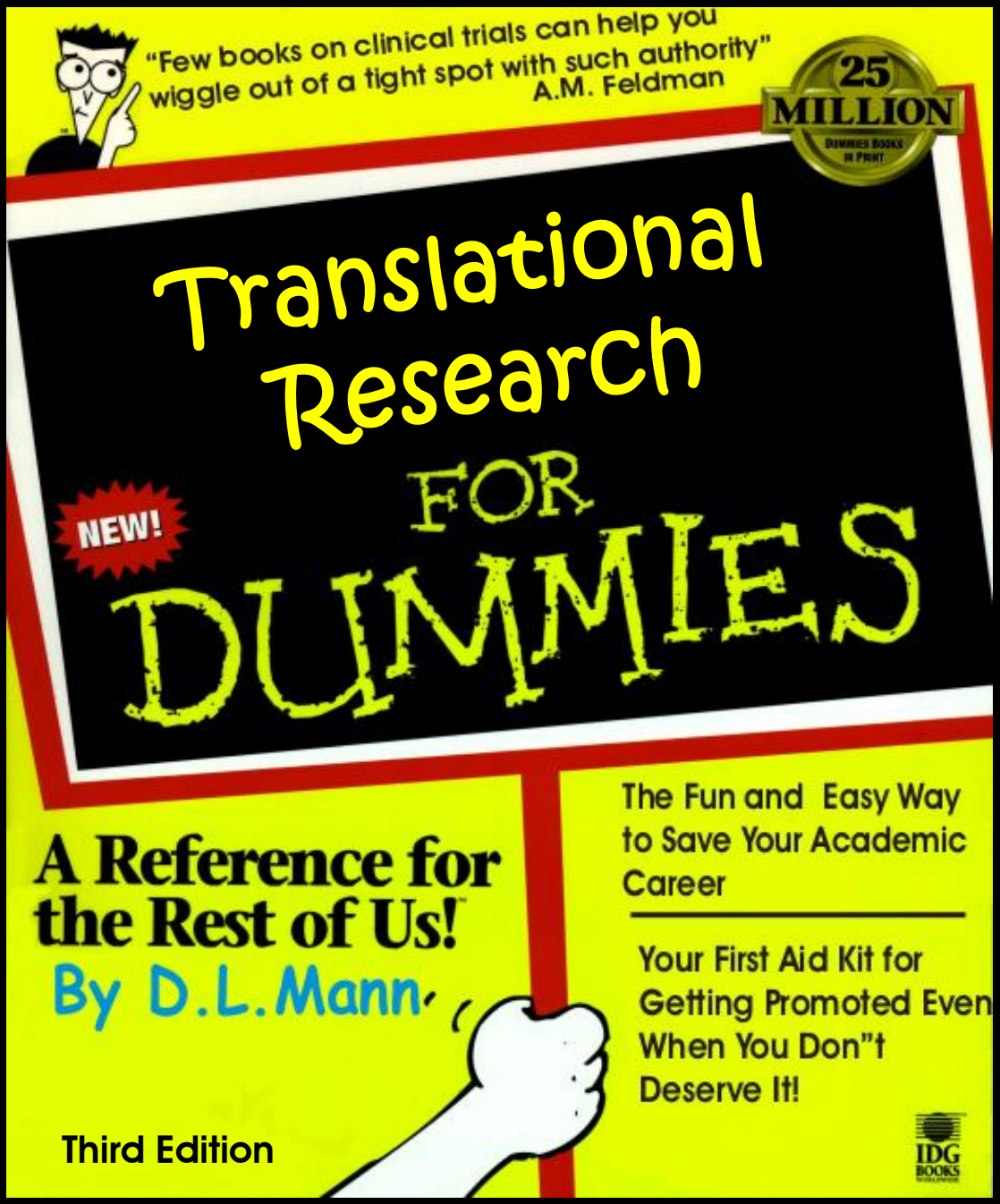
Early Career Day at AHA Scientific Sessions

