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

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Abstract:

The per capita cost of health care in the US, by far the highest in the world, is driven in part by the high cost of pharmaceuticals. The low conversion rate of promising agents into successful clinical therapeutics is an important contributor to the high cost of pharmaceuticals. For example, all of the ~150 drugs developed in the last 15 years in mouse models to treat sepsis have failed in clinical trials. Several NIH institutes and other funding agencies have recently eliminated or significantly curtailed their funding for animal-based studies. A number of *in vitro* models of living tissues, especially organoids and microphysiological systems, are playing an increasingly significant role in prescreening of promising therapeutics for safety, efficacy and toxicity prior to expensive animal and human trials, thus offering the promise of accelerated drug development. However, a data-based understanding of how and the degree to which these assays reproduce the biological signals of interest, as well as drug-cell interactions, is critical to their successful deployment in the field of drug discovery. It is therefore critical to decipher omic and other changes to map known response pathways/networks so that *in silico* models can be used to determine which components of the biological signaling in human cells is preserved in mouse cells to guide further optimization of *in vitro* assays. Development of appropriate analytical tools will be critical to the success of this hybrid approach to drug development.

Biography:

Dr. Mohammad F. Kiani is a professor of mechanical engineering, bioengineering and radiation oncology at Temple University. He served as the chair of Department of Mechanical Engineering at Temple University (2004-2014) and Department of Biomedical Engineering at the University of Tennessee Health Science Center (2003-2004). He received a B.S. in electrical engineering from the University of Oklahoma and M.S. and Ph.D. in biomedical engineering from Louisiana Tech University. He was an NIH postdoctoral fellow at the University of Rochester from 1990 to 1993. The current focus of his research is the development of organoids and microphysiological systems for rapid drug development and screening and targeted drug delivery. Dr. Kiani has received a number of scholarly research and teaching awards including the prestigious Established Investigator Award from the American Heart Association. His research has been funded by a number of government agencies and private foundations. He has published more than 80 peer reviewed scientific articles and has made more than 250 presentations at scientific meetings. Dr. Kiani is a fellow of the American Heart Association, a senior member of IEEE and several other scientific and engineering organizations and serves as a reviewer for several funding agencies and a number of scientific and engineering journals. He is also the co-founder and past president of Engineering World Health which is a major nonprofit organization delivering healthcare infrastructure and engineering support to a number of hospitals in Africa, Central America and Asia.

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Temple University

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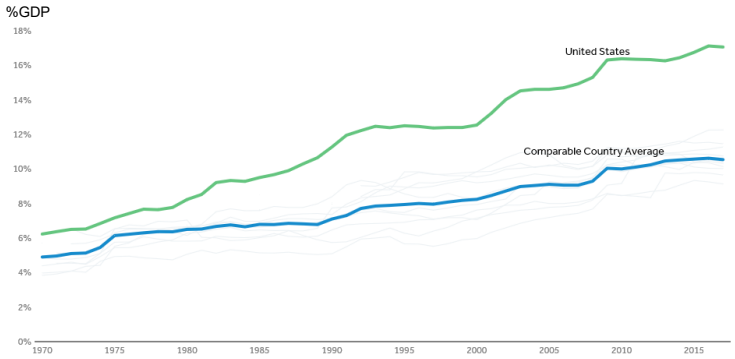
Cost of Health Care in the US

