Pilot Project Funding Opportunities

Nathaniel Hafer

University of Massachusetts Medical School

Et al.

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Pilot Project Funding Opportunities

September 20, 2012

Nate Hafer, PhD
Director of Operations
UMCCTS
Pilot & Collaborative
Translational & Clinical Studies

Programs

• Pilot Project Program (PPP)
• Life Science Moment Fund (LSMF)
• Pfizer CTI Program
• Next Hundred Million Pilot Projects (NHMPP)
UMCCTS Pilot Grant Programs 2009-2012

1. Life Sciences Moment Fund  $1.9M
2. Pilot Project Program   $2.4 M
3. WPI/UMMS Collaborative Pilot Project Program  $600K
Pilot Project Program

Specific Aims:

1. Stimulate the development of new clinical and translational inter- and multi-disciplinary teams
2. Provide novel support mechanisms for junior investigators
3. Increase the emphasis on pilot funding for community-based research
4. Develop new methodologies to leverage institutional strengths and new initiatives
5. Pursue high-risk, high reward studies
6. Support projects utilizing the unique core facilities at the medical school and throughout the University
7. Encourage collaboration across the five UMass campuses
Pilot Project Program

Individual Proposals
$100,000 max for 1 year
$150,000 max for 2 years

Projects span the translational spectrum, T1 – T4+

2 Stages
Letter of Intent (2 pages)
Full Proposal (Abbreviated NIH-style 10 pages)
Pilot Project Program – success rate

# of proposals vs. year

- LOI
- Full application
- Funded

## 2012 Pilot Program Project Recipients

<table>
<thead>
<tr>
<th>UMMS Collaborator(s)/Dept</th>
<th>UMass Collaborator/Dept</th>
<th>Project Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hua (Julia) Fang, PhD Department of Quantitative Health Sciences</td>
<td>DiFranza, Moormann, Ma, Kim, Houston, Barton, Allison, Ash</td>
<td>A New Tool for Studying Heterogeneity of Treatment Effects in Longitudinal Translational Research</td>
</tr>
<tr>
<td>Brian Lewis, PhD Program in Gene Function and Expression</td>
<td>Venu Bathini, MD Department of Medicine</td>
<td>Combined Inhibition of MEK and IGF1R as an Effective Therapeutic Strategy for Pancreatic Ductal Adenocarcinoma</td>
</tr>
<tr>
<td>Zuoshang Xu, PhD Biochemistry and Molecular Pharmacology</td>
<td>Guangping Gao, PhD MaPS Robert Brown, MD, PhD Department of Neurology</td>
<td>Deliver RNAi for Treatment of ALS using AAV</td>
</tr>
</tbody>
</table>
Pilot Project Program (PPP)

<table>
<thead>
<tr>
<th>Tentative Timeline:</th>
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</thead>
<tbody>
<tr>
<td>Request for Letters of Intent</td>
<td>Monday, November 19, 2012</td>
</tr>
<tr>
<td>Letters of Intent Due</td>
<td>Thursday, December 20, 2012</td>
</tr>
<tr>
<td>LOI Finalists Notified</td>
<td>Friday, January 11, 2013</td>
</tr>
<tr>
<td>Full Proposals Due</td>
<td>Friday, February 8, 2013</td>
</tr>
<tr>
<td>Full Proposal Finalists Notified</td>
<td>Friday, March 1, 2013</td>
</tr>
<tr>
<td>Project Start Date</td>
<td>Monday, April 1, 2013</td>
</tr>
</tbody>
</table>
UMass Life Sciences Moment Fund

Funds dedicated to multi-investigator pilot projects identified as key strategy to incentivize collaborative partnerships across campuses.

