The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
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Testimony of

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The Center for a Humane Economy, Animal Wellness Action, Animal Wellness Foundation, and SPCA International

Before the Subcommittee on Health of the Committee on Energy and Commerce

Thursday, March 17, 2022

The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

The FDA Modernization Act of 2021 (H.R. 2565 and S. 2952) seeks to amend the Federal Food, Drug and Cosmetics Act of 1938 to expand the types of test methods that can be used to determine the safety and effectiveness of drugs and vaccines. These bills do not ban animal testing but allow the government and industry to deploy the best and most predictive test methods in drug development protocols where scientifically suitable. In follow-up questions to his nomination process, FDA Commissioner Robert Califf had this to say about nonanimal testing method when asked about them directly:

> "We are entering a new era of systems biology with computational methods that enable a more efficient pre-clinical and clinical development and evaluation approach to drug and device development. I support the shift toward the use of non-animal methods where scientifically supported, and if confirmed would work to ensure the Agency continues its strong commitment to supporting the 3Rs: to replace, reduce, and refine the use of animals in studies. This effort must be done carefully to ensure that the system continues to protect human subjects during drug and device development and patients when products are marketed.[1]"

The legislation does not seek to settle the debate over animal testing, but to apply the widely accepted view that where alternative methods exist, they should be used. That nation is enshrined in the broad accept of the "3Rs" approach – Reduction, Refinement, and Replacement — developed more than a half century ago by Drs. William Russell and Rex Burch. In recent decades, almost all major research organizations, pharmaceutical companies, academic institutions, and even government agencies have embraced the principle. The FDA Modernization Act allows the government and pharmaceutical companies to act on their pledges. Without a lifting of the animal-testing requirement, and expanding the acceptability of non-animal methods, the Three Rs approach is just rhetoric, not reality.

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[1] Senate HELP : FDA Modernization Act Senator Rand Paul QFR to FDA Commissioner Nominee Califf

The legislation does not state or imply all animal tests can be replaced now. Congress writes legislation not just for today, but for 10 or 20 years down the road; innovation in the years ahead will almost certainly produce superior methods to animal testing in nearly all cases. The intent of the FDA Modernization Act is to open the door to the use of human-relevant test methods to improve the success rate in human clinical trials.

Sponsors of this legislation have taken FDA concerns to heart. FDA has provided two Technical Assistance documents to the Senate HELP Committee.   The Senate bill language differs from the House language based on suggestions from FDA in their first Technical Assistance. FDA's Second Technical Assistance suggested minor language modifications in the "Nonclinical Test or Study" definition, and the bill's sponsors are agreeable to those changes.

H.R. 2565 is a public health bill, addressing the problems with the current drug development model.

- Animal tests, in large part, are not predictive of the human response to drugs, with 90 to 95 percent of drugs and vaccines found safe in animal tests failing during human clinical trials.
- Most diseases have no treatment available. Adverse drug reactions are the fourth highest cause of death in the U.S. Use of human biology-based test methods would better predict how humans will respond to drugs in clinical trials.
- In addition to falsely identifying a toxic drug as "safe," animal tests can falsely label a potentially useful therapeutic agent as toxic. Thus, of the many thousands of drugs that have failed in animal tests, some might have worked in humans.
- The reduction in the number of false negatives (FN-drugs that are toxic but predicted by animal tests to be safe) directly increases consumer safety. Decreasing the rate of false positives (FP-drugs that are in reality safe but predicted to be toxic) has a direct effect on productivity and allows the marketing of products that would otherwise have been filtered out. The effect of allowing for safer products (low FN rate) and more marketable products from the discovery process (low FP rate) means increased business profit.
- A recent Phase 2b human clinical trial of Johnson & Johnson's HIV/AIDS vaccine failed because of lack of efficacy. Animal data had shown 90% efficacy.[2] This is consistent with the 30+ year effort to develop a HIV/AIDS vaccine. The animal data show promise, but the vaccines do not work in humans.
- On September 2, 2021, FDA's Cellular, Tissue, and Gene Therapies Advisory Committee said animal models are "problematic" in assessing the safety risks of gene therapies derived from adeno-associated virus (AAV) vectors. There have been "severe" adverse events in AAV vector clinical trials, including instances of acute liver and kidney failure in

