“Bridging the gap between clinical medicine and basic science: opening Pandora’s box”

Workshop

Filio Billia, MD PhD
Scientist, Toronto General Hospital Research Institute, University Health Network
Assistant Professor, Institute of Medical Sciences and Physiology, University of Toronto
Director of Research, Peter Munk Cardiac Centre
Co-Director, Peter Munk Cardiac Centre Cardiovascular Biobank
Divisions of Cardiology and Multi-organ Transplant, University Health Network

Anthony Gramolini, PhD
Professor, Department of Physiology, and Translational Biology and Engineering Program, Univ of Toronto
Scientist, Toronto General Hospital Research Institute, University Health Network
Heart and Stroke/Richard Lewar Centre of Cardiovascular Excellence
Disclosures

None
“Research into disease mechanisms and novel therapies is critical to the urgent need to stem the tide of cardiovascular disease and to “bend the cost curve” of associated expenditures.”

Workshop Objectives

1. to discuss challenges, potential solutions and examples for integrating basic science programs with clinical care
2. to describe translational research programs and how they can integrate into clinical care
3. to discuss biobanking and in large clinical centres and how they can provide important clinical information
Integration of basic science programs with clinical care
An “Ideal” Alignment

Basic Science Priorities

Clinical Science Priorities

Identify commonalities
Prioritize Value-added outcomes
Start basic science early!

- Role of basic science in the Medical school curriculum is critical
  - Foundation of sciences for the practice in medicine
- There is a redesign of medical school curricula across Canada to integrate
- Questions
  - Is basic science relevant to education in Medicine?
  - Or does science just need to be taught in a different way?
  - How can we deal with the explosion of new scientific information?
    - What needs to be taught?
    - When should that occur?
Key Question: In what way does basic science fit into competence as a physician

How is basic science incorporated into the practice of medicine depends upon basic assumptions about what medical practice is, or more specifically, what the “competence” of an individual physician means.

Epstein and Hundert defined competence as:

“the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, the values and reflection in daily practice for the benefit of the individual and community being served.”
Does science aid understanding

- In the past 2 decades, most of the focus has been on “making a diagnosis” rather than the broader concept of clinical decision-making
  - includes diagnostic and therapeutic planning, and shared decision making with patients and families.

- Is basic science knowledge required for developing diagnostic reasoning?
  - “Flexner model” - premedical training of 2 years of basic science was seen as a prerequisite for learning clinical medicine.

- What has become a commonplace is that clinicians do not “use” basic science in their decision-making and rely on pattern recognition.
  - Studies have shown that experts do, in fact, use a knowledge of basic science mechanism in solving more difficult problems.

- General principle of management by large clinical trials for both diagnosis and therapy, so-called “evidence-based medicine” (EBM), may HAVE REPLACED the understanding of mechanism of disease and/or therapy.
So where does basic science fit into practice in 2018 and beyond?

- In straightforward cases, clinicians do not articulate use of basic science in clinical reasoning because their knowledge is compiled or encapsulated and because the cases are routine and simple.

- However, physicians must be able to manage more difficult problems.
  - Medical education must train those who not only follow practice guidelines, but who can write such guidelines and who have the authority to deviate from these guidelines.
  - An understanding of science is essential.
  - Reality is we are all seeing more complicated patients as they live longer, with complex co-morbidities!
Basic science during medical training

Integration of Basic Sciences and Clinical Sciences in a Clerkship: A Pilot Study

IAMSE Editor
International Association of Medical Science Educators - IAMSE

John C. Sakles, M.D.¹, Renee J. Maldonado² and Vijaya G. Kumari, M.B.B.S., Ph.D.³

¹Department of Internal Medicine, ²Office of Curricular Support and
³Department of Cell Biology and Human Anatomy

University of California Davis, School of Medicine
Davis, CA 95616, U.S.A

ABSTRACT
Limited formal mechanisms exist for exploring basic sciences during the clinical clerkships in many medical schools. This study was

• N=48 4th year students in ER rotation.
• Basic scientists were included in teaching.
• Common clinical presentations were selected for a case-based approach.
• Students researched/discussed both basic science and clinical issues
• > 50% of clinical clerks felt that sessions enabled them to achieve a deeper understanding
Integrating basic and clinical science: The critical care module of the interdisciplinary foundations of medicine curriculum