- Inter-campus collaborative projects, involving at least one faculty member from the Worcester campus & one faculty member from another UMass campus.
- Collaborative projects must be oriented towards clinical and translational research.
- Funding levels and application review process same as PPP.
LOI

full application

funded

LSMF – success rate

# of proposals

year

2009a 2009b 2010 2012
<table>
<thead>
<tr>
<th>UMMS Collaborator(s)/Dept</th>
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<th>Project Title</th>
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<tbody>
<tr>
<td>Wenjun Li, PhD&lt;br&gt;Department of Medicine</td>
<td>Scott Crouter, PhD, FACSM&lt;br&gt;Department of Exercise and Health Sciences, Boston Campus</td>
<td>Residential Environment and Coronary Heart Disease Risk Factors (REACH) Pilot Study</td>
</tr>
<tr>
<td>William Theurkauf, PhD&lt;br&gt;Program in Molecular Medicine&lt;br&gt;Zhiping Weng, PhD&lt;br&gt;Biochemistry and Molecular Pharmacology</td>
<td>Lawrence Schwartz, PhD&lt;br&gt;Department of Biology&lt;br&gt;Amherst campus&lt;br&gt;Priscilla Clarkson, PhD&lt;br&gt;Department of Kinesiology&lt;br&gt;Amherst campus</td>
<td>microRNA Control of Muscle Atrophy and Death</td>
</tr>
<tr>
<td>Tiffany Moore Simas, MD, MPH, MEd&lt;br&gt;OB/GYN and Pediatrics</td>
<td>Ling Shi, PhD&lt;br&gt;College of Nursing and Health Sciences, Boston campus&lt;br&gt;Laura Hayman, PhD, RN, FAAN&lt;br&gt;College of Nursing and Health Sciences, Boston campus</td>
<td>Effects of soy protein and isoflavone supplementation for improved glucose metabolism and lipid profiles in pregnant women at high risk for gestational diabetes mellitus</td>
</tr>
<tr>
<td>Karl Simin, PhD&lt;br&gt;Cancer Biology</td>
<td>Joseph Jerry, PhD&lt;br&gt;Veterinary and Animal Sciences&lt;br&gt;Amherst campus</td>
<td>Gene expression signatures defining high risk premalignant breast lesions</td>
</tr>
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</table>
Life Sciences Moment Fund (LSMF)

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<tr>
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<th></th>
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<tbody>
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<td>Friday, March 8, 2013</td>
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<td>LOI Finalists Notified</td>
<td>Friday, March 29, 2013</td>
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<td>Full Proposals Due</td>
<td>Friday, April 26, 2013</td>
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<tr>
<td>Full Proposal Finalists Notified</td>
<td>Tuesday, May 28, 2013</td>
</tr>
<tr>
<td>Project Start Date</td>
<td>Monday, July 1, 2013</td>
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</table>
Centers for Therapeutic Innovation (CTI)

CTI VISION
Accelerate the translation of innovative discoveries from bench to the clinic

CTI STRATEGY
OPEN INNOVATION model that deploys Pfizer R&D resources where breakthrough science is happening

CTI APPROACH
A new entrepreneurial partnership at Academic Medical Centers focused on translational medicine
Inflammation (systemic Lupus Erythematosus/Lupus Nephritis)

Proposals are sought for novel large molecule applications with a path to a clinical proof of mechanism study.

Clinical Concept

New and more effective treatments that can induce and maintain remission

Mechanisms of interest

- Prevention of underlying dysregulation of B- and T- cells
- Modulation of innate immunity
- Targeting or interruption inducers of persistent immune activation/inflammation
- Inhibition or modulation of inflammatory processes involved in flares (renal, synovial or cutaneous)
- Regulation of handling and clearance of apoptotic bodies
- Promotion of immune homeostasis and immunoregulation (i.e., functional tolerance).