Translational Research, Bridging the Gap Between Clinical and Basic Research

2012 AH Scientific Sessions
Los Angeles, CA
Saturday, November 3rd, 2012

Washington University in St. Louis
School of Medicine

Dr. Mann has no conflicts relevant to this presentation



www.amazon.com

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Chapter 1	Mostly everything you need to know about translational research
Chapter 2	T1 Translation
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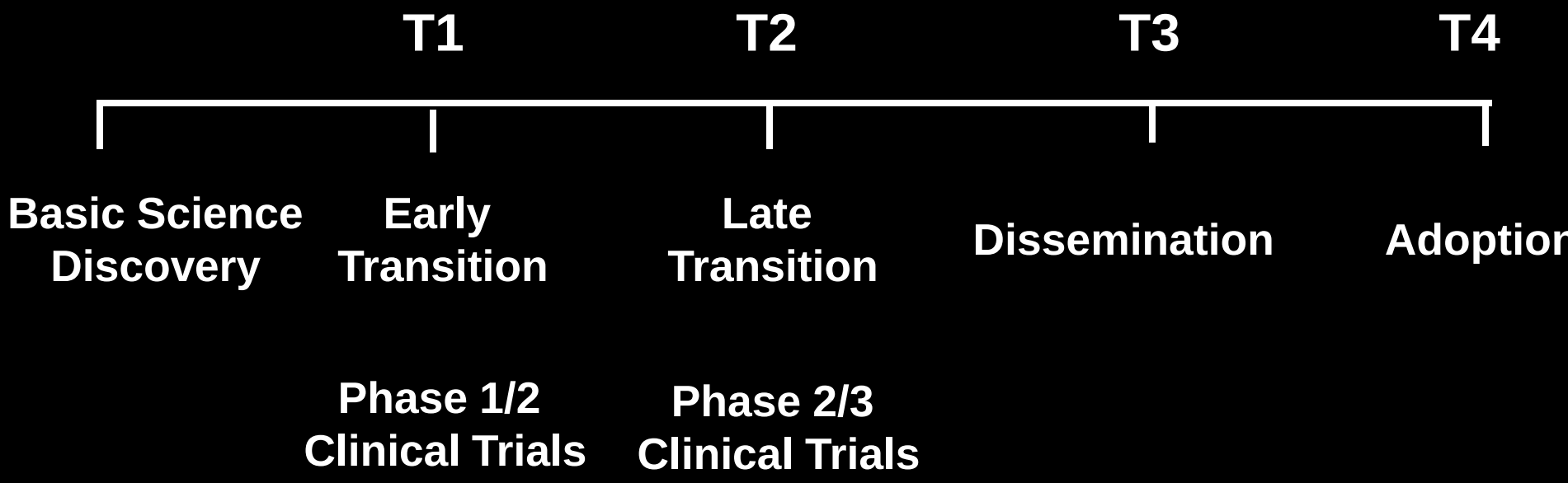
The Terminology of Translational Research