Robert G. Hendrickson, Ernest L. Yeh, Heatherlee Bailey, Barry Mann, Lewis J. Kaplan

Research output: Contribution to journal › Article

Abstract

Introduction: In an effort to better link the preclinical and clinical years, we designed a Critical Care Module (CCM) to underscore the dependence of clinical reasoning and decision making on basic science knowledge. Methods: A one-week module covered major topics introduced during the two preclinical years. These areas (sepsis, infectious disease, neural science, endocrine, renal, pulmonary, immunology, and cardiac) were explored using a case-based format that linked clinical
Contemporary issues in Medicine: Basic science and clinical medicine

2001 report by Association of American Colleges

- A recognition for a transformation of teaching in medical schools is needed
  - Major changes in the organization, content, and management of the curriculum was needed
    - Adoption of new pedagogical approaches for facilitating students’ learning
    - Establishment of a wider range of venues for providing clinical education
    - Individual basic science courses replaced by integration of basic science into clinical content, using small group or independent learning exercises as the primary instructional format.
What is the impact of these changes

1. Reduction of basic science component in medical curriculum
2. Argument is that new physicians must possess adequate knowledge of the basic sciences relevant to medicine if medical practice is to continue to evolve as a scientifically based endeavor.
3. Concern expressed that the reduced emphasis on basic science education in medical school, and the attendant diminished role of basic science departments in the education of medical students, may eventually impact adversely on the quality of medical practice.
4. Knowledge and understanding of the scientific principles that govern human biology provide the rationale for the contemporary practice of medicine and provide the rationale for incorporating new knowledge into their practices over the course of their professional careers.
Premedical preparation

1. Is it enough?
2. Medical practice should be based on a sound understanding of the scientific basis of diagnosis and management of patients
3. Knowledge and understanding of the scientific principles that govern human biology provide doctors not only with a rationale but also the framework for incorporating new knowledge into their practices
4. The problem of rapid and continuing expansion of knowledge, coupled with a commitment to life-long learning, requires that medical school graduates possess the appropriate skills to understand, critically assess, and incorporate into their clinical practice basic science concepts and facts that are as-yet unknown.
Medical education should develop:

- Knowledge of:
  - Normal structure and function
  - Molecular/biochemical/cellular mechanisms important homeostasis
  - Causes of disease
    - Genetic, developmental, metabolic, toxic, microbiologic, autoimmune, neoplastic, degenerative, and traumatic
  - Altered structure and function
  - Epidemiology of common diseases
  - Approaches to reduce incidence and prevalence
  - Ability to reason deductively in solving (clinical) problems
  - Ability to retrieve, manage, and utilize biomedical information for clinical decisions
  - Principles of pharmacology, therapeutics, and therapeutic decision making
  - Principles in the emerging disciplines of genomics, proteomics, and bioinformatics
  - Ability to critically evaluate the limitations of diagnostic methodologies
Medical education should develop:

A. Understanding the need to be a life-long learner
B. Understanding the power of the scientific method in establishing causation of disease and efficacy of traditional and non-traditional therapies
C. The capacity to recognize and accept limitations in one’s knowledge and clinical skills
The Vision:
We need better integration of translational research programs into clinical care
Hurdles

- Intellectual and cultural barriers
- Basic science starts with a hypothesis and designs experiments that validate or reject it
  - goal of acquiring knowledge, communicating it
- Translational science starts with a health need and looks for scientific insights or tools to address that need.
  - goal is improving health
Medicine today

- Is very different than 10 years ago
  - E.g. cancers, CVD, etc
- The ‘bench-to-bedside’ approach is the goal of translational research
  - converting basic science discoveries to effective targeted therapies
- Translational scientists have to ‘fluent’ in many languages, build a multi-disciplinary team and be a life-long learner
From the lab to the clinic and back

- To achieve advances in health care we need to develop translational research programs that bring together
  - Physicians
  - Bench scientists
  - Bioengineers
  - Epidemiologists
  - Patent experts
  - Quality assurance scientists
  - Cost-effectiveness experts
Translational science

