Defining Translational Research: Implications for Teaching and Training

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Q1

Translational research means different things for different people.

We all however agree that it means one thing, among five listed below (A-E), for all people:

A. Translational research should only be dominated by basic research

B. Translational Research Fosters the Multidisciplinary Integration of Basic Research, Patient-oriented Research, and Population-based Research, with the Long-term Aim of Improving the Health of the Public

C. Only patient-oriented research should be at its helm

D. Translational research should be split 50/50 between basic research and patient-oriented research

E. All translations should be kept in English or Spanish
Q2

- Patient-oriented Research, i.e. Research Conducted with Human Subjects Is Most Likely To Include Exploration of:

A. Mechanisms of Human Disease
B. New Diagnostic Tests, Disease Biomarkers
C. Therapeutic Interventions/RCT
D. Development of New Technologies
E. All the Above
Q3

- Precision Medicine, as a Quin of Translational Research, Is Most Likely to Represent the Following:

A. A long-term aim to generate knowledge based on whole-genome sequencing of 1 million of Americans applicable to health and disease in the setting of genetic variants and personalized medicine

B. Precise Approach to Mechanisms of Human Disease

C. Precise Harnessing Diagnostic Tests & Disease Biomarkers

D. Precise Therapeutic Interventions

E. Precise Development of New Technologies
Truly Translational Research, Expanding Our Knowledge of Patient Populations, Should Include Only the Following:

A. Epidemiology
B. Psychology
C. Economics
D. Behavioral Sciences
E. All the Above
NIH Has Made Translational Research a Priority Forming Centers for Translational Research with Total Funding 500 million/year Starting in Year:

A. 2004
B. 2006
C. 2008
D. 2010
E. 2012
Oh my!... Dr. Sarosiek is going to explain this better than me!!!
Defining Translational Research

- Translational Research Means Different Things to Different People, But It Seems to Be Important to Almost Everyone

- For Many, the Term Refers to the “Bench-to-bedside” Enterprise of Harnessing Knowledge from Basic Science To Produce New Diagnostic Tests, Devices, Drugs and Treatment Options in Humans/Patient Populations

- NIH Has Made Translational Research a Priority Forming Centers of Translational Research at Its Institutes ($0.5 billion/year) and Launching the Clinical & Translational Science Awards (CTSA) Nationwide in 2006

- By 2012, the NIH Funded 60 Clinical & Translational Science Academic Centers Nationwide

- *Translational Medicine* and the *Journal of Translational Medicine* are Devoted to the Topic

- EU Allocated €6 billion Budget and UK Invested £0.5 billion

_Woolf SH, JAMA, 2012;308:211-13._
Definitions of Basic Research

- Basic Research Represents Acquisition of Knowledge Without the Obligation to Apply It To Practical Ends
- Requires Mastery of Molecular Biology and Genetics/Genomics with Cutting-edge Technology
- Quest for Progressive Knowledge During Basic Research Further Our Understanding of Nature and Its Laws
- Basic Research Is Performed Without Thoughts Regarding Its Practical Aspect
- We Could Potentially Call it Starting Point, or $T_0$ (J.S.)

Definitions of Clinical Research

~ 30% NIH $$

- Patient-oriented Research, i.e. Research Conducted with Human Subjects Is Including Exploration of:
  - Mechanisms of Human Disease
  - New Diagnostic Tests, Disease Biomarkers
  - Therapeutic Interventions
  - RCT
  - Development of New Technologies

- Research Conducted on Material of Human Origin such as Tissues, Specimens & Cognitive Phenomena for Which an Investigator (or Colleague) Directly Interacts with Human Subjects

- Epidemiologic & Behavioral Studies (Health Habits Can Kill)

- Outcomes Research & Health Services Research Saving Lives

- We Could Potentially Call it In Depth Exploration, or $T_{xy}$ (J.S.)

