gene Therapy for Leber Congenital Amaurosis”.

Judith Colbert, R.N. (30% effort, 3.6 cal mos) will serve as the trial administrator performing and overseeing many diagnostic procedures. She will perform the visual acuity and color contrast sensitivity testing of all participants, and she will supervise the technicians performing the extensive ocular imaging.

Elena Filippova, MD. (30% effort, 3.6 cal mos) will serve as the clinician/research technician responsible for genotyping and drug dosing analysis. She will be responsible for registering subjects with the NIH eyeGENE clinical coordinating center, collecting and coordinating NEI required participant documentation for all recruited patients; she will oversee the collection, storage and shipment of all blood samples for genotyping. Dr. Filippova will also be responsible for collecting and collating data on serum VPA levels for all patients, and for the escalating dosing in cohort 2; she will be responsible for reporting results back to principal investigators.

Julie Wilson, (30% effort, 3.6 cal mos.) will serve as one of the ophthalmic imagers and technician. Julie is highly trained on the imaging equipment that will be used during this study including static and kinetic perimetry, fundus photography, optical coherence tomography and submicrovolt ERG.

Additional ophthalmic imager and technician (25% effort, 3 cal mos.) to be named later will be needed for the extensive diagnostic imaging that will be used during this study including static and kinetic perimetry, fundus photography, optical coherence tomography and submicrovolt ERG.

Biostatistician (4% effort, .48 calendar months) A senior biostatistician to be named later will be hired from the University of Massachusetts Medical School Quantitative Health Sciences Core Facility to consult with Dr. Clemson.

Travel. Year 1: For the PI or Co-PI to attend and report at scientific meetings. Year 2: For the PI and Co-PI to attend and report at scientific meetings.

Patient Care: The costs of safety labs (liver, renal and pancreatic function screening, CBC, chem7), pregnancy tests, VPA serum levels and supplies for preparing and mailing genotyping blood samples are included for the first and second year.

Supplies: The cost for participant stipends and pharmacy set up in the first year and pharmacy maintenance and study medication (Valproic Acid) is included in the first and second year.
# 4.5.1 Challenge Grant Budget

<table>
<thead>
<tr>
<th>Name</th>
<th>Role on Project</th>
<th>Clinical Employee (YR)</th>
<th>% of Time</th>
<th>Typi. Appointments</th>
<th>Inst. Salary</th>
<th>YR 1 CAL MOE % EFFORT</th>
<th>YR 2 CAL MOE % EFFORT</th>
<th>YR 3 CAL MOE % EFFORT</th>
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**Other REG Personnel**

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**Other REE Personnel**

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**Salary Totals:**

- Other REG Salary: 11,000 + 18,128 + 31,129 = 60,257
- Other REG Fringe: 4,865 + 4,865 + 3,154 = 12,884
- Other REG Total: 60,257 + 12,884 = 73,141

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210
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**TOTAL PROJECT COSTS (Direct + Indirect):** $497,599
4.6.1 FOUNDATION FIGHTING BLINDNESS/NATIONAL NEUROVISION RESEARCH INSTITUTE BUDGET
**CHAPTER 5: ALTERNATIVE STUDY DESIGNS**

**5.1 DELAYED START DESIGN**

In considering study design, I borrowed from the wealth of literature on Parkinson’s Disease (PD) trials. I first contemplated a delayed start design. This design is similar to a crossover design with some important differences. In a progressive neurodegenerative disorder it is important to tease out the symptomatic effects (like reducing inflammation) from the long term pathophysiology of the disease (like death of the photoreceptor cells). A crossover design has the potential to only measure the symptomatic effect in both arms since overall treatment time in both arms is shortened relative to other designs. This shortened time frame is may not allow enough time for the main outcome (ie. significantly fewer cells dying on treatment). A delayed start design overcomes the complications of the crossover design and directly addresses symptomatic benefit versus neuroprotection. I modeled my design after the PD ADAGIO study (Olanow et al., 2008). The basic outline of this model (see Figure 1) is to divide the subjects into two groups. The first treatment group receives the intervention for the entire 12 months, while the second group receives the placebo for the first 6 months. At 6 months, the control group would then be given the intervention for the remaining 6 months of the trial. If the treatment provides merely a symptomatic benefit, then the outcome in the treated and control group would be indistinguishable. If however, the study drug was neuroprotective, then the control group would never “catch up” to the treatment group. Ultimately I decided that symptomatic benefit in RP was not as big of a concern as in PD, so I abandoned the delayed start design.

