Early Career Day at AHA Scientific Sessions

Translational Research, Bridging the Gap Between Clinical and Basic Research

2012 AH Scientific Sessions
Los Angeles, CA
Saturday, November 3rd, 2012
Dr. Mann has no conflicts relevant to this presentation
Translational Research FOR DUMMIES

A Reference for the Rest of Us!

By D.L. Mann

Third Edition

www.amazon.com
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The Terminology of Translational Research
Translational Research

- Phase 1 translation (T1) research seeks to move basic discovery into a candidate health discovery.
- Phase 2 translation (T2) research assesses the value of T1 application for health practice leading to the development of evidence-based guidelines.
- Phase 3 translation (T3) research assesses attempts to move evidence-based guidelines into health practice, through delivery, dissemination and diffusion research.
- Phase 4 translation (T4) research seeks to evaluate the “real world” health outcomes of a T1 application in a practice.
The Translational Continuum

- **T1**: Basic Science Discovery
  - Early Transition
  - Phase 1/2 Clinical Trials
- **T2**: Late Transition
  - Phase 2/3 Clinical Trials
- **T3**: Dissemination
- **T4**: Adoption
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<td>1st administration of new treatment</td>
<td>Is further investigation warranted? <strong>SAFETY</strong></td>
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<td>Early trial in patients</td>
<td>Dose ranging, AE’s, pathophysiologic insights, <strong>EFFICACY</strong></td>
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Why Engage in Translational Research?

- Moral imperative of performing research that helps relieve human suffering and death
- Suttons’ Law
- Could lead to early retirement if your ideas work out
- It is the funnest thing you could possibly do with your career
Sutton’s Law

Willie Sutton Arrested 2/18/52
Funding Sources

- Howard Hughes (medical students)
- Howard Hughes “Med Into Grad” (PhD students)
- Sarnoff Foundation (medical students)
- Doris Duke Charitable Foundation
- NIH Clinical and Translational Science Awards
- Howard Hughes Early Career Awards
- Burroughs Welcome
  - Career Awards for Medical Scientists
  - Clinical Scientist Awards for Translational Science
What Skill Sets Will I Need to be Successful at Translational Research?
Life Cycle of T1/T2 Translational Research

Experimental Models

Human Disease

Phase I–III Clinical Trials

In Vitro and In Vivo Testing

Cellular and Molecular Mechanisms

Target Identification

One Person Cannot Learn All This Stuff!

Translational Science is Team Science
No clear training pathway for translational research
New training programs are emerging (CTSA)
The success of these newer programs is unknown
Clear training pathway for basic and clinical research
Marketable skill sets
Less dependent on other scientists for your success
Sustainable career
Pathway to promotion is clearer
Training Platforms for Translational Research

- Training pathways will require broader curriculum
- Training will need to start much earlier
- New funding pathways will be required to support investigators during the “early” vulnerable parts of their careers
- Industry needs to make a stronger commitment to training the next generation of translational scientists
Who should engage in translational research?
MDs, PhDs, MD/PhDs
"It's a tremendous leap of faith for young investigators to commit themselves to translational research. It takes a special sort of person; you have to be willing to take risks."

Anthony Hayward, NIH National Center for Research Resources
You have a better chance of winning big at Vegas than you do in translating your laboratory ideas into a successful phase III clinical trial.
Translational Science is the funnest thing you could possibly do with your career.
Can I be promoted if I engage in translational research?
Yes, but.....
Translating Success into Tenure

• Grant and tenure success depends on researchers' ability to publish in top journals
• Translational research deals with patients. Establishing causality is challenging. Translational trials are not likely to get into Science, Nature, NEJM or JAMA
• Many of the people who sit on tenure and promotions committees have never engaged in translational science
• Translational Science is Team Science, which means that promotion committees may not be able to recognize the contribution of individual members of the team
  - Universities are getting better at recognizing this
  - There is still a long way to go
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“FINER” Criteria for a Good Research Question

- Feasible
- Interesting
- Novel
- Ethical
- Relevant

How do I Move My Idea(s) From the Bench to the Bedside (T1)?
Pre-Clinical Steps for Validating a Target

- Protein must be elaborated in the disease you are studying
- Amount of protein must be sufficient to produce biological effects in disease
- Protein must mimic aspects of the disease
- Eliminating protein must eliminate some aspects of the disease syndrome

There is no one right way to do this, and there are no absolute rules!