- $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

www.cms.gov

US vs. other Developed Countries

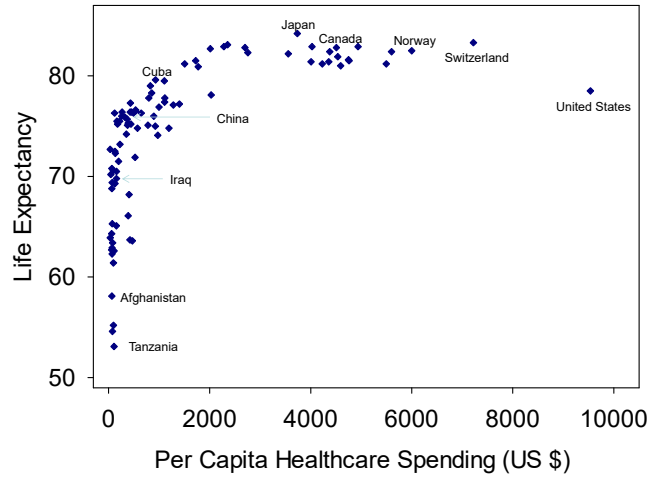


Cost of Health Care in the US

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

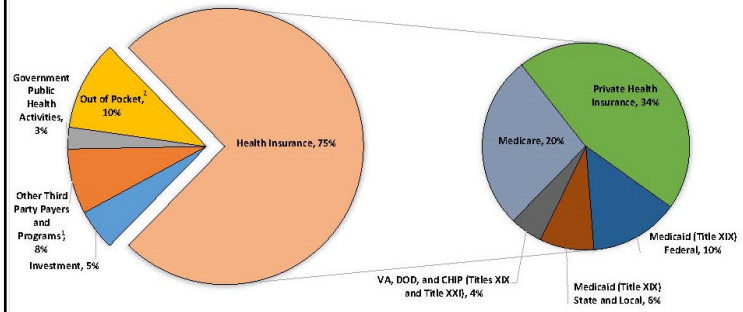
➢ The savings in healthcare costs would be larger than **ALL** income tax collected, if we spent as much as other OECD countries on healthcare

Is it all about money?



www.who.int/gho/publications/world_health_statistics/2018/en/

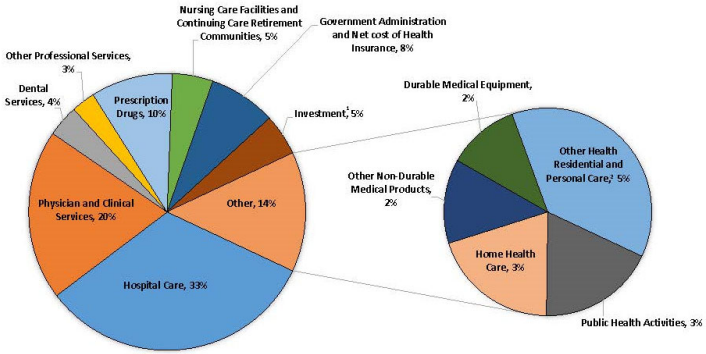
THE NATION'S HEALTH DOLLAR ($3.5 TRILLION), CALENDAR YEAR 2017: WHERE IT CAME FROM



[1] Includes worksite health care, other private revenues, Indian Health Service, workers' compensation, general assistance, maternal and child health, vocational rehabilitation, Substance Abuse and Mental Health Services Administration, school health, and other federal and state local programs.
[2] Includes co-payments, deductibles, and any amounts not covered by health insurance.
Note: Sum of pieces may not equal 100% due to rounding.

SOURCE: Centers for Medicare & Medicaid Services, Office of the Actuary, National Health Statistics Group.

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



[1] Includes Noncommercial Research and Structures and Equipment.
[2] Includes expenditures for residential care facilities, ambulance providers, medical care delivered in non-traditional settings (such as community centers, senior citizens centers, schools, and military field stations), and expenditures for Home and Community Waiver programs under Medicaid.
Note: Sum of pieces may not equal 100% due to rounding.

SOURCE: Centers for Medicare & Medicaid Services, Office of the Actuary, National Health Statistics Group.

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

Source: International Federation of Health Plans 2015 Comparative Price Report • Get the data • PNG

Peterson-Kaiser Health System Tracker

www.healthsystemtracker.org/chart-collection/recent-forecasted-trends-prescription-drug-spending/#item-average-price-tecfidera-united-states-174-higher-switzerland_2017

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!

	Preclinical Testing	File IND at FDA	Phase I	Phase II	Phase III	File NDA at FDA	FDA	↓	Phase IV
Years	3.5		1	2	3		2.5	12 Total	
Test Population	Laboratory and animal studies		up to 100 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers		Review process / Approval		Additional Post-marketing testing required by FDA
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

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

www.allp.com/drug_dev.htm
www.forbes.com/sites/matthewherper/2017/10/16/the-cost-of-developing-drugs-is-insane-a-paper-that-argued-otherwise-was-insanely-bad/#54f40292d459