Precision Medicine

It is preferred if submissions incorporate a hypothesis-driven strategy for patient selection, i.e. rationale for patient subset where drug would be most efficacious.
Proposals are sought for novel large molecule applications with a path to a clinical proof of mechanism study†

Clinical Concept

• Novel approaches (targets, pathways or interventions) that would alter the course of a disease which directly or indirectly results in kidney injury and failure

Mechanisms of Interest

• Block intrarenal inflammation
• Regulation of leukocyte-endothelial cell interactions
• Prevention of tubular atrophy and interstitial injury
• Inhibition of specific components of the immune response related to renal damage (i.e., aberrant mesangial Ab:IC deposition or handling).
• Approaches aimed at promoting responses leading to improved renal function, such as repair and/or restoration of renal epithelium and nephron integrity

Precision Medicine

It is preferred if submissions incorporate a hypothesis-driven strategy for patient selection, i.e. rationale for patient subset where drug would be most efficacious
Proposals are sought for novel large molecule applications with a path to a clinical proof of mechanism study.

**Clinical Concept**
Cardiac remodeling events post-MI and in CHF leads to progressive deterioration of health with few options for patients and physicians.
- Reduced mortality, CV events, and/or improved cardiac function is the ultimate goal.

**Mechanisms of Interest**
- Those that impact extracellular matrix turnover, fibrosis, restore cardiac tissue & function, apoptosis & proliferation, cardioprotection and neovascularization.
- Novel mechanisms that impact endothelial repair (beyond standard of care) such as plaque stabilization and dissolution, mast cell & macrophage regulation.

**Precision Medicine**
Defined patient populations at highest risk of CV events that would benefit most from this therapeutic approach is required.
CTI – Next Steps

- If interested in submitting a proposal, please contact the UMass Center for Clinical and Translational Science to inquire about meeting with CTI staff prior to submitting a proposal
  - Nathaniel Hafer, nathaniel.hafer@umassmed.edu, 508-856-2511

- Pre-proposals due to the UMass Center for Clinical and Translational Science by October 19th

To learn more and obtain the pre-proposal template, please visit https://ctipartners.ideareach.com and create a user profile
New UMCCTS-MassBiologics Collaboration
The Next Hundred Million Pilot Projects

- Inter-campus collaborative projects, involving at least one faculty member from MassBiologics & one faculty member from the Worcester campus.
- Collaborative projects must be oriented towards clinical and translational research.

Individual Proposals
$100,000 maximum for 1 year
$150,000 maximum for 2 years

2 Stages
Letter of Intent (2 pages)
Full Proposal (Abbreviated NIH-style 10 pages with presentation)
# The Next Hundred Million Pilot Projects

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<tr>
<td>Full Proposal Review/Presentations</td>
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<td>Project Start Date</td>
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Questions?
Research, Process Development, GMP Manufacturing, Education and Training at

MassBiologics of UMMS
## An Abridged History of MassBiologics of the UMMS

<table>
<thead>
<tr>
<th>Dates</th>
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<th>Affiliation</th>
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**Theobald Smith, MD**

**Captain**

Captain produced enough antitoxin in less than a year to protect 86,000 people from diphtheria
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</tr>
<tr>
<td>Between 1946 and 1968</td>
<td>Massachusetts Public Health Biologic Laboratories, Institute of Laboratories, Massachusetts Health Research Institute</td>
<td>Massachusetts Department of Public Health, Harvard</td>
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<tr>
<td>1969</td>
<td>State Laboratory Institute</td>
<td>Department of Public Health</td>
</tr>
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</table>
Dr. Edwin J. Cohn, at Harvard, demonstrating the feasibility of collecting blood and separating it into component parts — note donors above and fractionation machines below. (Taken at HMS Amphitheater, 1940s.)
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<td>Department of Public Health</td>
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<tr>
<td>1997-1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>MassBiologics Per FDA License #1779 to produce Td vaccine</td>
<td>UMMS</td>
</tr>
<tr>
<td>2012</td>
<td>MassBiologics of the UMMS</td>
<td>UMMS</td>
</tr>
<tr>
<td>Monoclonal Antibody</td>
<td>Indication</td>
<td>Stage of Development</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1 SARS1</td>
<td>Prevention of SARS</td>
<td>Completed through manufacturing</td>
</tr>
<tr>
<td>2 MBL-CDA1 and MBL-CDB1</td>
<td>Treatment of <em>C. difficile</em> infection</td>
<td>Phase 3</td>
</tr>
<tr>
<td>4 MBL-RAB1</td>
<td>Rabies post-exposure prophylaxis in conjunction with rabies vaccine</td>
<td>Phase 2/3 (India)</td>
</tr>
<tr>
<td>5 MBL-HCV1</td>
<td>Prevention and treatment of HCV infection</td>
<td>Phase 2</td>
</tr>
<tr>
<td>6 ALS</td>
<td>Treatment of Amyotrophic Lateral Sclerosis</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
## Millions of Life Saving Doses of “Medicine for Better Lives” from MassBiologics of UMMS