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[2] J &J's HIV vaccine fails phase 2b, extending long wait for an effective jab, Fierce Biotech, August 31, 2021
https://www.fiercebiotech.com/biotech/j-j-s-hiv-vaccine-fails-phase-2b-extending-long-wait-for-effective-jab
and https://www.statnews.com/2021/08/31/first-efficacy-trial-of-johnson-johnsons-hiv-vaccine-fails

children. One third of the 500 children under the age of 2 treated with Zolgensma had at least once adverse event of hepatoxicity.[3]

- Studies show that while toxicity in animals may also be present in humans these tests are not consistent or reliable and provide nearly no insight into the possibility or likelihood of toxicity or the absence of toxicity in humans.[4]

- In one protocol, researchers studied six drugs to determine which of the 78 adverse effects that occurred in humans would occur in dogs or rats. Effects that are undetectable in animals (e.g., headaches) were not taken into account. Less than half (46%) of the remaining side effects were detected in the animals - slightly less than the expected results from flipping a coin. In other words, animal tests were wrong 54% of the time.[5]

- Another study of drug registration files was conducted to determine whether post-marketing serious adverse reactions to small molecule drugs could have been detected on the basis of animal data. Of 93 serious adverse reactions related to 43 small molecule drugs, only 19% were identified in animal studies as a true positive outcome.[6]

The costs of solely relying on animal data are high:

- The cost for developing a single new drug may be from $1 - $6 billion, and the average timeline of development of a potential drug and vaccine from the lab to market is 10—15 years.
- Estimates suggest that, relative to *in vitro* models, animal testing is 1.5 to 30 times more expensive.[7]

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[3] Animal models have limitations for safety assessment of gene therapies: FDA adcomm, Regulatory Focus, September 2, 2021. https://www.raps.org/news-and-articles/news-articles/2021/9/fda-adcomm-points-to-limitations-of-animal-studies?utm_source=MagnetMail&utm_medium=Email%20&utm_campaign=RF%20Today%20%7C%202%20September%202021

[4] Bailey, J., Thew, M., Balls, M., An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety, *Alternatives to Laboratory Animals,* 2013, 41(5), pp. 335-350., Bailey J, Thew M, Balls M., An analysis of the use of animal models in predicting human toxicology and drug safety. *Alternatives to Laboratory Animals*, 2014;42:189–99., Bailey, J., Thew, M., Balls, M., Predicting Human Drug Toxicity and Safety Via Animal Tests: Can Any One Species Predict Drug Toxicity in Any Other, and Do Monkeys Help? Alternatives to Laboratory Animals, 2015, 43 (6), pp,393-403.

[5] Clin Pharmacol Ther 1962; pp665-672 https://doi.org/10.1002/cpt196235665

[6] Van Meer, P,J., Kooijiman, M., Gispen-de Wied, CC., Moors, E.H., Schellekens, H. The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited, *Regulatory Toxicology and Pharmacology*, 2012, 64 (3), pp. 345-349

[7] Rodent testing in cancer therapeutics adds an estimated 4 to 5 years to drug development and costs $2 to $4 million. Compared with the costs of in vitro testing, **animal tests range from 1.5× to >30× as expensive.** Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach? https://www.sciencedirect.com/science/article/pii/S2452302X1930316X

- Updates to the FFDCA would provide drug sponsors more options for testing the safety and efficacy of drugs to improve clinical trial attrition rates, cut time to market in half, and substantially reduce R & D costs which could cut drug prices fivefold.[8]

There are non-animal methods for testing skin irritation, eye irritation, phototoxicity, skin sensitization, reproductive and developmental toxicity, mutagenicity, and other endpoints, and FDA seems to accept that these alternatives are sound. There are, however, other non-animal methods that are sound, but FDA has not accepted them.

Examples of Non-animal Methods

A) Organs on Chips and Computer Modeling

- In a recent study, researchers assessed the performance of 780 human Liver-Chips across a set of 27 known hepatotoxic and non-toxic drugs. *Importantly, the study demonstrated that the Emulate Liver-Chip was able to correctly identify 87 percent of the tested drugs that caused drug-induced liver injury in patients despite passing through animal testing.* At the same time, the Liver-Chip did not falsely flag any drugs as toxic, supporting its use in toxicology screening workflows.
- The biotech company Quris uses Artificial Intelligence-powered miniaturized "patients-on-a-chip" to avoid the tremendous risks and costs of failed clinical trials and eliminate the reliance on ineffective animal testing.