- M.D./Ph.D. degrees train individuals in clinical and basic research
- Translational research programs strive to integrate these two sides of medical science by connecting people and building networks
- Basic scientist’s perspective - turn the medical objective that is written into a grant application into a real and achievable goal
Keys to success

- NEED TO TRAIN A NEW KIND OF RESEARCHER
  - Cross pollenate basic science WITH clinical
  - Multi-disciplinary teams
  - Multi-national teams

- Formalization of training in translational medicine/research
  - USA (Mayo)
  - UK (Cambridge, London, Newcastle)

- Healthcare landscape changing – changes in pharma, government, etc.
Translational axis:

Stage I studies:
to investigate basic mechanisms and discover new proteins and pathways

Stage II studies:
(exploratory studies), predominantly in mouse models, to conduct hypothesis-generating research and initial in vivo testing;

Stage III studies:
(confirmatory studies), as the last step before entering the clinical arena, involving rigorous research in a multicentre setting, with prospective registration of the key features of the study.
Select set of examples/areas of new research related to cardiovascular disease

- Setting the stage for clinical trials, next generation therapies, new areas of research...
Epigenomic profiling: human monocytes and endothelial cells.

- Annual Canadian Conference
- International initiative led UBC

Endothelial–cardiomyocyte interplay through paracrine factors.

>200 cardiac/endothelial experts in the country

Macrophage mediators and crosstalk after myocardial infarction.

Strong unanimous agreement that immunology is central to cardiac dysfunction

Lisa Honold, and Matthias Nahrendorf Circ Res. 2018;122:113-127
PI3K-mediated compartmentalization of β-adrenergic receptors-dependent Ca$^{2+}$ responses in cardiomyocytes.

-G-protein based Gordon and Keystone conferences routinely organized by Canadians

Most major institutions have developed informatics research programs and expertise.
Integration of science into clinical training and care is important.... But how do we achieve this??

Role of clinical biobanking
Definition: Biobank

▪ An organized collection of human biological material and associated information stored for more than one research purpose.
  ▪ Health information includes medical treatment, lifestyle data, clinical follow-up

▪ For genetics research
  ▪ Involves the collection of genomic DNA

▪ Informed, written consent required

▪ Can be:
  ▪ Disease-based (tumor, cardiovascular, etc)
  ▪ Population-based
  ▪ Twin-cohort studies
Why Biobank?

- To build a rich repository of biospecimens

- Resource for future discovery
  - Biomarkers, genetic, and mechanistic studies

Samples from heart failure patients are stored inside large tanks at the 14th floor, Toronto Medical Discovery Tower.
Biobanking – key for translational medicine

- Finding the right treatment for the right patient still remains a major challenge that is changing global healthcare
  - forms the basis for the rapid development of biobank facilities
- >7000 rare disease with <200 having available pharmacotherapy
Biobank papers published

year

# published

The promise of a healthy heart.
Biobanking

- Number of factors are reshaping the landscape of ‘biobanking’
  - Population growth
  - Powerful analytical technologies
  - Targeted therapies
  - Improvements in biorepository medicine
  - Changes in regulation and ethical considerations

- Ethical issues: safeguard against patient insure/employer discrimination, etc.
Biobanking

- Recents changes in technology for analysis of:  
  - Genome, Epigenome, Transcriptome, Proteome, Metabolome
- Has raised the ‘bar’ for biospecimen quality
- Researchers have procured biospecimens for decades
  - However lack of protocols for proper procurement, storage, database supports or quality control in the past.
Rich resource for research, BUT

- There is still debate on how to best provide:
  - Sampling procedures and protocols
  - Management and storage conditions
  - Identification of sample tubes, i.e. linked to a barcode
  - IT support allowing sample tracking ability
Formation of a biobank can be challenging

- Requires sustainability
  - Trained staff
  - Pathology/health care team
  - Integrated health information with adequate IT support and annotation is critical
Understanding best practice

- International Society of Biological and Environmental Repositories (ISBER) define what constitutes a high-quality biobank

- 2006: The Biospecimen Research Network was formed by the NCI
  - Provide lists of publications and searchable databases
  - Annual meetings to educate in the uniform and higher quality biosamples for personalized medicine research as well as diagnosis and therapeutics.
Multiple pre-analytical variables can affect the molecular integrity of the biospecimen

