May 20th, 8:30 AM - 9:00 AM

What is Translational Research?

Catarina I. Kiefe
University of Massachusetts Medical School

Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Community-Based Research Commons, Educational Assessment, Evaluation, and Research Commons, Health Services Research Commons, Science and Technology Studies Commons, and the Translational Medical Research Commons

This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.
What is Translational Research?

Catarina Kiefe, MD, PhD
University of Massachusetts Medical School
Dept of Quantitative Health Sciences
May 20, 2011
I have no actual or potential conflict of interest in relation to this program or presentation.
Overview

• Translational Science
  • Why?
  • What?
    • The translational spectrum: a changing nomenclature
• “Bench to beside”: a limited paradigm
  • Wrong endpoint (bedside)
  • Wrong direction: what about “bedside” to bench?
• Charge for the day
Why Translational Science?

• Median time from description of a new discovery in a basic science journal to publication of use of this discovery in a highly cited article in the medical literature: 24 years
  • Contopoulous-Ioannidis, Science, Sept 2008
• Mean time to implement a new clinical research finding into practice: 17 years
  • Balas, Boren, Yearbook Medical Informatics, 2000
Translational Blocks in the Clinical Research Continuum

Translational Research in US

- Introduced as part of NIH Roadmap

- NIH Definitions used in CTSA funding (e.g., RFA-RM-10-020)
  - Clinical research comprises studies and trials in human subjects
  - Translational research includes two areas of translation:
    - Applying findings from laboratory research and preclinical studies to the development of trials and studies in humans
    - Enhancing the adoption of best practices in the community
Translational Research in Europe

• **UK Cooksey Report:**
  - Process of taking the findings of either basic or clinical research to produce innovations in health care settings
  *Cooksey 2006. The Stationery Office. London*

• **The European Advanced Translational Research Infrastructure in Medicine (EATRIS)**
  - Funded in part by European Union, to be established through both public and private funds
  - “Maintain Europe's competitiveness in biomedical research and health industry”
The Continuum of Clinical and Translational Science

| T1 | First in Human Phase I-II Trials Proof of Concept |
| T2 | Phase III Trials Clinical Efficacy Clinical Guidelines |
| T3 | Dissemination Community Engagement Health Services Research Comparative Effectiveness |
| T4 | Public Health Prevention Population Health Impact Behavioral Modifications Lifestyle Modifications |

Adapted from Waldman and Terzic. Clin Transl Sc 2010 3(5): 254-7
The Continuum of Clinical and Translational Science

TO
- Targets
- Biomarkers
- Genes
- Pathways
- Mechanisms

T1
- First in Human
- Phase I-II Trials
- Proof of Concept

T2
- Phase III Trials
- Clinical Efficacy
- Clinical Guidelines

T3
- Dissemination
- Community Engagement
- Health Services Research
- Comparative Effectiveness

T4
- Public Health
- Prevention
- Population Health Impact
- Behavioral Modifications
- Lifestyle Modifications

Adapted from Waldman and Terzic. *Clin Transl Sc* 2010 3(5): 254-7
The Continuum of Clinical and Translational Science

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Targets, Biomarkers, Genes, Pathways, Mechanisms</td>
</tr>
<tr>
<td>T1</td>
<td>First in Human, Phase I-II Trials, Proof of Concept</td>
</tr>
<tr>
<td>T2</td>
<td>Phase III Trials, Clinical Efficacy, Clinical Guidelines</td>
</tr>
<tr>
<td>T3</td>
<td>Dissemination, Community Engagement, Health Services Research, Comparative Effectiveness</td>
</tr>
<tr>
<td>T4</td>
<td>Public Health, Prevention, Population Health Impact, Behavioral Modifications, Lifestyle Modifications</td>
</tr>
</tbody>
</table>

Adapted from Waldman and Terzic. *Clin Transl Sc* 2010 3(5): 254-7
The Broad Spectrum of Biomedical Research: Genomics  

- T0: Genome
- T1: Moves genome-based discovery into candidate health application (eg genetic tests)
- T2: Assesses value of application for health practice, leads to evidence-based guidelines
- T3: Moves guidelines/evidence into practice
- T4: Evaluates “real world” health outcomes of genomic applications
- T5: Studies genomics in the context of the social determinants of health
- <3% of genomic research focuses on T2 – T5
T1 vs. T2+: Changing Boundaries

- Initially, translational research required “whole humans” or human population groups as study units. Evolving nomenclature:
  - T1 research takes knowledge from the bench (“wet lab”) to clinical knowledge
    - Initially: Phase 1-3 clinical trial (including RCTs)
    - Recently: also “T0”, mice, even cells…
  - T2+ research takes clinical knowledge into realized human benefit
    - E.g. Group-randomized implementation trials
    - Recently: also phase 3 clinical trials
T1 versus T2+ Research