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria Antitoxin-Equine</td>
<td></td>
</tr>
<tr>
<td>Botulism Antitoxin-Equine</td>
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</tr>
<tr>
<td>Tetanus Antitoxin-Equine</td>
<td></td>
</tr>
<tr>
<td>Rabies Immunoglobulin-Equine</td>
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</tr>
<tr>
<td>Human Serum Albumin</td>
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<tr>
<td>Human Immune Globulin</td>
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<tr>
<td>Human Hyper-Immune Globulin to Scarlet Fever, Pneumococcus, Meningococcus,</td>
<td></td>
</tr>
<tr>
<td>Tetanus, Measles, CMV, RSV, Varicella-zoster, Rabies, Hepatitis A</td>
<td></td>
</tr>
<tr>
<td>Tetanus Toxoid Vaccine</td>
<td></td>
</tr>
<tr>
<td>Diphtheria Toxoid Vaccine</td>
<td></td>
</tr>
<tr>
<td>Td Vaccine</td>
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</tr>
<tr>
<td>Human Monoclonal Antibodies against SARS, C diff Toxins A and B, Rabies,</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C, Tetanus and Diphtheria Toxins, SOD1 for ALS, sFlt-1 for Pre-</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td></td>
</tr>
</tbody>
</table>
Going Forward

• Research on Human Monoclonal Antibody Development
• Research and Development of New Therapeutic MAbs
• Research and Development of New Prophylactic MAbs
• Innovation in Process Development, Manufacturing
• Innovation in Quality Assessment tools
• Innovation in Business Development
• Emphasis on Training/Mentoring
• Custom Contract Manufacturing
“The Next Hundred Million” Pilot Projects

DATE: September 4, 2012
TO: All UMass Faculty with an Interest In Clinical & Translational Science
FROM: Katherine Lazuza, MD, Director, UMass Center for Clinical & Translational Science; Mark Klempner, MD, Executive Vice Chancellor for MassBiologics of the University of Massachusetts Medical School
RE: NEW FUNDING OPPORTUNITY: The “Next Hundred Million” Pilot Projects (NHMPP)

Introduction
The University of Massachusetts Center for Clinical and Translational Science (UMCCTS) and MassBiologics of the University of Massachusetts Medical School are pleased to announce a funding call for “The Next Hundred Million” Pilot Projects (NHMPP). The NHMPP will serve as a dedicated pool of funding to spur innovative collaborations between UMMMS, MassBiologics of UUMMS and investigators across the UMass System with the goal of enhancing the translation of discoveries for clinical use.

