Drug Development Pipeline Running Low, What's Data Got to Do With It?

Mohammad F. Kiani
Departments of Mechanical Engineering, Bioengineering, and Radiation Oncology
Temple University

Cost of Health Care in the US

- $3.5 trillion in 2017
- $10,739 per person
- Accounted for 17.9% of Gross Domestic Product (GDP)
- Projected to grow at an average rate of 5.5% per year, to reach ~$6.0 trillion by 2027

US vs. other Developed Countries

Cost of Health Care in the US

- $3.5 trillion in 2017
- $1.6 trillion total individual income tax collections in 2017

➢ The savings in healthcare costs would be larger than ALL income tax collected, if we spent as much as other OECD countries on healthcare
Is it all about money?

Per Capita Healthcare Spending (US $)

Life Expectancy

United States Switzerland Norway Canada Japan China

Norway

Canada

Switzerland

Life Expectancy

0 2000 4000 6000 8000 10000

THE NATION'S HEALTH DOLLAR ($3.5 TRILLION), CALENDAR YEAR 2017: WHERE IT CAME FROM

Health Insurance, 7%

Mental Health Insurance, 3%

Medicaid, 3%

Medicare, 38%

Private Health Insurance, 10%

Other Health Insurance and Programs, 2%

Uninsured, 4%

V.A., Other Federal and Veterans Affairs, 1%

Other Public Health Activities, 2%

The average price of Tecfidera in the United States is 174% higher than in Switzerland

Average price, Tecfidera, 60 capsules, 240 mg, 30 day supply, 2014

United States

$5,089

United Kingdom

$663

Switzerland

$1,855

Source: International Federation of Health Plans 2015

New drug development

- A long, difficult and expensive process
- The average cost per new drug is in the range of $650 million to $2.5 billion!

<table>
<thead>
<tr>
<th>Preclinical Testing</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Total FDA Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>3.5</td>
<td>1</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Test Population</td>
<td>Laboratory and animal studies</td>
<td>File IND at FDA</td>
<td>up to 100 healthy volunteers</td>
<td>File NDA at FDA</td>
</tr>
<tr>
<td>Purpose</td>
<td>Assess safety and biological activity</td>
<td>Determine safety and tolerance</td>
<td>Evaluate effectiveness and side effects</td>
<td>Verify effectiveness, monitor adverse reactions from long-term use</td>
</tr>
<tr>
<td>Success Rate</td>
<td>5,000 compounds evaluated</td>
<td>5 volunteers</td>
<td>100 to 300 patient volunteers</td>
<td>1000 to 3000 patient volunteers</td>
</tr>
</tbody>
</table>

Investigational New Drug Application (IND)
New Drug Application (NDA)

Figure 14–2. Approved New Drug Applications, 1940–2011


Sepsis

- Definition
  - Life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis-3 JAMA 315:801, 2016)

- Epidemiology
  - Incidence >1,700,000 cases/year in the US & increasing
  - Mortality >250,000 deaths/year in the US
  - Associated costs >$20 billion/year

- Sepsis-induced Acute Lung Injury

- Treatment
  - Antibiotics
  - Supportive therapy
  - No specific pharmacologic therapies for sepsis

Key Questions in Sepsis Pathophysiology

- How do leukocytes migrate through the endothelium during sepsis?
- How is the vascular endothelium damaged during sepsis?
A rat model of CLP- polymicrobial sepsis-induced Acute Lung Injury

- Intra-abdominal sepsis (cecal ligation and puncture (CLP)) produces lung pathology through leukocyte-endothelial interaction
- Characterized by significant organ damage as well as inflammation

**Experimental Conditions**

1. CLP or Sham Surgery
2. Intra-tracheal administration of vehicle (PBS) or PKCδ inhibitor (200µg/kg) post-surgery
3. Lungs harvested 24 hrs post surgery

---

**Current state of therapeutics for treating sepsis**

All of the ~150 drugs recently developed in animal models have failed in clinical trials

Reductions in mortality primarily due to supportive care rather than effective medicines

A meta-analysis of a large number of studies found little overlap in gene activity between mouse models of inflammation and its clinical manifestations

The need is for “translational medical research to focus on the more complex human conditions rather than relying on mouse models to study human inflammatory diseases” by developing a realistic fluidic model for “in vitro reconstitution of disease-related cell types or tissues”
The New York Times: Much time and money has been wasted studying mouse models of inflammation.

Microvascular network on a chip (bMFA)

Cremaster Muscle Preparation

Microvascular network on a chip (bMFA)
Mouse models may underestimate therapeutic impact of a drug!