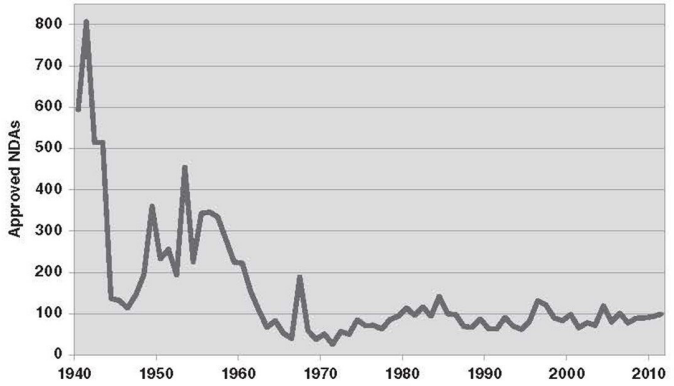


Figure 14–2. Approved New Drug Applications, 1940–2011
Source: US FDA (2013). "Summary of NDA Approvals & Receipts, 1938 to the Present," last updated January 18. Retrieved from http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts19.

The rise and fall of American growth : the U.S. standard of living since the Civil War / Robert J. Gordon

Sepsis

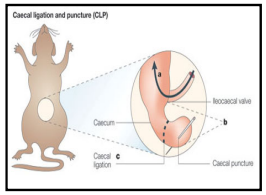
- Definition
  - Life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis-3 *JAMA* 315:801, 2016)
- Epidemiology
  - Incidence >1,700,000 cases/year in the US & increasing
  - Mortality >250,000 deaths/year in the US
  - Associated costs >$20 billion/year
- Sepsis-induced 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

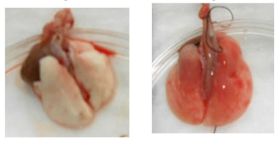


Nature Reviews Drug Discovery 4:854, 2005

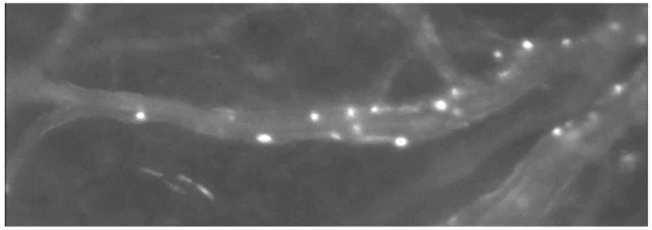
Experimental Conditions

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

Sham lungs (24 hrs) **CLP lungs (24hrs)**



Leukocyte-endothelial interaction *in vivo*



Leukocyte-endothelial interaction *in vivo*

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

THE NEW YORK TIMES **NATIONAL** TUESDAY, FEBRUARY 12, 2013 A19

Mice Fall Short as Test Subjects for Deadly Illnesses

By GINA KOLATA

For decades, mice have been the species of choice in the study of human diseases. But now, researchers report evidence that the mouse model has been totally misleading for at least three major killers — sepsis, burns and trauma. As a result, years and billions of dollars have been wasted following false leads, they say.

The study's findings do not mean that mice are useless models for all human diseases. But, its authors said, they do raise troubling questions about diseases like the ones in the study that involve the immune system, including cancer and heart disease.

"Our article raises at least the possibility that a parallel situation may be present," said Dr. H. Shaw Warren, a sepsis researcher at Massachusetts General Hospital and a lead author of the new study.

The paper, published Monday in Proceedings of the National Academy of Sciences, helps explain why every one of nearly 150 drugs tested at a huge expense in patients with sepsis has failed. The drug tests all were based on studies in mice. And mice, it turns out, can have something that looks like sepsis in humans, but is very different from the condition in humans.

Medical experts not associated with the study said that the findings should change the course of research worldwide for a deadly and frustrating condition. Sepsis, a potentially deadly reaction that occurs as the body tries to fight an infection, afflicts 750,000 patients a year in the United States.

Dr. H. Shaw Warren was a lead author of a study reporting that testing on mice was misleading for at least three major killers.

Clifford S. Deutschman, who directs sepsis research at the University of Pennsylvania and was not part of the study.

The ramped-up immune system releases its own proteins in such overwhelming amounts that capillaries begin to leak. The leak becomes excessive, and serum seeps out of the tiny blood vessels. Blood pressure falls, and vital organs do not get enough blood. Despite efforts, doctors and nurses in an intensive-care unit or an emergency room may be unable to keep up with the leaks, stop the infection or halt the tissue damage. Vital organs eventually fail.