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



Phases of Evaluations of New Therapies

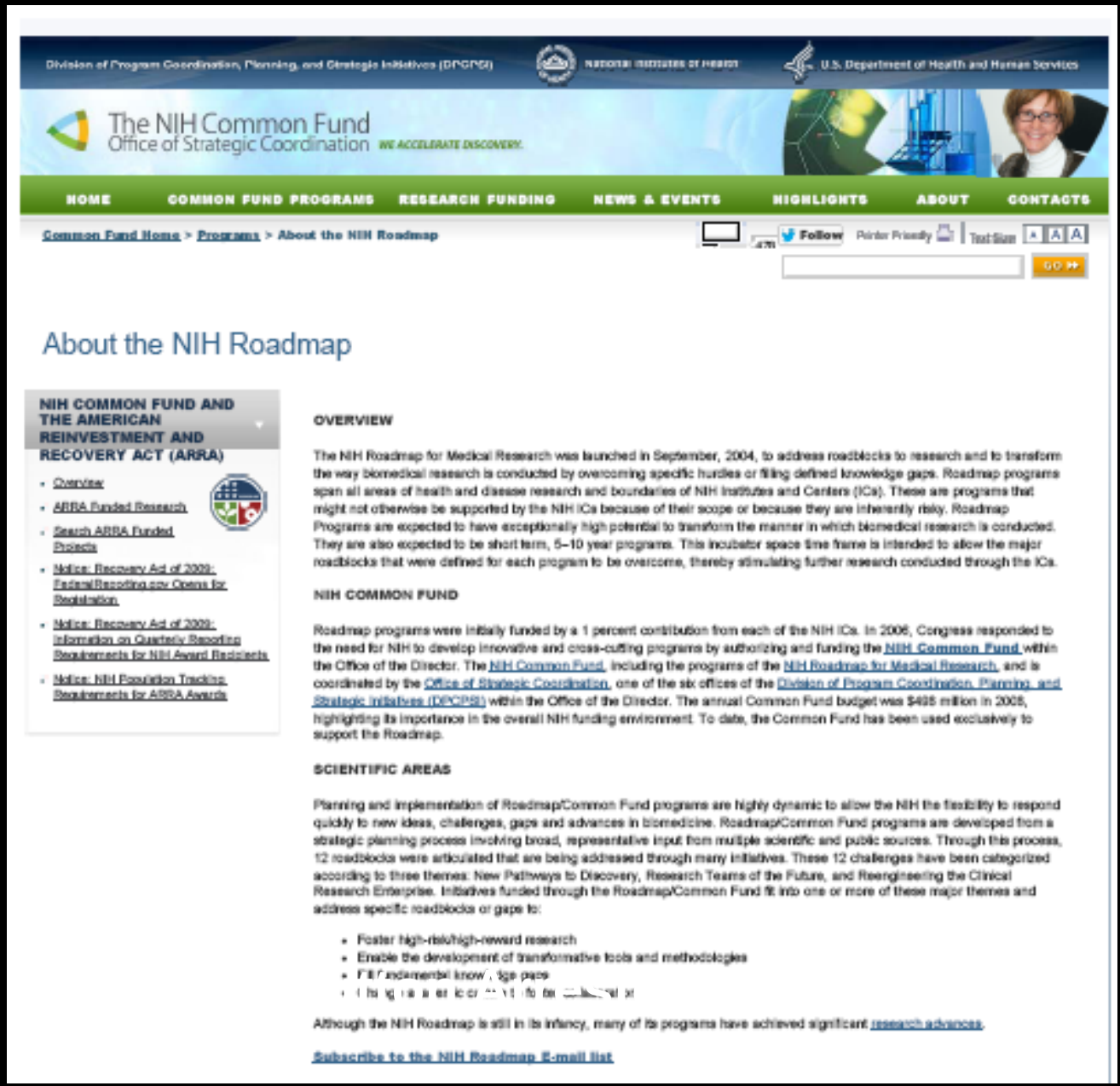
Phase	Features	Purpose
I	1st administration of new treatment	Is further investigation warranted ? SAFETY
II	Early trial in patients	Dose ranging, AE's, pathophysiologic insights, EFFICACY
III	Large scale comparison vs standard treatment	Definitive evaluation "REGISTRATION PATHWAY"
IV	Monitoring in clinical practice	POST MARKETING SURVEILLANCE

Adapted from Meinert C : Clinical trials. Design, conduct, and analysis. New York, Oxford University Press, 1986 and Stanley, Circulation 115:1164, 2007.

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



Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) | National Institutes of Health | U.S. Department of Health and Human Services

The NIH Common Fund
Office of Strategic Coordination WE ACCELERATE DISCOVERY.

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About the NIH Roadmap

NIH COMMON FUND AND THE AMERICAN REINVESTMENT AND RECOVERY ACT (ARRA)

- Overview
- ARRA Funded Research
- Search ARRA Funded Projects
- Notice: Recovery Act of 2009: FederalReporting.gov Opens for Registration
- Notice: Recovery Act of 2009: Information on Quarterly Reporting Requirements for NIH Award Recipients
- Notice: NIH Population Tracking Requirements for ARRA Awards

OVERVIEW

The NIH Roadmap for Medical Research was launched in September, 2004, to address roadblocks to research and to transform the way biomedical research is conducted by overcoming specific hurdles or filling defined knowledge gaps. Roadmap programs span all areas of health and disease research and boundaries of NIH Institutes and Centers (ICs). These are programs that might not otherwise be supported by the NIH ICs because of their scope or because they are inherently risky. Roadmap Programs are expected to have exceptionally high potential to transform the manner in which biomedical research is conducted. They are also expected to be short term, 5–10 year programs. This incubator space time frame is intended to allow the major roadblocks that were defined for each program to be overcome, thereby stimulating further research conducted through the ICs.