Flow patterns are more heterogeneous near bifurcations

PKCδ inhibition is location dependent

Blood-brain barrier on a chip (B³C)
Blood-brain barrier on a chip (B³C)

Permeability of B³C approximates the *in vivo* conditions

Barrier electrical resistance in B³C is higher than transwell

Tumor on a chip (bMTM)
Tumor type impacts liposome permeation in bMTM

In silico model of inflammatory response in lung cells

Proteomic analysis of signaling pathways after cytomix treatment of pulmonary endothelial cells

Integrating microfluidic, omic, and in silico models to screen therapeutics for sepsis
What are the funding agencies saying?

- National Institute of General Medical Sciences (NIGMS):
  “Specific topics of research interest include:
  Application of new research methods and models such as in silico approaches, cell culture, and organoids to early-stage testing and validation of potential sepsis diagnostics and therapeutics”

  “NIGMS considers the following areas to be of low priority:
  Studies using rodent models of sepsis unless uniquely well-justified in terms of potential for providing novel insights into human sepsis”

- Department of Defense Joint Program Committee-6 (JPC-6) & National Heart, Lung, and Blood Institute (NHLBI):
  “The program will also facilitate collaborations between hematologists/vascular biology experts and BBB tissue chip developers to create enhanced/modified platforms that more closely model the human BBB for assessment…”

  “Applications that focus only on animal models and/or in silico predictive models of the BBB will not be responsive to the FOA”

What are the funding agencies saying?

- National Science Foundation:
  Understanding the Rules of Life: Microbiome Theory and Mechanisms
  “New computational, engineering, biological, physical-chemical and/or social networking approaches to understand and predict how a host’s genetic composition, physiology, and behavior influence the genetics, physiology, and behavior of the microbiome and vice versa”

Opportunity

- Collaborate with an established biomedical scientist
  “Multiple PI with established collaborative relationship and complementary skill set”

- Focus on clinically relevant questions
  “Employing computational, cell-culture and organoid methods in preclinical discovery with validation using human clinical material and research endpoints that align with therapeutic target discovery”

- Develop a multi-disciplinary approach
  “Comprehensive approach utilizing in vitro, in vivo, human, and in silico techniques”

The People who actually did the Work!

Ramin Ansari
Xin Chen
Rabee Cheheltani
Elizabeth Curran
Fred Donelson
Mohamed El-Sayeed
M. Waleed Gaber
Jeanie Haybert
Zhana Ivanov
Giuseppina Lamberti
Michael D. Naimark
RK Nallamothu
Vinh Nguyen
Christopher Patillo
Balabhaskar Prabhakarapandian
Jenna Rosano
Noah M. Roth
Farid Saraf
Robert C. Scott
Fartiborz Soroush
Yuan Tang
Nazanin Tousi
Bin Wang
Hong Yuan

Temple University
University of Alabama
Boston Consulting Group
NAVY Hazardous Materials Management
Syracuse University
University of Michigan
Baylor College of Medicine
Transretyx, Inc.
Ross University School of Medicine
Medtronic CardioVascular
CARE, Inc.
Mylan Pharmaceuticals
University of Alabama, Birmingham
Louisiana State University, Shreveport
CFD Research Corp.
CFD Research Corp.
ICON Medical Holdings, LLC
Novartis, MA
Dartmouth University School of Medicine
Rowan University
University of Toledo
Case Western Reserve University
Widener University
UNC, Chapel Hill
The People who helped!

Mohan Achary  
Carlo Massimo Casciola  
Deborah Crabbe  
Parkson Chong  
M. Waleed Gaber  
Douglas J. Goetz  
Andrew C. Issekutz  
Laurie E. Kilpatrick  
Linda Knight  
Barbara Krynska  
Thomas E. Merchant  
Curtis Miyamoto  
Kapil Pant  
Nancy Pleshko  
Balabhaskar Prabhakarpandian  
Yao Sun  
Karl T. Weber  
George C. Wood  
Temple University  
Sapienza University of Rome  
Temple University  
Temple University  
Baylor College of Medicine  
Ohio University  
Dalhousie University  
Temple University  
Temple University  
Temple University  
St. Jude Children’s Research Hospital  
Temple University  
CFD Research Corp., AL  
Temple University  
CFD Research Corp., AL  
University of Tennessee Health Science Center  
University of Tennessee Health Science Center  
University of Tennessee Health Science Center

$$$ Funding $$$

DTRA  
National Institutes of Health  
American Heart Association  
Shriners Hospitals for Children  
NASA

Bubble Art!  
(Dan Mirer, Tyler School of Art)