The new study, which took 10 years and involved 39 researchers from across the country, began by studying white blood cells from hundreds of patients with

that was how you validate things," he said. "They are so ingrained in trying to cure mice that they forget we are trying to cure humans."

That started us thinking," he continued. "Is it the same in the mouse or not?"

The group decided to look, expecting to find some similarities. But when the data were analyzed, there were none at all.

"We were kind of blown away," Dr. Davis said.

The drug failures became clear. For example, often in mice, a gene would be used, while in humans, the comparable gene would be suppressed. A drug that worked in mice by disabling that gene could make the response even more deadly in humans.

Even more surprising, Dr. Warren said, was that different

whether it had even been submitted to them. But, Ginger Pinholster of Science said, the journal accepts only about 7 percent of the nearly 13,000 papers submitted each year, so it is not uncommon for a paper to make the rounds.

Still, Dr. Davis said, reviewers did not point out scientific errors. Instead, he said, "the most common response was, 'It has to be wrong. I don't know why it is wrong, but it has to be wrong.'"

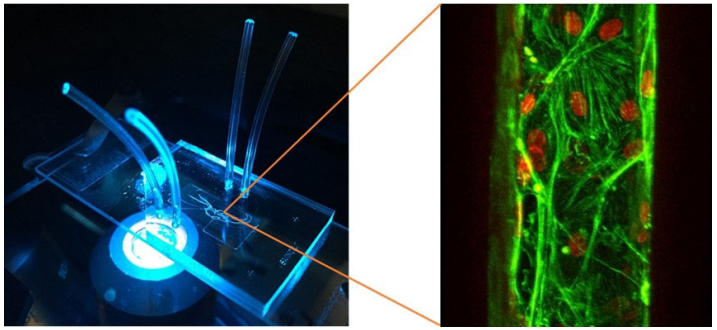
The investigators turned to Proceedings of the National Academy of Sciences. As a member of the academy, Dr. Davis could suggest reviewers for his paper, and he proposed researchers who he thought would give the work a fair hearing. "If they don't like it, I want to know why," he said. They recommended publication, and the editorial board of the journal, which independently assesses papers, agreed.

Some researchers, reading the paper now, say they are as astonished as the researchers were when they saw the data.

"When I read the paper, I was stunned by just how bad the mouse data are," Dr. Fink said. "It's really amazing — no correlation at all. These data are so persuasive and so robust that [I think funding agencies are going to take note." Until now, he said, "to get funding, you had to propose experiments using the mouse model."

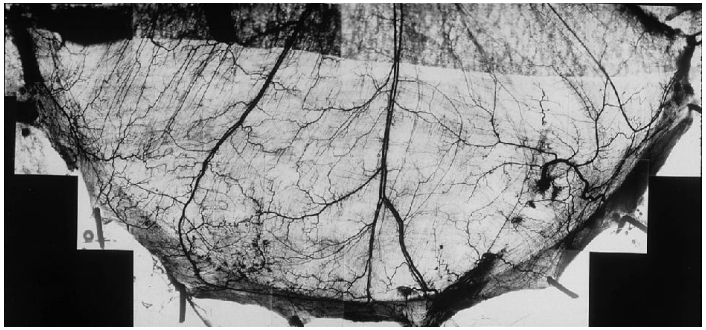
Yet there was always one major clue that mice might not really mimic humans in this regard: it is very hard to kill a mouse with a bacterial infection. Mice need a million times more bacte-

Microvascular network on a chip (bMFA)



