Translational Research

What is it and what does it entail?

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Evolving Public Health Challenges

- Acute to Chronic Conditions
- Aging Population
- Health Disparities
- Emerging Diseases
- Biodefense
Multi- and Interdisciplinary Research Will Be Required To Solve the “Puzzle” of Complex Diseases and Conditions

- Genes
- Behavior
- Diet/Nutrition
- Infectious Agents
- Environment
- Society

???
Translational Research

Definition:

Research at the bench-bedside interface designed to define disease pathobiology and to explore innovative approaches to treatment and prevention.

Translational research fosters the multidirectional integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving the health of the public.

Acad Med. 2010 Mar; 85(3): 470–475
Translational Research Model

Basic Research $\xleftarrow{T_2}$ Clinical Investigation $\xrightarrow{T_2-T_3}$ Clinical Trials $\xleftarrow{T_2}$ Practice In the Community

Bench: Molecules & Cells
Bedside: Patients
Community: Community & Populations
Definitions of Basic Research and Basic Science

Basic research is performed without thought of practical ends. It results in general knowledge and an understanding of nature and its laws.

This general knowledge provides the means of answering a large number of important practical problems, though it may not give a complete specific answer to any one of them. The function of applied research is to provide such complete answers.

Definitions of Clinical Research

- Patient-oriented research. Research conducted with human subjects for which an investigator directly interacts with human subjects.
- Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.
- Epidemiologic and behavioral studies.
- Outcomes research and health services research.

Types of translational research

T1 research expedites the movement between basic research and patient-oriented research that leads to new or improved scientific understanding or standards of care.

T2 research facilitates the movement between patient-oriented research and population-based research that leads to better patient outcomes, the implementation of best practices, and improved health status in communities.

T3 research promotes interaction between laboratory-based research and population-based research to stimulate a robust scientific understanding of human health and disease.

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- T1: Bench to bedside translation (clinical investigations and clinical trials)
- T2: Bring advances in clinical trials to practice in the community- translation to patients (Guideline development, meta-analyses, systemic reviews)
- T3: Practice-based dissemination research and implementation research (translation to practice)
Success Story in Translational Research in HCV infection

1989: HCV discovered
1991: Interferon FDA approved for HCV
1998: Combination IFN + Riba
2001: Combination Peg-IFN + Riba
2002: Peg-IFN
2009: Oral Antiviral Regimen
2014+: Broad Genotype Coverage

Mouse model of HCV infection
HCV replicated in vitro
Discovery of NS3/4A serine protease activity
COMPONENTS OF THE TRANSLATIONAL RESEARCH ENTERPRISE

- Bench and clinical scientists
- Specialized resources: animals, tissues
- Specialized cores providing shared resources
- Specialized services: nursing, pharmacy, dietary
Re-Engineering the Clinical Research Enterprise

Molecular Libraries and Imaging

Building Blocks, Biological Pathways and Networks

Structural Biology

Bioinformatics and Computational Biology

Nanomedicine

New Pathways to Discovery

Clinical Enterprise

Public-Private Partnerships

High-Risk Research

Interdisciplinary Research

Implementation Groups

Research Teams
Translational Research in Action: Alcoholic Liver Disease

Basic Research $T_1$

Clinical Investigation

Clinical Trials $T-2-T_3$

Practice In the Community

Bench

Bedside

Community

Molecules & Cells

Patients

Community & Populations
Inflammasome is activated in alcoholic liver disease

Lieber-DeCarli ethanol diet or control diet (pair-feeding); 4 weeks, wild-type mice

Data presented as mean ± SEM (N=7-12 mice/group). Original magnification 200x.
Could IL-1 inhibition be beneficial in ALD?

**IL-1β**

- Upregulates other cytokines
- Sensitizes hepatocytes to cell death
- Impairs hepatocyte regeneration
- Promotes liver fibrosis

**IL-1Ra**

- Interleukin-1 receptor antagonist (IL-1Ra)
- Endogenous competitive antagonist: anakinra

**Target cells**

Kubes et al., Gastroenterology 2012;143(5):1158-72
Pharmacologic inhibition of IL-1 attenuates alcoholic liver disease in mice
Focus on key elements of the pathogenesis of alcoholic hepatitis

• Inflammatory cascade and innate immune activation
  • a demarcating feature of AH compared to mild to moderate alcoholic liver disease

• Gut integrity
  • that is significantly altered in alcoholic hepatitis allowing pathogen-associated molecular patterns (PAMPs) to enter the liver and systemic circulation and induce innate immune activation,