Definitions of Translational Research Evolving ~ 1993

- Spanning Basic & Clinical Research, i.e., Applied Research; The Interface Between Basic Science & Clinical Medicine
- NIH 2011 Definition Includes Two Areas of Translation
  - Application of Basic Research & Preclinical Studies Discoveries to the Development of Promising New Drugs, Design of Further Exploratory Studies and Trials/RCTs in Humans
  - Research Aimed at Enhancing the Adoption of Best Practices/EBM in the Community Including Cost-effectiveness of Prevention and Treatment Strategies – US Patients Receive only 50% of Recommended Services: QI !!!

Definitions of Translational Research Evolving (cont.)

- Translational Research Is Part of a Unidirectional Continuum In Which Research Findings/Knowledge Are Moved from Researcher’s Bench to
  - The Patient’s Bedside/Clinical Research Trials (T1 or First Stage)
  - And Transfer Findings From Clinical Trials to Practice Setting and Communities, Where Harnessing RCT Findings and Knowledge (EBM) to Primary Care Improves Health (T2; Second Stage)

Still Translational Research Evolving (cont.)

- However, Translational Research May Still Mean Different Things to Different People

- Sometimes T1 or First Stage as Well as T2 or Second Stage are Too Narrowly Defined & Interpreted

- If T2 Translational Research is Going to Result in the Knowledge Needed to Improve Health & the Quality of Life, Then T1 Research Must Include Science Related to Populations, e.g.:
  - Epidemiology
  - Psychology
  - Economics
  - Behavioral Sciences

Still Translational Research Evolving (cont.)

- The Translational Research Working Group of the NCI, NIH and The Institute of Medicine (IOM) Included Both Basic & Clinical Research in the T1 Segment of the Continuum:
  - Translational Research Transforms Scientific Discoveries Arising from Laboratory, Clinical, or Population Studies Into Clinical Applications to Reduce Cancer Incidence, Morbidity, and Mortality

- But Given the Basic Research and Clinical Research Involve Inherently Different Knowledge Sets and Methodologies, Including Both of Them in the Same Segment of the Continuum (i.e., in T1) Obscures the Fact that Multidisciplinary Translational Research Can Also Occur at the Interface of Basic and Clinical Science

Working Definition of Translational Research

- In Order to Develop a Framework to Assess NIH Translational Research Programs, Competency Requirements Need to Be Defined and Determined Whether These Requirements Are Being Met

- Therefore, the Following Working Definition of Translational Research Is Developed:
  - Translational Research Fosters the Multidisciplinary Integration of Basic Research, Patient-oriented Research, and Population-based Research, with the Long-term Aim of Improving the Health of the Public
  - T1 Research Expedites the Movement Between Basic Research and Patient-oriented Research that Leads to New or Improved Scientific Understanding of Standards of Care; Basic Science Translated to Clinical Efficacy
  - 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; Efficacy Translated to Clinical Effectiveness
  - T3 Research Promotes Interaction Between Laboratory-based Research and Population-based Research to Stimulate a Robust Scientific Understanding of Human Health and Disease (Figure 1); Effectiveness Translated to Health-care Delivery

Figure 1. Model for translational research as proposed by the Evaluation Committee of the Association for Clinical Research Training. 

In Model Presented in Figure 1, the T1, T2, and T3 Arrows Represent Bridges Leading From One Type of Research to Another.

Examples of T1 Research are: Drug Development, Pharmacogenomics, and Some Studies of Disease Pathomechanism and Research Into New Areas such as Genetics, Genomics, and Proteomics.

*Precision Medicine*, Announced by Mr. President Obama 1 Year Ago, Is Providing Funding for NIH to Cover the Cost of 1 Million of Complete Genome Sequence Among Patients with Various Types of Cancer, Other Systemic Diseases and Asymptomatic Volunteers, Represents the Most Innovative, Adventurous and Progressive within Translational Research Enterprise.

Examples of T2 are Clinical Epidemiology, Health Services (Outcomes) Research, and the Newly Developing Methodology of Community-based Participatory Research.