- **T2+ defining elements:**
  - “dry lab” research that uses statistics and epidemiology as its basic tools
  - The study units may be individual humans, groups of humans (populations), or health systems

- **T1 defining elements:**
  - May also use “wet lab” tools but used to involve “whole humans”
  - Study unit now from lab animal to individual patient

- **Cultural innovations for both:**
  - Transdisciplinary, team science
  - Bidirectionality as emerging concept
Overview

✓ Translational Science
  ✓ Why?
  ✓ What?
    ✓ The translational spectrum: a changing nomenclature
  • “Bench to beside”: a limited paradigm
    • Wrong endpoint (bedside)
    • Wrong direction: what about “bedside” to bench?
  • Charge for the day
Example: Type 2 Diabetes Prevention

- Chronic hyperglycemia causes severe end-organ damage through fairly well understood pathophysiology (T0, T1)
- T0-T1 research has resulted in multiple medications that control hyperglycemia
- Solid clinical research links Type 2 diabetes to overweight/obesity (T2 - T3): the diabesity epidemic
Why T2+ Research?

• The diabesity epidemic

Prevalence of obesity among men in the US

With a parallel rise in the incidence of diabetes

Freedman MMWR 2011
Important Translational Question

- Weight loss and other lifestyle modifications improve glucose control in patients with diabetes
- Can lifestyle modification and weight reduction PREVENT diabetes?
Diabetes Prevention Program (DPP)

- Cumulative incidence of DM2 lowest in lifestyle group:
  - 58% lower incidence at 1 year
  - 34% lower incidence at 10 years
- Classical efficacy study (T1 – T2)
  - Oral GTT as the screening tool
  - Very intensive, expensive one-on-one intervention
  - Educated population, all literate
  - Overweight/obesity assumed important mediator
Why Research Beyond the “classical” RCT?

• DPP efficacy study notwithstanding, diabesity epidemic marches on

• Lawrence Latino “DPP” (LLDPP)
  • community-based effectiveness study – “real world”
  • 252 at risk pts randomized
  • Group-based less intensive intervention
  • Inexpensive
  • 30% of population illiterate in Spanish and English
### DPP vs. LLDPP outcomes at 1 year

<table>
<thead>
<tr>
<th></th>
<th>DPP</th>
<th>LLDPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (lbs)</td>
<td>17</td>
<td>3.1</td>
</tr>
<tr>
<td>HgbA1c (%)</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Numbers approximate; personal communication from I Ockene

### Why similar effect of intervention on hyperglycemia, yet much weaker effect on weight??
Why different effects 
LLDDP vs. DPP?

- **Efficacy vs. effectiveness study?**
  - But effect on HgbA1c was similar
- **Different populations?**
  - Some Latino groups, Native Americans known to be exquisitely sensitive to weight gain re diabetes incidence
  - Are we seeing reverse effect here?
- Need to investigate mechanism that underlies these differences: genetics?
Bidirectionality

• Should our approach remain linear?

OR

• Should transdisciplinary teams implement true bidirectionality?
Team Science, Bidirectionality

T5 → T0

T4 → Molecules

T3 → Population Health

T2 → Health Care
3 Historical Examples of Bidirectionality

Rutter and Plomin, Psychol Med 2009

- **Tobacco and lung cancer**
  - First: Epidemiologic studies *Doll and Hill, BMJ 1950 and 1954*
  - Later: clinical and animal studies, then gene expression studies *Wen, Mod Path 2011*

- **Lipids and heart disease**
  - Initial rabbit studies ignored (1913)
  - Epidemiologic evidence in 1956
  - Basic lab research in ‘70s: model of how LDL causes atherosclerotic lesions
  - LRC trial in the 80s, large statin RCTs in 90’s

- **Fetal alcohol syndrome**
  - Clinical observations define syndrome *Kl Jones, Lancet 1973*
  - Mice studies confirm
SUMMARY

• Translational research is
  • Transdisciplinary
  • Bidirectional
  • Driven by the need to move from knowledge for the sake of knowledge to realized human benefit
  • Reminds us that
    “Science without conscience is the soul’s perdition” Rabelais, Pantagruel, 1572
QUESTIONS??????
Charge for the Day

- Look for bidirectionality
  - Keynote lecture
  - Mini-symposia
  - Posters
- Think transdisciplinary teams
  - Next presentation, lunch, coffee breaks
- Tell us how to do better
  - Fill-out evaluations
- HAVE FUN
  - All day long and evening reception with posters
  - 5 prizes for best posters at evening reception