TRENDS AND CHALLENGES IN TRANSLATIONAL RESEARCH

ED MILLER SYMPOSIUM
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THREE CORE MESSAGES

- TRANSLATIONAL RESEARCH IS IN TROUBLE
- WE NEED TO RE-INVENT TRANSLATIONAL RESEARCH
- ACADEMIC HEALTH CENTERS WILL BE KEY TO ITS RECOVERY
The Fundamental problem

Thanks to progress made in the biomedical sciences, the number of potential biological disease modifying targets has dramatically increased.

but TRANSLATABILITY of those advances into tangible health benefits seems to have decreased.

Academia, Government and Industry need to implement more innovative solutions.
A spectacular drop in worldwide R&D productivity

Clinical timelines increasing

Mean clinical development time (years)

<table>
<thead>
<tr>
<th>Year</th>
<th>Clinical Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-89</td>
<td>4.5</td>
</tr>
<tr>
<td>1990-94</td>
<td>5.6</td>
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<tr>
<td>1995-99</td>
<td>6.7</td>
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<tr>
<td>2000-04</td>
<td>7.7</td>
</tr>
<tr>
<td>2005-10</td>
<td>7.9</td>
</tr>
</tbody>
</table>

NME approvals by FDA decreasing

Number of NCEs and NBEs approved

<table>
<thead>
<tr>
<th>Year</th>
<th>NCE</th>
<th>NBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-89</td>
<td>126</td>
<td>46</td>
</tr>
<tr>
<td>1990-94</td>
<td>187</td>
<td>54</td>
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<tr>
<td>1995-99</td>
<td>241</td>
<td>13</td>
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<tr>
<td>2000-04</td>
<td>210</td>
<td>84</td>
</tr>
<tr>
<td>2005-10</td>
<td>162</td>
<td>24</td>
</tr>
</tbody>
</table>

Rising R&D costs

R&D expenditure per drug ($M)

- 2000 M
- 2005 M
- 2010 M

Source: FDA; EvaluatePharma; Tufts CSDD 2007; Parexel; CMR; Paul et al, 2010,

1 2010 data is from Paul et al Nature Feb-10, rest of data from Tufts
Evolving Unmet Needs in Public Health

- Shift from Acute to Chronic Conditions
- Aging Population
- Global Health Disparities
- Emerging and Re-emerging Infectious Diseases
- Emerging Non-communicable Diseases – Depression, Allergy, Obesity
The Future Paradigm: The 4 P’s
Transform Medicine from Curative to Preemptive

PERSONALIZED

PRETEND MEDICINE!
Today, a fundamental scientific barrier is our limited ability to study complex and dynamic biological systems in health or disease!
NEED TO BETTER UNDERSTAND BIOLOGICAL COMPLEXITY
From the “Hardware” of Life to the “Software” of Life

Understanding Molecular Pathways and Their Regulation in Health and Disease

Will lead to a functional and more precise re-classification of most diseases based on their specific Molecular Pathways

Help better Understand environmental drivers
WHAT NEEDS RE-INVENTION?

- Scientific Factors
- Professional Factors
  - Clinician-Scientists
  - Professional career pathways
  - The changing roles of academic medical centers
- Socio-economic factors
Bridging the translational divide
Standard Model

Laboratory Research

T1 T2 T3 T4

Translational Research

Clinical Research

Population Research

Public Health
Bridging the translational divide
The Way it Should Work

Laboratory Research

Patient-oriented Clinical Research

Population-based Clinical Research

Clinical Trials

TRANSLATIONAL MEDICINE
A NEW DISCIPLINE
Scientific Factors
T1 translational research

- Many targets, many cellular and animal models but low predictivity in human disease
- Heavy reliance on insufficient surrogate biology away from human biology
- NEEDS:
  - More systematic validation of published findings
  - Development of specific biomarkers related to hypothesized mode of action in humans
  - Access to Human disease samples as early as possible to validate hypothesis
  - Introduce more potent emerging sampling and analytical methods for human materials- LCMass Spec, Array readouts, proteomics, single cell analyses
Scientific Factors
T2 Translational Research

- **Core issues: Predictive Efficacy and Safety**
  - A clear readout of efficacy via surrogate markers
  - Development of novel methods of predictive safety
  - Phase 0 and investigational exploratory trials to confirm mode of action, validate biomarkers

- **Need for centers with access to human pathologies and leading edge analytical methodologies**
Scientific factors
T3 Translation

- **Problem: from translation to effective diffusion of translation**
  - Many advances are not applied to the degree necessary to achieve expected results
  - Typical of chronic diseases (hypertension, diabetes)
  - Discovering new therapeutic models: Chronic disease management, novel drug delivery approaches
Scientific Factors
T4 Translation

- Limited understanding of population epidemiology especially chronic diseases
  - Natural prevalence and incidence are estimates
  - No rigorous system to track epidemiologic trends
  - Need to use e-Health technologies
  - Establish surveillance cohorts
  - Behavioral and social sciences research
Professional Factors

- Clinician-Scientists
  - Lack of critical « bridge » scientists who understand basic research and experimental medicine
  - Specific translational medicine training centers

- Professional career pathways
  - Need to define a discipline of translational medicine with a multidisciplinary viewpoint
The changing roles of academic medical centers

« THE TYRANNY OF RVUs »
- Economic model leads to overwhelming clinical service demands
- Focus away from experimental medicine (T1 & T2) to later stages clinical research (T3&T4)
- Inadequate for research on chronic diseases
- Need to re-balance clinical service and science based translational investigations
- Interdisciplinary barriers

NEED TO CREATE FLUID MULTIDISCIPLINARY ENVIRONMENTS
BIOMEDICAL RESEARCH NOW REQUIRES STRONG MULTIDISCIPLINARY EFFORTS

MOLECULAR BIOLOGY

PHYSICAL SCIENCES

CLINICAL INVESTIGATIONS

MEDICAL RESEARCH

BIOENGINEERING

COMPUTER SCIENCE

MOLECULAR PATHOLOGY
A New Paradigm is Needed: A Systems Based Approach

- Integrated approaches to research and discovery
- Interdisciplinary training
- Translational research as a recognized discipline
- Evolution from departments to interdisciplinary research centers
- Widely shared resources
TO SUCCEED IN THE LONG TERM

AN ACADEMIC HEALTH CENTER HAS TO BE MORE THAN A HOSPITAL AND A MEDICAL SCHOOL ….

BUT ALSO A CENTER OF MULTIDISCIPLINARY EXCELLENCE

IN THE RELATED PHYSICAL AND BIOLOGICAL SCIENCES WITHOUT ARTIFICIAL BARRIERS