Modified from Divecha and Irvine, Cell 1995;80:269-278
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Chapter 6: What to do when you find yourself on the wrong side of the Kaplan-Meier Curve

a) Blame the marketing team for including the wrong patients in the trial

b) Blame the study drug/device

c) Blame the Republicans

d) Crawl back into the laboratory and design a better way

e) All of the above
What Nobody Talks About
With Translational Research

DARK SIDE
Tumor Necrosis Factor (U/ml)

Levine et al., NEJM 1990; 323:3236-41
Phase I

Phase III

Proposal To Immunex Management, Seattle Washington 12/1/97
RECOVER, RENAISSANCE and RENEWAL

Study Design and End-Points

- **RENAISSANCE**
  - Clinical status
  - $n=900$, $\alpha = 0.04$

- **RECOVER**
  - Clinical status
  - $n=900$, $\alpha = 0.04$

- **RENEWAL**
  - Death or CHF hospitalization (event driven), $\alpha = 0.01$
  - Death (secondary end-point)
Early Termination for Lack of Benefit

Observing an estimate of the effect of etanercept on the morbidity/mortality endpoint that was unfavorable, the Independent Data Safety Monitoring Board recommended early termination of the two trials.

The DSMB recognized that “even by conservative bounds that adjusted for the interim nature of the analysis, the confidence interval for this estimate ruled out...a 10% benefit from (etanercept), crossing the established boundary for lack of efficacy on the morbidity/mortality endpoint.”
Primary End-Point (Death or CHF Hospitalization)

Event-free survival %

Weeks

Placebo
Etanercept biw + tiw

RR = 1.10
95% CI: 0.91-1.33
P = 0.33

Mann et al., Circulation 2004; 109: 1594-1602
Immunex Corporation History

Wholly owned subsidiary of Amgen, Inc

Key Dates:

1981: Steven Gillis and Christopher Henney found Immunex in Seattle.
1987: First clinical studies of Leukine are initiated.
1991: Leukine is marketed for bone marrow transplant patients and receives FDA approval; ground is broken for a new pharmaceutical manufacturing facility in Bothell, Washington.
1993: Shareholders approve merger with Lederle, a division of American Cyanamid; plans are announced for new research and development center.
1996: FDA approves Novantrone for use in hormone-refractory prostate cancer patients; scientists discover RANK, a molecule involved in the regulation of bone formation/degradation.
1998: Researchers clone TACE, a key immune system enzyme, and TRAIL, a gene critical to healthy immune systems; Enbrel receives FDA approval as first in a new class of drugs for treatment of moderate to severe rheumatoid arthritis.
1999: Immunex stock splits two-for-one; Enbrel is approved for treatment of juvenile rheumatoid arthritis; total product sales reach $376 million and construction starts on new process development facility.
2000: Immunex stock splits three-for-one; Novantrone is approved by FDA for treatment of worsening multiple sclerosis.
2001: Enbrel is approved by the FDA for psoriatic arthritis and shows positive results in psoriasis trials; Immunex acquisition by Amgen is announced.
2002: Immunex is acquired by Amgen Inc.

http://www.fundinguniverse.com/company-histories/immunex-corporation-history/
What Happens to Your Career After Your Clinical Trial Fails in Phase III

• Your family will still love you
• Your friends will send you comforting emails and will still talk to you at meetings
• You will spend a lot time soul searching
• You may also:
  - Have a harder time getting your papers published
  - Have a harder time getting your grants funded
  - Have to explain yourself in a public forums for the next 10 years
  - Grow as a scientist
It's about the biology stupid!
Clear training pathway for basic and clinical research
Marketable skill sets
Less dependent on other scientists for your success
Sustainable career
Pathway to promotion is clearer
Translational research will require new training pathways that will take longer
- Career training needs to start earlier

Young investigators should proceed with optimism and appropriate caution

Funding agencies will need to commit to a longer term strategy that will fill the pipeline with translational investigators, as well as maintain the pipeline at least at steady state for 2-3 generations of investigators

Institutions will need to learn how to critically evaluate translational investigators and adjust tenure and promotion policies accordingly
Translationalists Credo

“If at first you do not succeed, you are running about average”

By M.H. Alderson