Examples of T3 are Emerging Disciplines such as Molecular and Genetic Epidemiology Generating Strong Database that May Set the Stage for New Hypotheses that Can be Tested in Basic Science Labs (T1 Again) and Potentially New Biomarkers Identified in Animal Models Can Translate Into Population-based Screening Tools (Back to T2 and Returning to T3 In the Future).

Implications for the Design of Training Programs

- The Interaction of Several Disciplines Is Required To Translate Knowledge from One Type of Research to Another, e.g., To Move a Basic Science Discovery to the Bedside.

- Collaboration Among Disciplines Through Multidisciplinary Teams Facilitates the Emergence of Novel Concepts and Approaches To Addressing Important Health Issues

- The Emergence and Development of New Ideas Are Goals of Translational Research, and There are Many Possible Models of Training that Can Provide the Academic Path to These Remarkable Goals

Implications for the Design of Training Programs (cont.)

- Training in Translational Research Will Vary Depending on the Background of Trainees and the Areas of Research They Plan To Pursue

- Given the Diversity of Educational Backgrounds and Research Interests, It Will Be Necessary To Design a Customized Curriculum for Almost Every Trainee

- To ensure an Understanding of Complementary Disciplines and To Enhance Communication and Collaboration, Trainees Who Have Focused on Basic Laboratory Research Will Need to Become Immersed in Clinical Science and Clinical Practice, While Trainees with a Clinical Focus Will Need to Gain Exposure to Basic Science Research

Implications for the Design of Training Programs (cont.)

- For Example, Trainees Interested in Neuroscience May Wish to Accompany Clinicians in a Psychiatry or Neurology Clinic and Trainees Working on Bone Tissue Regeneration May Participate in the Activities of a Clinical Orthopedic Surgery Program.

- Trainees Seeking Laboratory Immersion Could Take Courses in Technique of Molecular Biology or Genetics and Work at the Bench for a Concentrated period of 3-4 Months.

- All Trainees Could Benefit from Fundamental Instruction Concerning Study Design, Data Collection, Statistical Analysis, Ethics and Research Integrity, IRB, the Search for Funding, Writing Grant Applications and the Pursuit of Patents and Technology Transfer.

- The Competencies Needed To Thrive in a Multidisciplinary Collaborative Teams such as Communication, Negotiation Skills as Well as Ethical and Humanitarian Attitudes Have To Be Acquired by Trainees.

Implications for the Design of Training Programs (cont.)

- An Individualized Curriculum for Each Trainee, Guided by a Customized, Learner-centered Advisory Committee that Includes Mentors with Various and Complementary Backgrounds in Clinical Practice and Basic and Clinical Research Needs to be Designed and Implemented.

- One of the Mentors Would Assume the Role of Primary Mentor to Ensure Coordination of Efforts and the Success of the Mentoring Process Letting also Trainees to Acquire Critical Thinking Skills and Practical Knowledge about how To Work Collaboratively and Manage Teams.

- Most of Medical Schools Shifted Recently Emphasis to Training Medical Students and Residents How To Think Critically and To Follow Present Algorithms and Decision Trees Necessitating Out-of-the-box Thinking and Learning how To Excel as Critical Thinkers.

Conclusions

- We Believe that Translational Research Moves in Bidirectional Manner From One Type of Research to Another:
  - From Basic Research to Patient-oriented Research
  - To Population-based Research
  - And Back- and Involves Collaboration Among Scientists From Multiple Disciplines

- The Design and an Effective Training Program in Translational Research is a Challenge Because the Program Must Offer Each of Its Trainees the Opportunity to Master a Combination of Skills that Are Not Taught Together in Traditional Training Program

- The Approach to Evaluating the Success of Translational Training Program Must Be Flexible Enough To Accommodate the Needs of Individual Institutions and Individual Trainees Within the Institutions, but It Must Also Be Rigorous Enough to Document that the Program Is Meeting Its Short-, Intermediate-, and Long-term Objectives and Its Trainees Are Meeting Pre-established Competency Requirements