Figure 1: Delayed Start Design
5.2 Futility Study

A futility study is another trial design borrowed from PD literature (see Figure 2). This kind of study is generally used to rule out therapies with modest hypothetical effects on outcome measures. They are typically short trials (6 to 18 months) and relatively inexpensive since historical controls are used for comparisons (Voss and Ravina, 2008). These studies are well powered for their small sample size as their goal is to quickly rule out interventions (ie. prove futility), not prove efficacy. Ultimately given the large effect on outcome predicted by our pilot analysis, this design was abandoned for a modified design (the one armed self controlled study below) that targeted efficacy.

5.3 One Armed Self-Controlled Study

Given the promising nature of the pilot analysis, the futility study was abandoned in favor of a design that was powered to elucidate efficacy. The historical control aspect was retained and modified, however to allow for a longitudinal analysis of baseline rate of vision loss for each subject (Figure 3). Given the heterogeneity of the RP population, adequately controlling for the very different rates of vision loss that are associated with the different RP mutations (Berson et al., 2002; Hartong et al., 2006; Sandberg et al., 2005; Sandberg et al., 2007; Sandberg et al., 2008) was a significant concern. This is the design that was developed and explained in detail in the Challenge Grant Application (Chapter 4, page 191). In brief, subjects would be followed for at least 3 months prior to the start of the study to ascertain their baseline rate of vision loss. This single arm of subjects would then be treated with the intervention for the entire 12 months. The follow up visual field area for each subject would be compared to their predicted loss (calculated from their current rate of vision loss).
loss ascertained during the longitudinal baseline analysis). Ultimately this trial design was abandoned in favor of the randomized placebo controlled design due to feedback from the FDA as described above in the introduction to Chapter 3 (page 40 above).

5.4 Stratified Randomization based on RP genotype.

With the abandonment of the longitudinal self controlled aspect of the trial design, the heterogeneous nature of the RP diseases was a primary concern. Reports in the literature illustrate the varying rates of vision loss associated with the different RP genotypes. For example, patients with X linked RP with RPGR mutations were found to have an annual rate of visual field loss of 4.7%, while those with the more common autosomal dominant RHO mutations have a predicted rate of loss of 2.9% (Sandberg et al., 2007). To address this we proposed a stratified randomization schema.

Patients included in our preliminary clinical analysis were not well characterized in regards to their RP genotype. To examine this in more detail, we proposed to perform molecular genotype analysis on each enrolled patient and target enrollment of approximately 20 patients with P23H opsin mutations.

The genotyping would be done through the NEI eyeGENE protocol as described in the protocol above (page 60). Getting these results quickly was important to the feasibility of this kind of design, and we made arrangements with Stephen Daiger, PhD, the director of the Laboratory for the Molecular Diagnosis of Inherited Diseases in Houston Tx, (which is one of the EyeGENE testing centers) to have our subjects samples expedited. Dr. Daiger estimated that he would be able to return genetic testing results within 3 weeks.

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**FIGURE 4:** RANDOMIZATION SCHEME
Accounts for a maximum of 45 patients per arm with no attempt to balance arms

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Strata 1

- ADRP

Strata 2

- Randomized
- Group: Placebo, VPA
- Capsule Code: A, B

Other forms RP

- Randomized
- Placebo, VPA
- Capsule Code: A, B
The block randomization would be stratified based on RP genotype (see Figure 4). The rationale for randomizing within the blocks is to more evenly distribute patients between the two experimental groups (VPA vs. placebo) and possibly eliminate differences in disease progression rates due to different mutations.

Ultimately this stratified randomization was abandoned due to the FDA’s concern over generalizability and reduction in power associated with this kind of recruitment schema.

References


CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 GOAL 1: TO LEARN THE INSTITUTION INDEPENDENT CLINICAL TRIAL DEVELOPMENT PROCESS

6.1.1 STRENGTHS
The first goal of this project was to learn the institution independent clinical trial development process. I took this project from a pilot study to the final IND submission. In doing this I considered and incorporated multiple study designs, established connections with personnel at the FDA and pharmaceutical companies and authored both a protocol and complete case report form data set. The measures of my accomplishment toward this goal include a successful IND submission, three approved IRB applications with associated consent forms and two submitted clinical manuscripts.