Variables (examples):
- Antibiotics
- Other drugs
- Type of anesthesia
- Duration of anesthesia
- Arterial clamp time

Time 0

Variables (examples):
- Time at room temperature
- Temperature of room
- Type of fixative
- Time in fixative
- Rate of freezing
- Size of aliquots

Pre-acquisition

Post-acquisition

The promise of a healthy heart.
1. Biospecimen collection and shipping
   - Tissue collection
   - Preliminary pathology and histology review
   - Quality validation
   - Specimen recording
   - Consent documentation
   - Bar code labeling and scanning
   - Data collection
   - Packaging and shipping

2. Biospecimen processing
   - Detailed pathology, imaging, and molecular analysis
   - Bioinformatics system data entry
   - Link assay, test results, and annotation to specimens
   - Bar code labeling and scanning

3. Biospecimen storage management
   - Liquid nitrogen, -80°C, and room temperature storage
   - Inventory control
   - Bar code scanning
   - Freezer room monitoring and physical security
   - Climate control, backup, and alarm systems
   - Periodic auditing of inventory

4. Biospecimen retrieval and distribution
   - Specimen retrieval equipment
   - Bar code scanning
   - Packaging and shipping
   - Inventory reconciliation
   - Validation of customer receipt
   - Customer sales and invoicing

5. Infrastructure and administration
   - Bioinformatics core/IT
   - Building and facilities
   - Management and personnel

The promise of a healthy heart.
Use of biobanks for genetic studies

- Have the capacity to generate a large amount of genetic data
- Need to consent patients for
  - Future contact
  - Desire to know about critical results
    - For critically meaningful research results to participants, processes need to be in place for a referral to a genetic counsellor/geneticist
Biobanked information

- Clinical samples (tissue/blood) + health information
- Data security is paramount
- Patients do care about the confidentiality
  - Patients wanted to have a sense of control
  - Patients needed a sense of protection from the possible dangers of disclosure (insurance/employment discrimination)
Scientific milestones

- Human genome project (1995-2006) and its off-shutes
  - Human Proteome Project
  - Chromosome Consortia
  - Novel informatics tools

- Question: What is the best way forward in correlating clinical and disease data?
Papers – personalized medicine
Personalized medicine – buzzword?

- ‘Personalized medicine seeks to improve stratification and timing of healthcare by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics, as well as metabolomics’

Omics, Big Data, and Precision Medicine in Cardiovascular Sciences

Edward Lau, Joseph C. Wu

How do our individual genomes and environment affect our well-being, risk for disease, and medical treatments? This is the fundamental question medicine seeks to address. Understanding these interplays will shape future medical practice.

Emerging Role of Precision Medicine in Cardiovascular Disease

Jane A. Leopold, Joseph Loscalzo

Abstract: Precision medicine is an integrative approach to cardiovascular disease prevention and treatment that considers an individual's genetic, lifestyle, and environmental determinants of their cardiovascular health and disease. This presumes that all patients with a similar phenotype can be treated similarly. Precision medicine (ie, transcriptomics, proteomics) and these phenotypic data can

A decade of genome-wide association studies for coronary artery disease: the challenges ahead

Jeanette Erdmann1,2,3*, Thorsten Kessler4,5, Loreto Munoz Venegas1,2,3, and Heribert Schunkert4,5*

1Institute for CardioGenetics, University of Lübeck, Maria-Geoppeert-Str. 1, 23562 Lübeck, Germany; 2DZHK (German Research Centre for Cardiovascular Research), Partner Site Hamburg/Lübeck/Kiel, 23562 Lübeck, Germany; 3University Heart Center Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany; 4Deutsches Herz Zentrum München, Klinik für Herz- und Kreislauferkrankungen, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany; and 5DZHK (German Research Centre for Cardiovascular Research) e. V., Partner Site Munich Heart Alliance, 80636 Munich, Germany

promise of a healthy heart.
Personalized medicine

- Considered to be one of the more promising applications of the ‘-omics’ world
- Utilization of health data to be more precise
- Degree of impact
  - Revolutionary vs modest contribution?
  - Vagueness surrounding public perception
Classic example – UK Biobank