NIH COMMON FUND

Roadmap programs were initially funded by a 1 percent contribution from each of the NIH ICs. In 2006, Congress responded to the need for NIH to develop innovative and cross-cutting programs by authorizing and funding the NIH Common Fund within the Office of the Director. The NIH Common Fund, including the programs of the NIH Roadmap for Medical Research, and is coordinated by the Office of Strategic Coordination, one of the six offices of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the Office of the Director. The annual Common Fund budget was $495 million in 2008, highlighting its importance in the overall NIH funding environment. To date, the Common Fund has been used exclusively to support the Roadmap.

SCIENTIFIC AREAS

Planning and implementation of Roadmap/Common Fund programs are highly dynamic to allow the NIH the flexibility to respond quickly to new ideas, challenges, gaps and advances in biomedicine. Roadmap/Common Fund programs are developed from a strategic planning process involving broad, representative input from multiple scientific and public sources. Through this process, 12 roadblocks were articulated that are being addressed through many initiatives. These 12 challenges have been categorized according to three themes: New Pathways to Discovery, Research Teams of the Future, and Reengineering the Clinical Research Enterprise. Initiatives funded through the Roadmap/Common Fund fit into one or more of these major themes and address specific roadblocks or gaps to:

- Foster high-risk/high-reward research
- Enable the development of transformative tools and methodologies
- Fill fundamental knowledge gaps
- [illegible]

Although the NIH Roadmap is still in its infancy, many of its programs have achieved significant research advances.

Subscribe to the NIH Roadmap E-mail list

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

One Person Cannot Learn All This Stuff!

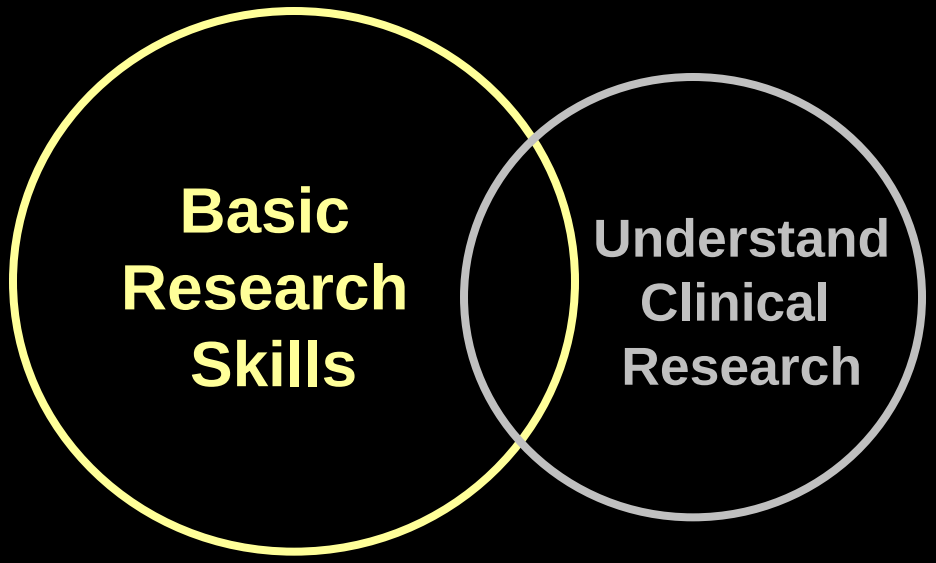
Translational Science is Team Science

Training Platforms for Translational Research

- No clear training pathway for translational research
- New training programs are emerging (CTSA)
- The success of these newer programs is unknown