Purposes
In 2013, MassBiologics of the University of Massachusetts Medical School (www.umassmed.edu/massbiologics) will celebrate discovery, manufacture and delivery to the American people of 100 Million doses of vaccines and immunotherapies during its 118 year history. We are looking for pilot projects that will contribute to the discovery, preclinical and clinical research, manufacture and delivery of the “next hundred million doses” of products to improve public health. The NHMPP will serve as a dedicated pool of funding to spur inter-campus collaboration and strengthen the University’s research portfolio in clinical and translational research. To support this mission, projects must include at least one investigator from MassBiologics of UUMMS (see below and www.umassmed.edu/massbiologics) and a faculty investigator from at least one UMass campus. Inclusion of collaborators from UUMMS is highly encouraged but not required. The following Division Leaders (all are UUMMS faculty) should serve as initial points of contact for expertise at MassBiologics:

- For discovery research, Greg Babcock, greg.babcock@umassmed.edu
- For clinical research, Deb Molrine, deborah.molrine@umassmed.edu
- For process development and manufacturing research, Bill Thomas, william.thomas@umassmed.edu
- For quality assessment, regulatory or business process proposals, Mark Lercy, mark.lercy@umassmed.edu

By providing seed funding to outstanding faculty members, this fund facilitates the development of faculty-to-faculty networks within the University system.

MassBiologics of the UUMMS is the only FDA licensed biologics production facility owned and operated by a university in the United States. It has unique discovery, preclinical, clinical, regulatory, quality assessment and GMP manufacturing expertise. The academic affiliation of MassBiologics also allows it to serve as an incubator to innovate and improve the process of vaccine and biological and immunologic therapeutics development.

Current and future projects supported by this fund are envisioned to develop into larger initiatives that attract substantial funding from extramural sources, including the Federal Government, the Commonwealth, industry, foundations and others.
Process Development
Human Monoclonal Antibodies
Process Development Overview

• Focus on proteins produced by CHO cells
  – Human monoclonal antibodies

• Cell culture, purification, formulations and analytical support

• 4 PhD’s and 13 technicians

• Supplemented by MAb Manufacturing team
• Upstream process development
• Downstream process development
• Analytical method development
• Formulation development
• Tech Transfer and Manufacturing support
MBL Process Development Platform Technology

• CHO cell expression host and vector
• Proprietary media and feeds
  – Chemically defined, animal component free
• Fed-batch culture method up to 5 gm/L
• Purification platform for MAbs
• Formulation platform for 25-100 mg/ml
Upstream Process Development

Small Scale Shaken Cultures

Bench top DasGip Reactors

60 L Applikon Reactor
Upstream Process Development Activities

• Cell Line Development (transfection, cloning)
• Cell Line Characterization (growth, production kinetics, max cell density, specific productivity, stability, etc)
• Process for Seed-train and Bioreactor (pH, DO, Temp)
• Fed-batch Bioreactor Optimization (feeding, pH, DO, Temp)
• Material for Downstream and Analytical Process Development
• Process Scalability, Tox material production (IND), and Tech transfer (Ph I/II)
CHO Cell Line Selection

DG12-02: Comparison of Top 4 Clones in Dasgips

Antibody Titers (Octet)

- Das 1: 440.1
- Das 2: 586.7
- Das 3: 1022.9
- Das 4: 1043.10
- Das 5: 440.1
- Das 6: 586.7
- Das 7: 1022.9
- Das 8: 1043.10

Days in Culture

Antibody Titer (mg/L)
Downstream Process Development
Current MBL Purification Platform

- Bioreactor
  - Protein A resin used as a capture step. Specific for Abs

- ProSep vA Ultra
  - Anion exchange membrane for removal of CHO cell-related contaminants

- Mustang Q

- Fractogel Hicap SE
  - Cation exchange resin very effective in removal of high molecular weight MAb contaminants
Downstream Process Development

• Optimize chromatography steps
  – Establish set points, ranges and hold times

• Virus inactivation and removal studies
  – Prosep, low pH, nanofiltration

• MAb development purification scale >10 g

• Pre-clinical material (toxicology, reference standard)
Analytical Development

- Antibody characterization
- Tox lot, reference standards, Mfg in-process samples
- Support Upstream, Downstream, and Formulation Development
- Development of New Assays, Methods
- Comparability Studies
- Improve Throughput of the Assays
Formulation Process Development

