Division of Infectious Diseases

From molecular pathogenesis to translational therapies

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Introduction

- Historic advances in biomedical research - unprecedented opportunities to understand and ameliorate the burden of human diseases.

- To seize these opportunities - academic medicine must produce and support sufficient cadres of highly trained clinician-investigators to propel scientific advances into better diagnosis, treatment, and prevention of disease.

- Widespread concern that structural barriers in academic medical institutions do not sufficiently provide the necessary support to facilitate this endeavour.

AAMC Task Force Report, 2006
Background

• The field of Infectious Diseases has a rich tradition in the study of pathogens and pathogenesis.
• At one time, most ID Division Chiefs in the USA were either trained by NIH or CDC EIS.
• Physician-scientists bring a unique perspective coined as “from bench-to-bedside”.
• Increasing pressures and challenges had led to relatively few physicians pursuing traditional tenure-track research careers.
• However, there are many pathways to engage in research to advance our understanding of infectious diseases for the benefit of human health.
From Bench to Bedside: Application of the Scientific Method to Clinical Medicine

• Laboratory of Sir William Osler, circa 1900
• Catalogued and related autopsy findings to the bedside.

Slide adapted from S. Berman, IDSA
From: The Physician-Scientist Career Pipeline in 2005: Build It, and They Will Come

Figure Legend:

A, Percentage of Association of American Medical Colleges (AAMC) questionnaire respondents (surveys taken at medical school matriculation or graduation) exhibiting an exclusive or significant interest in pursuing research as a career activity, 1987-2003. B, Percentage of graduating respondents who exhibited an interest in clinical or basic science teaching or research as part of their careers, 1977-2003. Source: AAMC Matriculating and Graduating Medical Student Questionnaires.
Annual Spending on Research and Development by Drug Companies and the National Institutes of Health

(Billions of 2005 USD)

Congressional Budget Office, 2006
Research Pathways

- Academia
  - Traditional independent investigator tenure-track biomedical, translational, or clinical research (physician-scientist, clinician-investigator)
  - Academic clinician research (clinician-educator)
  - Pharma-funded clinical research (i.e. HIV, hepatitis C, anti-infectives, etc.)
- Public Health Epidemiology
  - CDC, WHO, NGO’s, etc.
  - State Health Departments
- Pharma/Biotech
  - Clinical trials
- Private Practice (Solo, Group, Multi-specialty Group, Employed)
  - Pharma-funded clinical research
I’m going into private practice – why do research?

- Develop special expertise/knowledge base in a particular area.
- Enhance credentials (potential employers, peers, patients).
- Understand fundamentals of research – strengthen critical thinking and other important skills, evaluate clinical studies and whether they should change your practice.
- Opportunities for pharma-sponsored research studies.
- Required by ACGME during training.
- Because it’s challenging, interesting and fun!
  - (At least I think so.)
Infectious Diseases - Biomedical Research

- Pathogenesis
  - Molecular Microbiology
  - Host-Pathogen Interactions
  - Immunology
- Applied
  - Drug design (in silico)
  - Drug discovery (rational drug design, high-throughput screening, drug repurposing)
  - Medicinal chemistry, pharmacology
  - Diagnostics (biomarkers, antibodies, antigens, molecular, transcriptional signatures, etc.)
# Infectious Diseases - Clinical-Translational Research

## Clinical and Translational Research Spectrum

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<th>Basic Scientific Discovery</th>
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<th>T4 Translation to Population Health</th>
<th>Improved Global Health</th>
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### Examples Include:
- Preclinical and Animal Studies
- Human Physiology
- First in Humans (FiH) (healthy volunteers)
- Proof of Concept (POC)
- Phase 1 Clinical Trials

### Examples Include:
- Phase 2 Clinical Trials
- Phase 3 Clinical Trials

### Examples Include:
- Phase 4 Clinical Trials
- Health Services Research
  - Dissemination
  - Communication
  - Implementation
- Clinical Outcomes Research
  - Community-Based Participatory Research (CBPR)
  - Cost Effectiveness/Comparative Effectiveness
  - Health Disparities
  - Public Policy

### Examples Include:
- Observational Studies
- Personalized Medicine
- Guideline Development
- Systematic Reviews/Meta-Analyses

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**Control of Experimental Conditions**

**Sample Size**

Harvard CTSC 2013
Clinical Study Designs

**STUDY DESIGNS**

- **Population**
  - Random Allocation
    - Group A
    - Group B

- **Experimental Design**
  - Disease
  - No Disease

- **Observational Design**
  - Disease
  - No Disease

- **Disease “Cases”**
  - Exposed
  - Not Exposed

- **No Disease “Controls”**
  - Exposed
  - Not Exposed

K. Ghanem, Johns Hopkins 2013
But wait, there’s more

- Epidemiology
  - Descriptive epidemiology (outbreaks/epidemics), cross-sectional studies (point prevalence), field epidemiology, hospital epidemiology, etc.
- Systematic Meta-analyses
- Surveys
- Case series
- Scholarly activities: Reviews, chapters, case reports
Center for Global Health