Training Platforms for Translational Research

Basic Skill Sets



Clinical Skill Sets

- 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

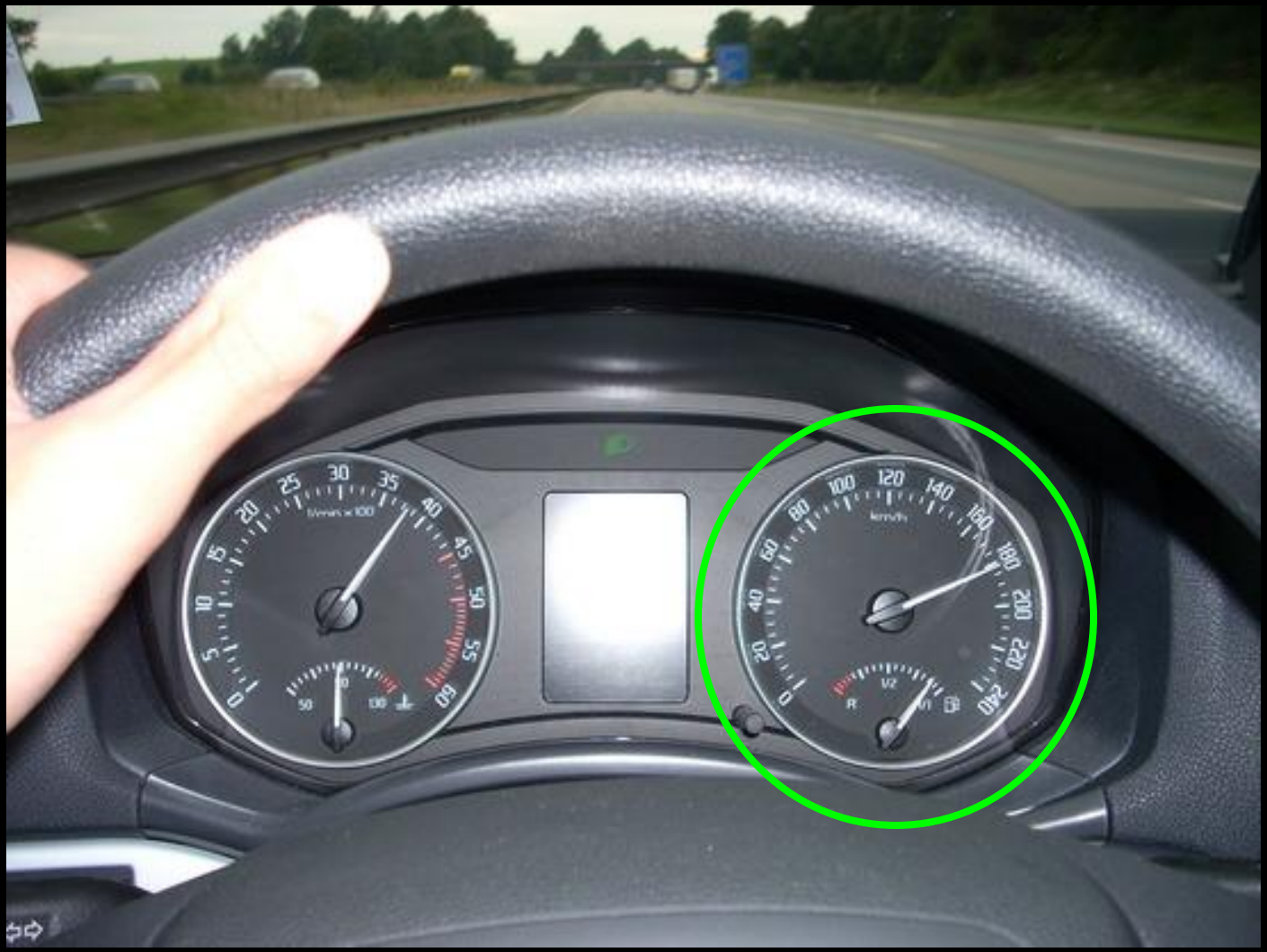
Who should engage in translational research?

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

SB Hulley, SF Cummings, WS Browner, DG Grady, TB Newman. Designing Clinical Research. 3d edition. Philadelphia, Lippincott Williams and Wilkins, 2007.