Biomed. Microdevices, 2008
Biomed. Microdevices, 2009

Cremaster Muscle Preparation



Ann. Biomed. Engr. 1999

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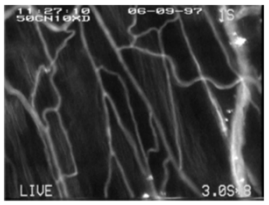
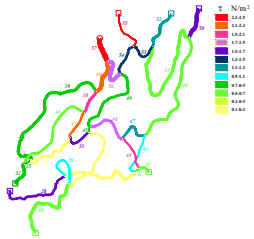
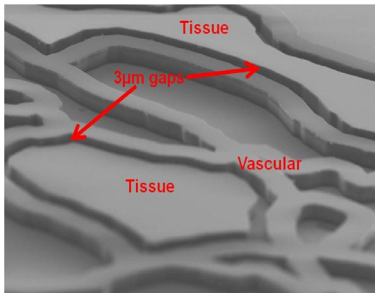
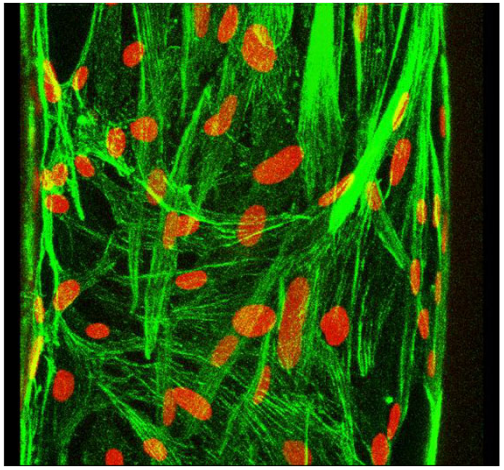