• Cell survival and death pathways
  • that contribute to liver dysfunction and the release of damage-associated molecular patterns (DAMPs) that further fuel inflammation.
Multicenter randomized double-blind pilot study in severe alcoholic hepatitis

**Study Design**

MELD 20-31 + DF>32

MELD >31 + DF>32

Prednisone (n = 65)

IL-1RA * + pentoxiphylline + zinc (n = 65)

* IL-1RA: Interleukin-1 Receptor Antagonist
Team of Clinical Research

Common Core Knowledge

- Patient
- Disease
- Clinical Trialist
- Clinical Pharm
- Behavioral Scientist
- Statistician
- Clinician
Why do a clinical trial?

• To answer a clinical problem
• To gain new knowledge about a new or established treatment
• To support a “claim”
  • For gaining government regulatory approval
  • For marketing a drug, device, or technique
What is a clinical trial?
A clinical trial is a tool for testing

- Drug
  - New drug
  - Old drug in new disease
  - Drug combination

- Device
  - Fibrometer - new device for invasive measurement of liver fibrosis

- Technique
  - Biomarker analysis for indication of the extent of liver inflammation
Guiding principles

• Ethics
• Scientific validity and integrity
• Medical relevance
• Regulatory and medicolegal issues
• Costs
What is step one?

• Start with a hypothesis
  • Must be in the form of a statement

• Then turn it into a specific question
  • The question must be “answerable”
  • This form the basis of the study “Objectives”
Next steps

- The study specifics flow from the objectives
  - Intervention efficacy
  - Intervention safety
- Design the details of your intervention
- Choose the outcome you wish to measure
It is good to be a control freak

- Intervention must be a compared to something else
- How do you choose a control intervention?
- Usually compare study intervention to standard intervention
- Go back to your original question
Who is going to be recruited in the trial?

• Go back to your original question
• Determines the patient population to which the study results will apply
• Minimize the effect of confounding variables
• Eligibility: inclusion and exclusion criteria
• Determine the sample size
Eligibility pitfalls

• Narrow definition
  • Homogenous patient group, fewer confronting variables
  • Results applicable to narrow patient profile
  • Harder to recruit patients

• Broad definition
  • Greater potential for confounding variables to affect results
  • Results more broadly applicable
  • Easier to recruit patients
Typical inclusion criteria

• Subject must have disease of interest
• Subject must have a certain “amount” of disease
• Subject must understand study and agree to participate
• Other
Study procedures

• Divide your study patients into groups
• Administer the study and control interventions to the respective groups
• Measure the outcome
Data analysis

- Record the outcome(s) of interest
- Compare the data for each intervention group
- Derive conclusions
Recording data

• Outcomes must be quantifiable

• Outcomes must be standardized

• “A/E” - adverse effects must be recorded
Study conclusions

• Two possibilities
  • The study and control interventions are different
  • The study and control interventions are the same

• How do we decide?
Statistics

- Used to determine the significance of the study data based on laws of probability
- P<0.05 - what does this mean?
- Also used to determine the power of a study (i.e. the number of patients needed to recruit)
What is the clinical trials’ s greatest enemy?

• BIAS
How do we minimize bias?

- Make sure groups are equivalent
- Standardize outcome assessment
- Randomization
- Blinding
  - Single- or double-blind versus open-label
  - Role of placebo
  - ?triple-blind
Anatomy of a typical study protocol

1. Introduction
2. Study objectives: primary and secondary
3. Overall study design
4. Study flowsheet
5. Enrollment criteria
6. Specific study procedures
   - Randomization
   - Intervention
   - Outcome measures
   - Protocol deviations
7. Data analysis and statistics
8. Ethical considerations
Type of trials

• Phase I
• Phase II
• Phase III
• Phase IV
Phase I

- Early use of drug
- Mainly aimed at establishing safety and toxicity limits
- Study subjects often “normal”
- No control groups
- Usually open-label
Phase II

- “Proof of Principle” stage
- Intervention studied in patients with disease
- Dose-finding
- More safely data
- Sometimes combined with Phase I
Phase III

• Randomized controlled trial
• Double-blind whenever possible
• More patients
• Multicenter
• Ongoing safety data
Phase IV

- Post-approval studies
- Further exploration of intervention
- New indications or new uses of drug
Summary

Translational research can change medical practice, cure disease and impact millions of lives! Your research should make a difference!
THANK YOU