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 your 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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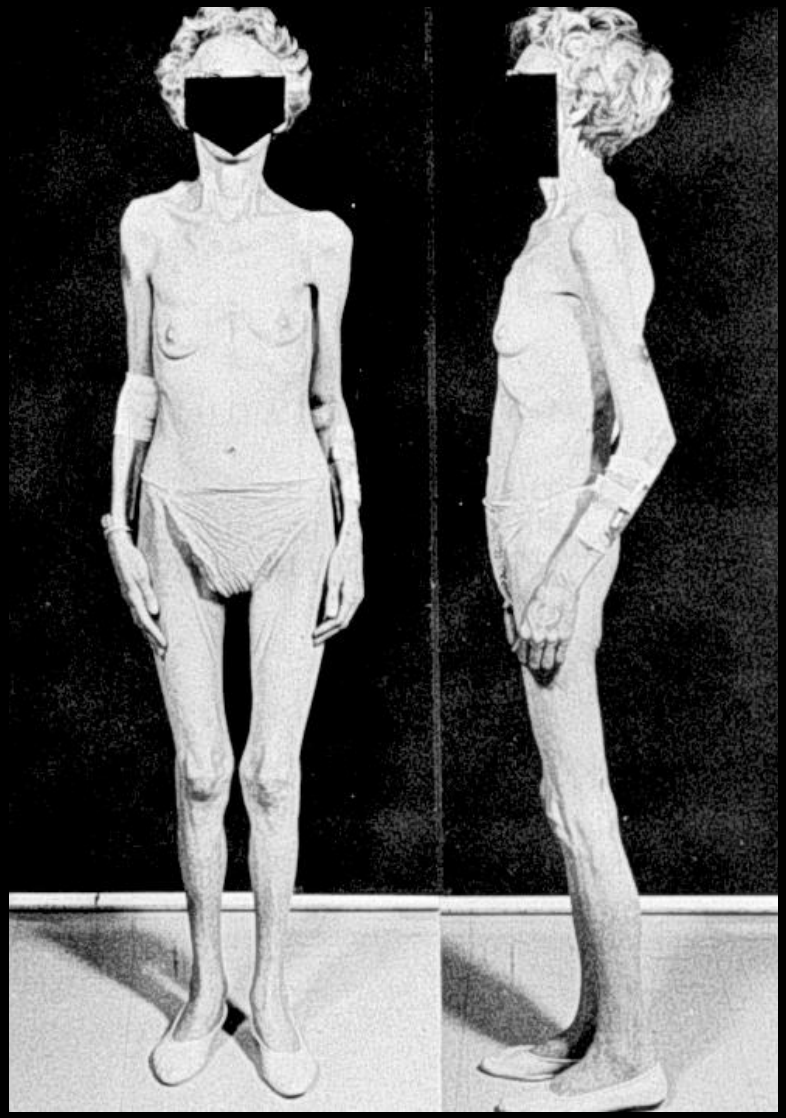
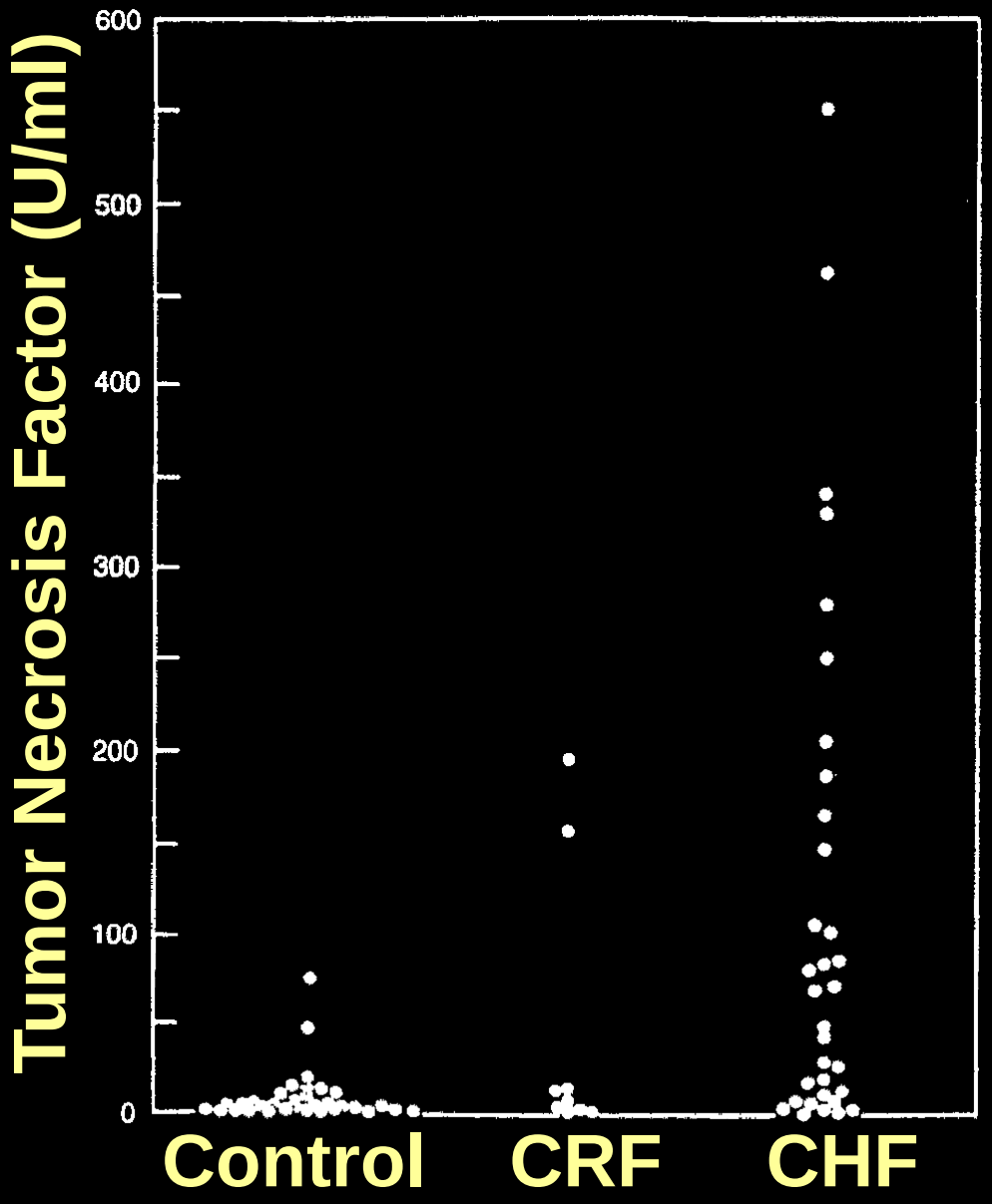
Chapter 6: What to do when you find yourself on the wrong side of the Kaplan-Meier Curve