- At least 500,000 patient samples recruited 2006-2010
- Ages 40-69
- Provides a powerful platform for studying a range of complex disease
- Genetic data, imaging data, biomarker profile
- PIs can submit proposals for access
Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants

Carlos A Celis-Morales,1 Paul Welsh,1 Donald M Lyall,2 Jana Anderson,2 Stamatisia Ilidromiti,1 Anne Sillars,1 Jill P Pell,2 Jason M R Gill,1 Naveed Sattar,1 Stuart R Gr
d ABSTRACT

OBJECTIVE
To investigate the association of grip strength with disease specific incidence and mortality and whether grip strength enhances the prediction ability of an established office based risk score.

DESIGN
Prospective population based study.

SETTING
UK Biobank.

PARTICIPANTS
502 293 participants (54% women) aged 40-69 years.

MAIN OUTCOME MEASURES
All cause mortality as well as incidence of and mortality from cardiovascular disease complications.

Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression

Major depressive disorder (MDD) is a common illness accompanied by considerable morbidity, mortality, costs, and heightened risk of suicide. We conducted a genome-wide association meta-analysis based on 135,458 cases and 344,901 controls and identified 44 independent and significant loci. The genetic findings were associated with clinical features of major depression and implicated brain regions exhibiting anatomical differences in cases. Targets of antidepressant medications and genes involved in gene splicing were enriched for smaller association signal. We found important relationships of genetic risk for major depression with educational attainment, body mass, and schizophrenia: lower educational attainment and higher body mass were putatively causal, whereas major depression and schizophrenia reflected a partly shared biological etiology. All humans carry lesser or greater numbers of genetic risk factors for major depression. These findings help refine the basis of major depression and imply that a continuous measure of risk underlies the clinical phenotype.

MDD is a notably complex and common illness. It is often chronic or recurrent and is thus accompanied by considerable morbidity: disability, excess mortality, substantial costs, and depression (Table 1 and Supplementary Tables 1–3). The methods used by these cohorts were thoroughly reviewed, drawing on the breadth of expertise in the PGC and we assessed the comparability...
Concepts of personalized medicine

- Precision medicine
- 4 Ps
  - Predictive
  - Preventive
  - Personalized
  - Participating medicine
- Utilization of genomic information
Precision Medicine at PMCC

- Novel Treatments for Genetic Diseases
- Integration with the DCHP
- Collaboration with Industry Partners
- Healthcare Policy Development

PMCC Precision Cardiovascular Medicine Program

- Clinician-Scientists
- Genetic Counsellors
- Bioinformatics
- Biobanking
Personalized medicine – genetic discrimination

- Examples include:
  - Huntington’s disease screening for individuals at risk (33% of patients surveyed) – Goy et al., 2013 Mol. Biomarkers 17:115
  - BRCA1/2 mutations Matloff et al., J. Genet Counsel 2014 23:164

- In the US: Genetic Information Nondiscrimination Act (GINA) enacted in 2008 – designed to prohibit insurers and employers from discrimination;

- Canadian version May 2017
Patient expectations

- Expectation for more individualized, personal treatment that incorporates their physical, mental and spiritual well-being
- Growing hope that the focus on personalized medicine will lead to the development of new therapies
Expectations from Biobanking

▪ Building large biobanks will provide a future scientific solution to many challenges we have in treating patients today.
  ▪ Form the future knowledge base to the scientific community
  ▪ Clinical databases that hold the sample history/ diagnosis and other clinical variables are highly valuable

▪ Huge unmet need in cancer, diabetes, cardiovascular disease, neurodegenerative diseases
The reality is that many of the basic science discoveries made in the recent years may not quickly yield more effective, affordable, or safe medical therapies for our patients.

The path from discovery to the clinic is long, arduous, and has a high failure rate.
Knowledge translation in personalized medicine

- The advancement of ‘omics’ field has great potential
- Can provide ‘patient-centered’ approach to care in clinical practical
- Need for mandates involving more public engagement as important stakeholders
  - But a paucity of research relating to public perceptions, values, concerns and expectations
Take-home messaging from today

- Demonstrated the importance of strong basic science programs in Medicine
- Requirement for engagement at all levels
- There IS enthusiasm from all involved: just need to connect!