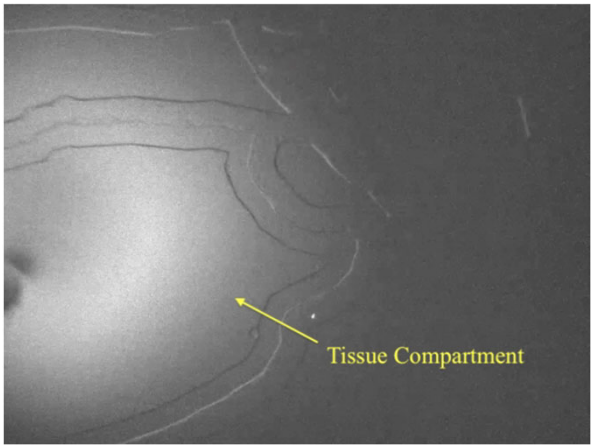


Ann. Biomed. Engr. 1999
Biomed. Microdevices, 2008
Biomed. Microdevices, 2009

3D culture of endothelial cells in bMFA

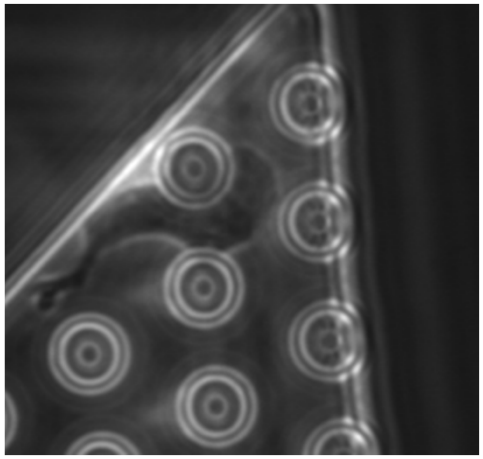


Leukocyte-endothelial interaction in bMFA



Analytical Chemistry 2014

Leukocyte-endothelial interaction in bMFA

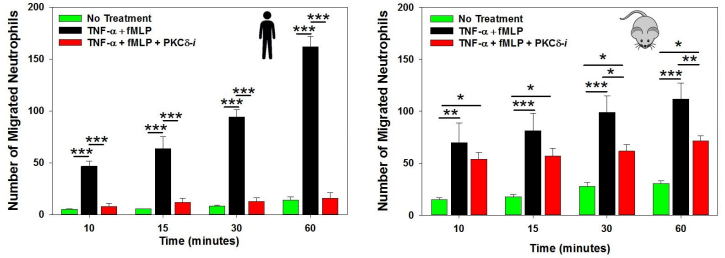


Top 10 Innovations 2013

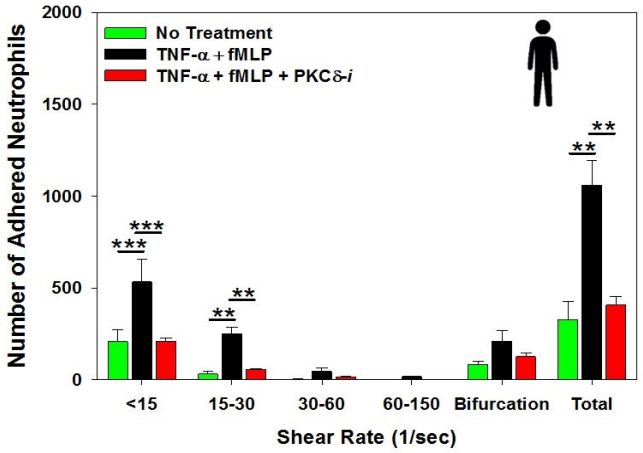
TheScientist

EXPLORING LIFE, INSPIRING INNOVATION

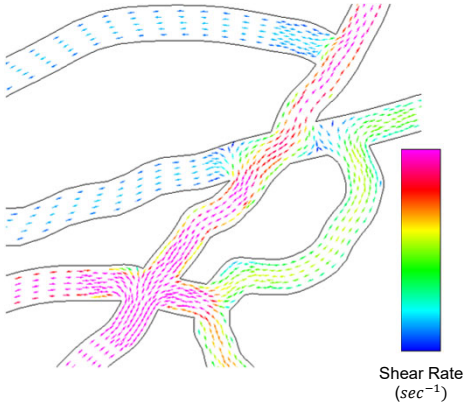
Mouse models may underestimate therapeutic impact of a drug!



PKCδ inhibition is location dependent

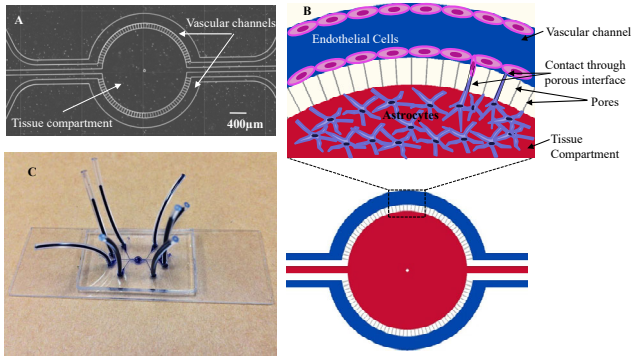


Flow patterns are more heterogeneous near bifurcations



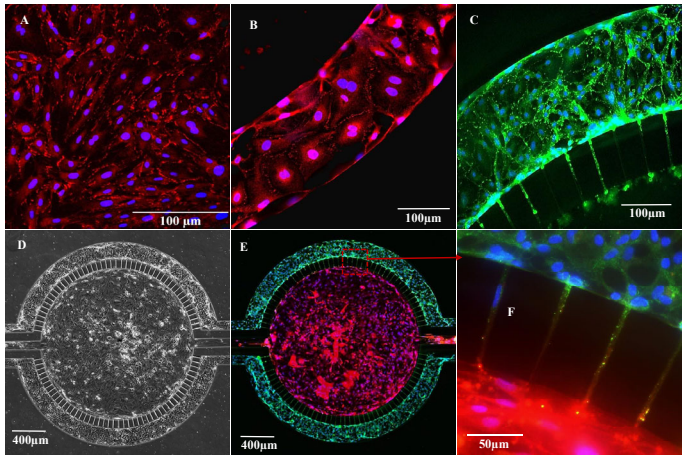
Journal of Leukocyte Biology 2016

Blood-brain barrier on a chip (B^3C)



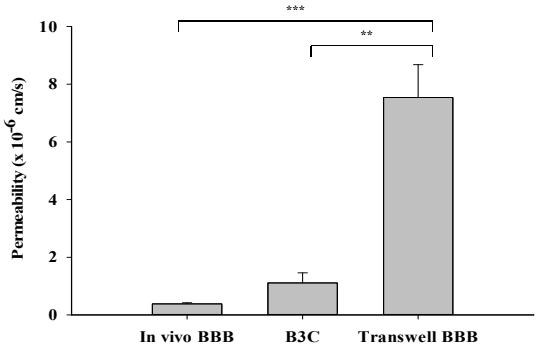
Journal of Neuroinflammation 2018

Blood-brain barrier on a chip (B^{3}C)



