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What is Translational Research?

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What is Translational Research?

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Dept of Quantitative Health Sciences
May 20, 2011
DISCLOSURE

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

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

T0
- 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>Stage</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Targets</td>
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The Broad Spectrum of Biomedical Research: Genomics


- **T0**: Genome
- **T1**: Moves genome-based discovery into candidate health application (e.g., 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?

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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)

- RCT: 3,234 persons at 27 centers, followed for 10 years. \( \text{Knowler, NEJM 2002; Knowler, Lancet 2009} \)
- 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>Improvements in Outcomes at 1 year *</th>
<th>DPP</th>
<th>LDPPP</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 know 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

T0 → T5
T5 → T0
T0 → T1
T1 → T0
T1 → T2
T2 → T1
T2 → T3
T3 → T2
T3 → T4
T4 → T3
T4 → T5
T5 → T4

Molecules
Population Health
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