• Formulation development
• High concentration formulations (100 mg/L)
• High throughput analytical for Mabs
• Accelerated stability testing for formulation development
• Platform formulation
  – 20 mM citrate, pH 6.0, 150 mM NaCl, Tween 80
Research, Process Development, GMP Manufacturing, Education and Training at
MassBiologics of UMMS
MassBiologics, Product Discovery

Greg Babcock, Ph.D.
Associate Professor, Medicine, UMMS
Deputy Director, Discovery, MassBiologics
Product Discovery

- Focus is the development of human monoclonal antibodies from initial concept to completion of preclinical activity to support an IND application

- Extensive experience in identifying novel antibody molecules

- Infectious disease targets (mostly but not all)

- Various technologies used for human antibody development

- Four human monoclonal antibodies developed from concept to phase 2 human studies
Four distinct genetic modifications functionally replace the mouse immunoglobulin loci with human immunoglobulin transgenes.
Antibody secreting cells

1. Draw blood Day 7 post vaccine
2. Stain PBMCs to isolate ASCs
3. Sort individual ASCs into 96-well PCR plates
4. Perform separate cloning PCRs
5. Run products on gel to determine positive clones
6. Perform 1-step RT-PCR on ASC-RNA (H+L)
7. Ligate “valid” antibodies into expression vectors
8. Transfect to produce antibody and screen against Tet/Dip toxoid via ELISA
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em> antibody combination</td>
<td></td>
<td></td>
<td></td>
<td>Licensed to Merck</td>
</tr>
<tr>
<td>Rabies virus</td>
<td></td>
<td></td>
<td></td>
<td>Licensed to Serum Institute of India</td>
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<tr>
<td>Hepatitis C virus</td>
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<tr>
<td>SARS virus</td>
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<tr>
<td>anti-hSOD1 (ALS)</td>
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<tr>
<td>Discovery Target #1 - Infectious Disease</td>
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<tr>
<td>Discovery Target #2 - Infectious Disease</td>
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<tr>
<td>Discovery Target #3 - Endogenous Target</td>
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</table>
Ex: HCV mAb Development

Hybridomas produced from 51 HuMAb mice

- ELISA recognition of CO-E$_{260}$
  - 487 hybridomas
  - ELISA recognition of E2-1b
    - 50 hybridomas
    - Neutralization of HCVpp
      - 20 hybridomas
      - Sequence comparison
        - 2 hybridomas (HCV1 and 95-2)
        - Antibody cloning and expression
          - Extensive characterization
HCV mAb HCVpp Neutralization

HCV1 neutralized all genotypes tested
HCV1 Prevents HCV Infection of Chimpanzees

A

- Viral RNA levels
- Urinalysis
- Safety labs and HCV1 antibody levels
- HCV1 infusion then challenge with 32 CID HCV H77 genotype 1a

B

<table>
<thead>
<tr>
<th>Days in Relation to Viral Challenge</th>
<th>Chimp #1</th>
<th>Chimp #2</th>
<th>Chimp #3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV1 (mg/kg)</td>
<td>0</td>
<td>50</td>
</tr>
</tbody>
</table>

LLQ = 500 Ge/ml

Log₁₀ HCV Genome equivalents / ml

Days 0 5 10 15 20 25 30 35 40 45 50

Chimpanzees

HCV1 prevents HCV infection of chimpanzees.
HCV1 Treats HCV Infection of Chimpanzees

Log$_{10}$ HCV IU/ml vs Day in relation to HCV1 treatment

LLQ = 15 IU/ml

Chimp A
Chimp B
Chimp C
N417S

HCV1 Treats HCV Infection of Chimpanzees
Product Discovery

- Skilled in in vitro assays to determine mAb activities

- Adept at understanding requirements for animal studies to support human studies

- Preparing Pharm-Tox section of IND to the satisfaction of the FDA

- Proven track record of developing human monoclonal antibodies from bench to bedside