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





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, α = 0.04

RECOVER
Clinical status
n=900, α = 0.04

RENEWAL

Death or CHF hospitalization (event driven), α = 0.01

Death (secondary end-point)

RENEWAL

Early Termination for Lack of Benefit

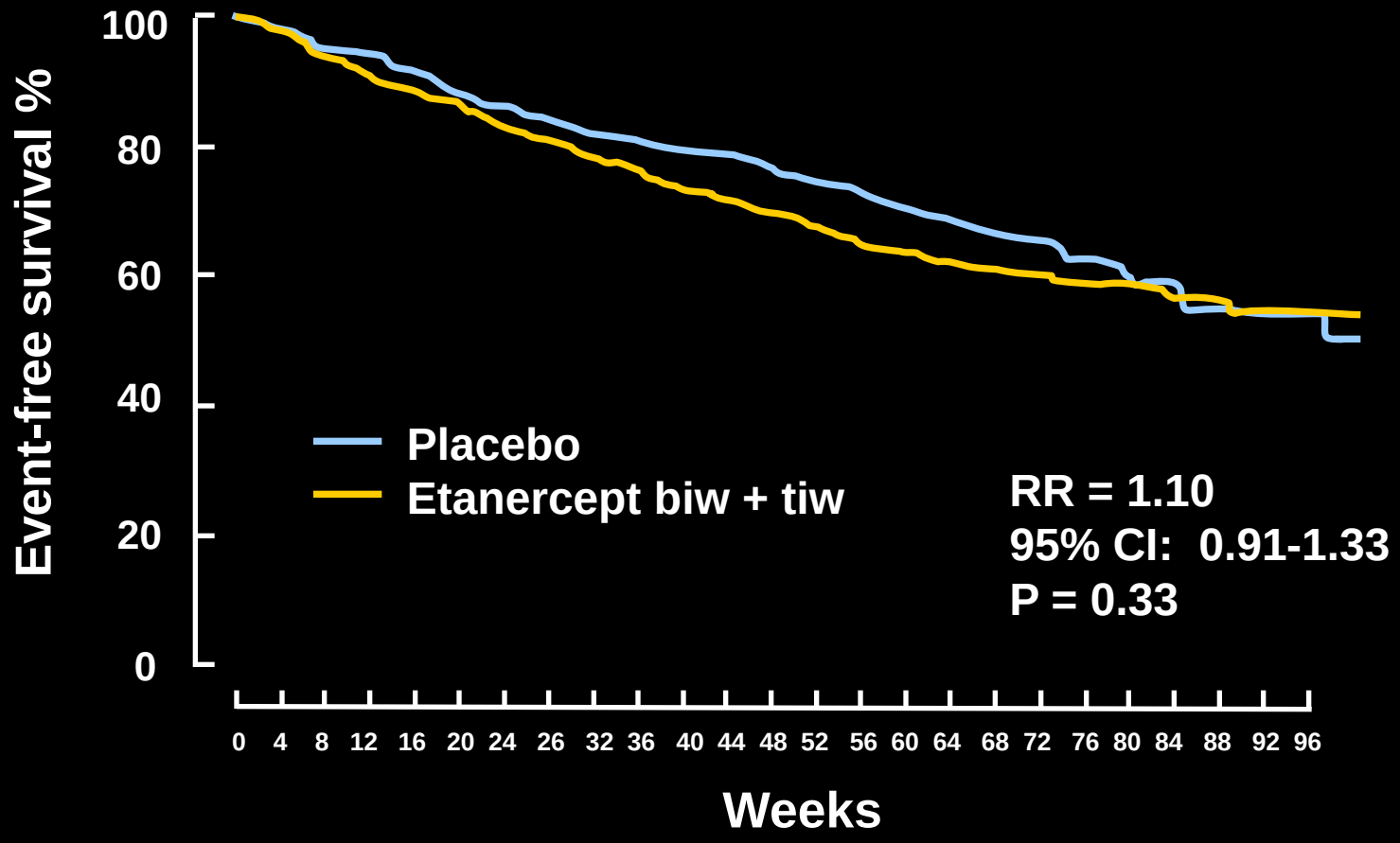
18 March 2001

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."*

RENEWAL

Primary End-Point (Death or CHF Hospitalization)



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.
1994: American Home Products buys American Cyanamid; Edward Fritzky joins Immunex.
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.
1997: Immunex partners with Wyeth-Ayerst Pharmaceuticals to market Enbrel in North America.
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/

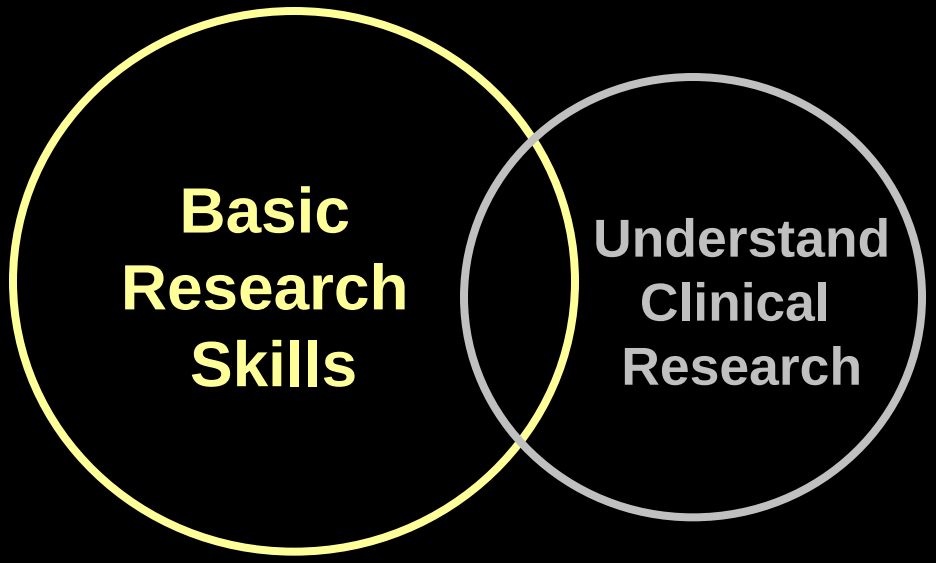
What Happens to Your Career After Your Clinical Trial Fails in Phase III

- 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

Its about the biology stupid!

Training Platforms for Translational Research

Basic Skill Sets



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Translational Research

- 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

By M.H. Alderson

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