6.1.2 FUTURE DIRECTIONS
There were areas of drug development and human studies that were not covered in this project. The initial in vitro and animal pharmacokinetic and safety studies, both short and long term were circumvented in this project due to the nature of the study drug. Additionally, first in human Phase I and early Phase II studies were not necessary with this abbreviated trial development process. These are important aspects of clinical studies that I hope to learn and experience in my next endeavor.

6.2 GOAL 2: INFORMAL AUDIT OF UMMC’S CORE CAPABILITIES
The next goal of this project was to understand and annotate the resources available at our institution for investigator initiated clinical trials. To this end I collected a series of observations and recommendations to aid the institution as we develop the infrastructure to help many investigators initiate clinical trials. Below are summaries of the recommendations detailed in the introduction sections to Chapter 1-4 above.

6.2.1 RECOMMENDATIONS CONCERNING THE IRB SUBMISSION PROCESS
- Centralize all information through a dedicated web portal with detailed, clear pathways for each step.
- All forms for each stage of the submission process should be linked to these steps.
- Electronic submission of forms will alleviate the administrative complications and confusion.
- Online sample templates of protocols and case report forms (which are difficult to acquire due to intellectual property issues) should be available through the web portal.

6.2.2 RECOMMENDATIONS CONCERNING THE RESEARCH PHARMACY
- Drug source information needs to be centralized and readily accessible.
- Outsourcing contacts for drug and placebo manufacture need to be developed and available as resources for investigators.
The Research Pharmacy is understaffed and given inadequate resources for their existing capabilities. If the expectation is that they will be instrumental in the strategic push towards more clinical trials, this inadequacy needs to be addressed through hiring of more personnel and investment in equipment and space.

6.2.3 RECOMMENDATIONS CONCERNING BIOSTATISTICAL SUPPORT

- Dedicated core biostatisticians are needed.
- These professionals are needed continuously throughout the entire dynamic process and should be able to immerse themselves in the relevant literature pertaining to the particular disease, outcome measure and testing equipment.
- These biostatisticians should be part of the data management tool design process.
- Statistical outcome of the data once the trial is completed should be an integral part of the study design process.

6.2.4 RECOMMENDATIONS CONCERNING THE IND SUBMISSION PROCESS

- A detailed step by step description of the IND Process needs to be incorporated into the web portal resource for investigators.
- In-house experts on FDA processes should be developed and/or recruited and will be an important part of the internal FDA knowledge base development.
- Relationships with key personnel at FDA need to be established and continuously cultivated.
- The contact information for in-house and extramural FDA resources should be linked with every step in this pathway.
- Enterprise solution for electronic clinical trial reporting requirements to the FDA should be established now.

6.2.5 RECOMMENDATIONS CONCERNING CLINICAL TRIAL FUNDING

- Sample and template clinical trial budgets for NIH proposals should be available as these are quite different from “typical” NIH research grant budgets.
- Resources and forms associated with budget and contract negotiations need to be centralized and available through the web portal.
- Procedure and laboratory costs are critical for creating relevant clinical trial budgets and should be readily available and accessible through the web portal.

6.3 GOAL 3: TREATMENT FOR A BLINDING DISEASE

6.3.1 STRENGTHS

This was clearly the most important and relevant goal of this proposal. There was significant progress made toward this end. The pilot analysis revealed the potential to reverse loss of visual field, which is a staggering clinical outcome for a disease that previously had no therapy that significantly affected progression. Dr. Kaushal and the UMMC Ophthalmology community are now poised to implement this study protocol by virtue of the FDA and IRB”s approval. Additionally, the
manuscript in submission will inform others in the RP community of the potential benefit of this medication.

6.3.2 Future Directions
Efforts to procure funding for this trial are ongoing. The extensive costs associated with this large trial mean that no intervention can occur until funding is secured. We are actively pursuing both foundation and NIH funding. In retrospect, a smaller less expensive pilot study that incorporated standard of care treatment would have been a valuable interim measure. If prospects for funding the larger trial do not materialize, this will be an important future direction.

6.4 Intangibles Learned
In this thesis I have attempted to comprehensively annotate the steps and overall process needed to take a drug into the clinic for a new indication. There were four key lessons that may not be adequately documented in the applications and documents included above. These “intangibles” were hard fought lessons and are the final points that I feel are important to emphasize and pass on to others who may be embarking upon the process of the investigator initiated clinical trial.

1. Talk to the FDA early and often – an accessible, knowledgeable, decision maker is key!!!
2. “Perfect” study design often conflicts with what is feasible.
3. Small changes in the trial design/protocol can have large implications.
4. Despite #3, be open to changes in direction at EVERY point in the pathway.