- DJ Perkins, Ph.D – severe anemia and malaria, malaria and HIV (Africa)
- Ravi Durvasula, MD – epidemiology of leishmaniasis, trypanosomiasis, paratransgenic therapies (India)
- Steven Bradfute, MD – hemorrhagic fever viruses, development of pan-Ebola virus vaccine
- Ariel Rivas, Ph.D – geo-epidemiology and bioinformatics in global health
- Julie Lovchik, Ph.D – anthrax vaccine
Center for Global Health

- Ivy Foo-Hurwitz, PhD – paratransgenic therapy of leishmaniasis
- Prakash Kempaiah, Ph.D – host genetic diversity and host susceptibility of tropical diseases
International Health

- Gregory Mertz, MD – epidemiology and treatment of hantavirus cardio-pulmonary syndrome (Chile)
- Marcos Burgos, MD – clinical epidemiology and studies of tuberculosis
- Nicole Klein, MD – new epidemiology of Chagas disease with increasing globalization
Microbial Pathogeneisis

- Samuel Lee, MD Ph.D – *Candida albicans* molecular pathogenesis, antifungal drug discovery, antifungal lock therapy
- Thomas Byrd III, MD – pathogenesis of non-tuberculous mycobacteria
- Renee Mercier, PharmD (College of Pharmacy) – MRSA epidemiology, drug resistance
Hospital epidemiology, health outcomes, service delivery, bioinformatics

- Susan Kellie, MD, MPH – hospital epidemiology of MRSA colonization and invasive disease, *C. difficile*
- Meghan Brett, MD, MPH – hospital epidemiology, field epidemiology
- Karla Thornton, MD, MPH – ECHO Program, health care delivery models for HCV across disadvantaged populations
- Bruce Struminger, MD, MA – ECHO Program as medical consultation and training, clinical outcomes, cost effectiveness
- *Christophe Lambert, Ph.D – Bioinformatics for use in big data research*
HIV/AIDS Research

- Karla Thornton, MD – HIV and HCV co-infection
- Michelle Iandiorio, MD – NM AIDS Education and Training Center, HIV in adolescents and young adults, medical education
- Bruce Williams, MD MPH – HIV clinical care
- *Staci Lee, MD – HIV clinical care, comparative effectiveness of educational methods
- Elaine Thomas, MD – HIV and STDs
- Robert Munk, Ph.D – AIDS InfoNet
- #Joel Gallant, MD, MPH – HIV international clinical trials
- #Trevor Hawkins, MD – HIV, HCV clinical trials
Clinical Research

- *Cristina Vazquez-Guillamet – infections in the ICU, retrospective cohort studies, biomarkers of infections in the ICU
- All ID faculty … additional clinical research
  - investigational Rx of HSV
  - Phase IV clinical trials (industry)
  - Clinical epidemiology of cryptoccocus infection in non-HIV patients (NIH)
  - Retrospective studies, case series, case reports, review articles
Future Directions

• Incoming Chief – Ravi Durvasula, MD
• Multiple recruitments of funded investigators
• Global Health and Infectious Diseases to merge
• Expansion of collaborations
  o Epidemiology, Translational Informatics, Molecular Genetics and Microbiology, Pharmacy, Biochemistry, Center for Molecular Discovery, IDIP, CIDI, CTSC, etc.
• Development of a global health track in the ID Fellowship
  o Our ID Fellows and other trainees have performed research in India, Kenya, South America, and elsewhere
• These are exciting times!
Candida Biofilm Formation

Adhesion

Filamentation

Antifungal Resistance

Persister Cells

Dispersion

Quorum Sensing

Candida Biofilm Formation

Simple observation

Scanning electron microscopy

In vitro Studies

Amphotericin B

% Metabolic activity

Concentration of AMB (μg/ml)

Fluconazole

% Metabolic activity

Concentration of FLU (μg/ml)

Miceli et al. Int J Anticmicrob Ag 2009a
In vitro Effect of Doxycycline Against *C. albicans* Biofilms

*P < 0.05

**P < 0.0001 compared to higher DOX concentrations
Anti-Vacuolar Agent: Quinacrine

**Prevention**

$\text{MIC}_{50} = 512 \text{ug/ml}$  
$\text{MIC}_{80} = 1024 \text{ug/ml}$

**Treatment**

Kulkarny et al., submitted
Quinacrine prevents biofilm formation

0 ug/ml
128 ug/ml
256 ug/ml
512 ug/ml
1024 ug/ml
2048 ug/ml
Heparin and Parabens - *C. albicans* Biofilm Formation

Miceli et al. *Antimicrob Ag Chemother* 2012
In vitro effect of 0.5 - 24h ethanol treatment against *C. albicans* biofilms

Rane et al. *Antimicrob Ag Chemother* 2013
Some Final Thoughts

• “We didn’t need clinical trials in my day ... if we gave ‘em penicillin they lived, if we didn’t, they died.”
  
  Vincent T. Andriole, MD

• And:

  Good luck with your research!
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