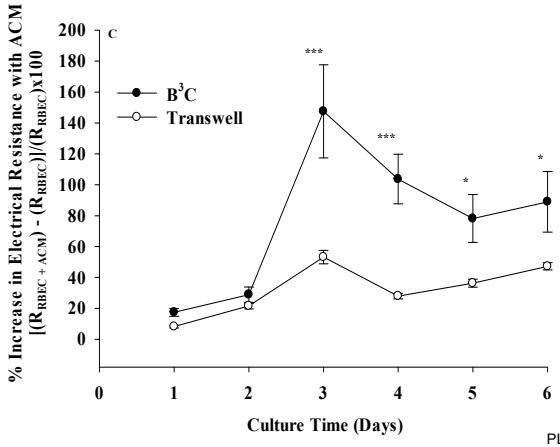
Journal of Neuroinflammation 2018
PLoS One 2015

Permeability of B^{3}C approximates the *in vivo* conditions



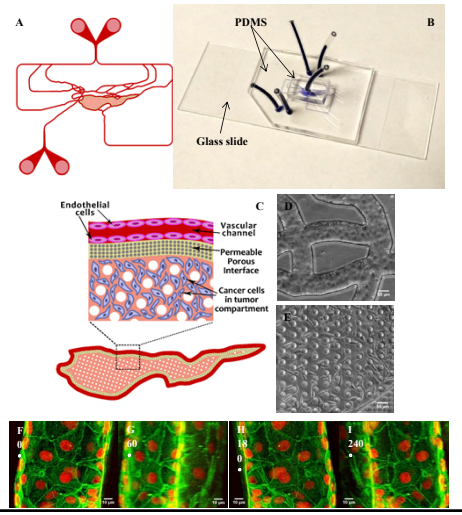
PLoS One 2015

Barrier electrical resistance in B^{3}C is higher than transwell



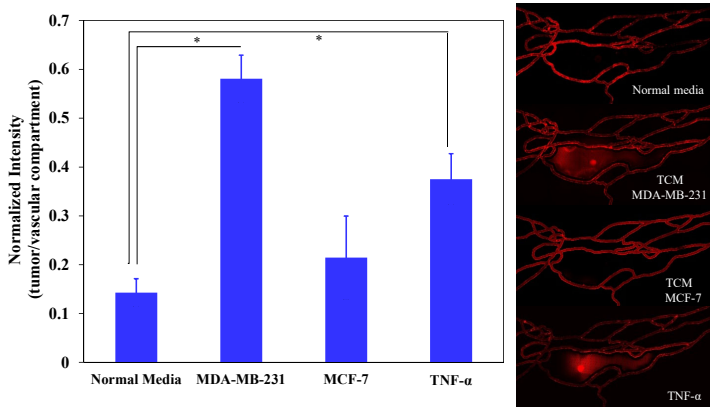
PLoS One 2015

Tumor on a chip (bMTM)