A New Initiative on Precision Medicine

- The concept of precision medicine – prevention and treatment strategies that take individual variability into account – started with blood typing guiding blood transfusions for more than a century.
- But the prospect of applying this concept broadly has dramatically improved by recent development of large-scale biologic databases (large sets of individual patient data) such as human genome sequence characterizing each patient in terms of:
  - Genomics
  - Proteomics
  - Metabolomics
  - Diverse cellular assays
  - And even mobile health technology; needed to guide clinical practice.

A New Initiative on Precision Medicine (cont.)

- The proposed by NIH and National Cancer Institute Initiative, outlined also in President Obama *State of the Union Address*, has 2 main components:
  - A near-term focus on cancers, especially that each cancer has its own genomic signature interacting greatly with patients inherited genetic variants of highly personalized sequence
  - A long-term aim to generate knowledge applicable to the whole range of health and disease in the setting of genetic variants of personalized medicine

- We should never underestimate the value of our growing population of internet, social media and mobile devices savvy & well educated patients with growing desire to be active partners in medical research

A New Initiative on Precision Medicine (cont.)

• To accelerate this progress one can envisage assembling over time a longitudinal “cohort” of 1 million or more Americans who volunteered to participate in genetic/genomic research involving whole-genome sequencing as well as behavioral data all linked to their electronic health records.

• Such a varied array of research activities will propel our understanding of diseases – their origins, mechanisms, and opportunities for prevention and very accurate/successful treatment.

A New Initiative on Precision Medicine (cont.)

• Study of the large research cohort exposed to many kinds of therapies may provide early insights into pharmacogenomics – enabling the provision of:
  – the right drug
  – at the right dose
  – to the right person

Fig 1. Biomedical research translation continuum.
Figure 1 Research papers published from 1993 to 2012.
Figure 4 Annual journals distribution of WoS papers.
Figure 2 Main subjects of WoS papers on translational medical research.
Three-phase translational research

The current National Institutes of Health (NIH) Roadmap for Medical Research includes 2 major research laboratories (bench and bedside) and 2 translational steps (T1 and T2). Historically, moving new medical discoveries into clinical practice (T2) has been haphazard, occurring largely through continuing medical education programs, pharmaceutical detailing, and guideline development. Proposed expansion of the NIH Roadmap (blue) includes an additional research laboratory (Practice-based Research) and translational step (T3) to improve incorporation of research discoveries into day-to-day clinical care. The research roadmap is a continuum, with overlap between sites of research and translational steps. The figure includes examples of the types of research common in each research laboratory and translational step. This map is not exhaustive; other important types of research that might be included are community-based participatory research, public health research, and health policy analysis.
Four-phase translational research model
Schematic illustration of different types of database sources that need to be created for the analysis of cases (patients) versus healthy individuals (controls). Since these data are as a rule stored in different domains (clinical and research), a single case-control study needs to collect the data several times during a study, and this cycle must be repeated whenever a new case-control study is initiated.
THE LAST MILE
The Road to Improved Chronic Kidney Disease Outcomes
Translational Research

Outcomes obtained in "Laboratory" are applied to "Clinical Site"

Issues found in "Clinical Site" are studied in "Laboratory"

Bench (Laboratory)

Bedside (Clinical Site)
Survey B: Distributed six weeks post-completion.

Would you recommend the INTREPID Summer Program to a colleague?

- Yes: 6
- No: 0

How has your participation in this program affected your career goals?

- Very strongly: 1
- Somewhat strongly: 2
- Somewhat: 1
- Not at all: 2

How effective was this program in addressing your gaps in knowledge?

- Very effective: 2
- Effective: 4
- Partially: 0
- Not at all: 0

Figure 4. Survey B results
All participants (n=6) completed a second survey 6 weeks after the course completion, when they had returned to their professional responsibilities and duties.