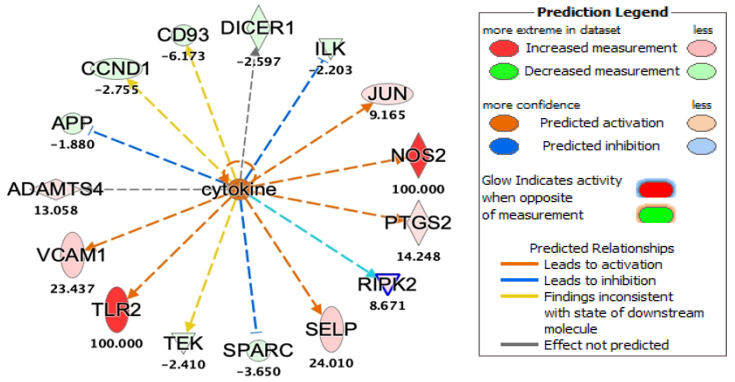
Scientific Reports 2017

Tumor type impacts liposome permeation in bMTM

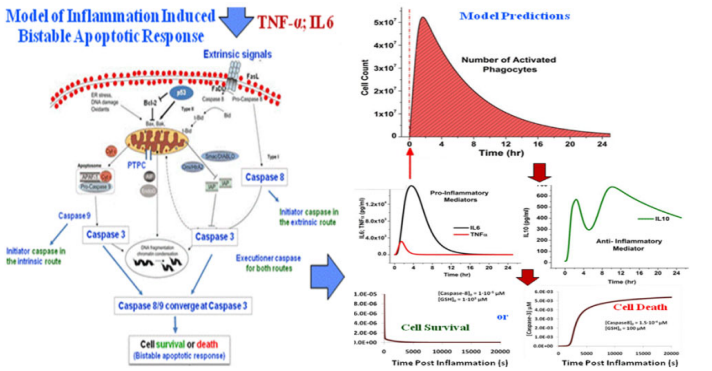


Scientific Reports 2017

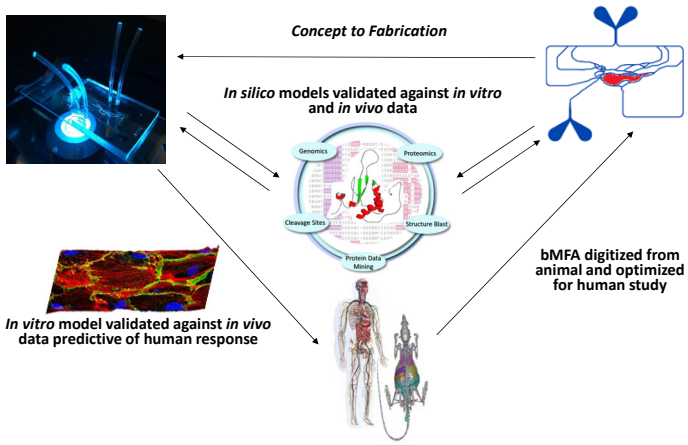
Proteomic analysis of signaling pathways after cytomix treatment of pulmonary endothelial cells



In silico model of inflammatory response in lung 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"

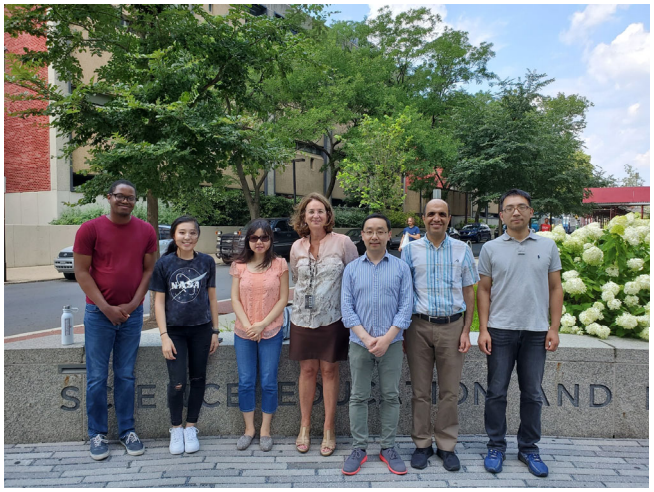
❖Develop a multi-disciplinary approach
"Comprehensive approach utilizing *in vitro*, *in vivo*, human, and *in silico* techniques"

The People who actually did the Work!

Ramin Ansari	Temple University
Xin Chen	University of Alabama
Rabee Cheheltani	Boston Consulting Group
Elizabeth Curran	NAVY Hazardous Materials Management
Fred Donelson	Syracuse University
Mohamed El-Sayeed	University of Michigan
M. Waleed Gaber	Baylor College of Medicine
Jeanie Haybert	Transnetyx, Inc.
Zhanna Ivanov	Ross University School of Medicine
Giuseppina Lamberti	Medtronic CardioVascular
Michael D. Naimark	CARE, Inc.
RK Nallamothu	Mylan Pharmaceuticals
Vinh Nguyen	University of Alabama, Birmingham
Christopher Pattillo	Louisiana State University, Shreveport
Balabhaskar Prabhakarpandian	CFD Research Corp.
Jenna Rosano	CFD Research Corp.
Noah M. Roth	ICON Medical Holdings, LLC
Farid Saraf	Novartis, MA
Robert C. Scott	Dartmouth University School of Medicine
Fariborz Soroush	Rowan University
Yuan Tang	University of Toledo
Nazanin Tousi	Case Western Reserve University
Bin Wang	Widener University
Hong Yuan	UNC, Chapel Hill

The People who helped!

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



$$$ Funding $$$

"Hey, bucko…I'm *through* begging."

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

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