B) Disease-Specific Models

- **Cystic Fibrosis** — Microfluidic organ-on-a-chip preclinical models of the cystic fibrosis lung airway could help bring new and much-needed drugs, and personalized medicine approaches to patients. Studies using organs-on-a-chip models have been funded by the Cystic Fibrosis Foundation.
- **ALS** — Lab on a chip can make a major contribution as a biomimetic micro-physiological system in the treatment of neurodegenerative disorders such as ALS.
- **Alzheimer's Disease** — Preclinical stages of Alzheimer's disease (AD) and mild cognitive impairment have been modeled with a Human-On-A-Chip SYSTEM. To date, more than 100 potential therapeutics in development for AD have been abandoned or failed during clinical trials. These therapeutics relied on research conducted in preclinical animal studies, which often are unable to accurately capture the full spectrum of the human disease.
- **Parkinson's Disease** — Scientists have designed an "organ-on-a-chip" device that can grow the brain cells most affected in people with Parkinson's Disease. The Michael J. Fox Foundation has funded studies using organs on chips using the Lung-Chip device, to

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[8] Marx, U., Andersson, T. B., Bahinski, A. et al. (2016). Biology-inspired microphysiological system approach to solve the prediction dilemma and substance testing. *ALTEX* 33, 272- 321. doi:10.14573/altex.1603161

determine exactly how safe are specific Parkinson's drugs and to try to understand why they have a negative effect on the lungs.

C) Cancer

- Organ-on-a-Chip technology allows researchers to recreate the [human tumor microenvironment](#) in vitro, enabling mechanistic studies of cancer cell behavior and drug efficacy and safety.
- [Organ-Chips and Omics Advance Cancer Research](#) — groundbreaking research is being performed as a Cancer Grand Challenges research project, namely, STrOmal ReprograMming Cancer — or STORMing Cancer.

D) SARS-CoV-2

- The Biomedical Advanced Research and Development Authority (BARDA) awarded Harvard's Wyss Institute funding to develop to study vaccine responses. "The ongoing COVID-19 pandemic has made clear the need for rapid vaccine development, and this can be hampered by the lack of animal models that faithfully replicate human vaccination responses," said Donald E. Ingber, M.D., Ph.D., Founding Director of the Wyss Institute for Biologically Inspired Engineering at Harvard University.
- The Chemical Biological Center at the U.S. Army Combat Capabilities Development Command (CCDC) is working to better understand how COVID-19 attacks lung cells using the [Emulate Alveolus Lung-Chip](#) that recreates human biological systems. "In the past, the closest researchers could get to something like this was by introducing a virus into animals and then dissecting them," according to Dan Angelini, Ph.D., a Center research biologist. "With this, there is no need for animals in performing toxicological research."

Does FDA Have Discretion to Accept Non-animal Test Methods Without Amendments to the Federal Food Drug and Cosmetics Act?

FDA has suggested to staff on Capitol Hill that the agency already has discretion to authorize non-animal tests for preclinical testing.

This assertion by some FDA personnel does not appear to have a solid grounding. That assertion from FDA is vitiated by any plain reading of the statute (FFDCA), the agency's failure to respond to two thoroughly researched petitions urging it to make plain that alternative methods can be used to replace animal tests where scientifically supported, and a relatively recent judicial decision in a case where a drug sponsor objected to prolonged testing in dogs. Assuming, arguendo, that FDA does indeed have the discretion to accept non-animal tests, over the past 15 years it has repeatedly refused to exercise this discretion.

<u>A U.S. District Court case makes it clear that the statute and regulations do not allow drug sponsors to proceed to clinical trials without animal tests.</u>

A recent federal case addressed this issue in the context of clinical (human) trials. The Court's decision is unambiguous in directing drug developers who seek relief from the animal-testing mandate to turn to Congress and secure a statutory change. That's the prescription provided by the FDA Modernization Act.

Vanda Pharmaceuticals v. FDA[9]

In 2019, Vanda sued FDA over a clinical hold. Specifically, FDA required that Vanda conduct a nine-month dog study. It had previously conducted a 3-month dog study. The District Court ruled in FDA's favor.

> "Vanda's argument is unpersuasive for the basic reason that the statutory and regulatory scheme here explicitly contemplates that the results of animal studies are predictive of the results of human trials. See, e.g., 21 U.S.C. § 355(i)(1)(A) (authorizing FDA to promulgate regulations for the 'protection of the public health'" that require drug sponsors to submit "preclinical tests (including tests on animals) . . . adequate to justify the proposed clinical [human] testing"); see also id. § 355(i)(2)(B) (requiring drug sponsors to submit "primary data tabulations from animal or human studies" (emphasis added) 21 C.F.R. § 312.23(a)(8) (requiring drug sponsors to submit "[a]dequate information" about studies "involving laboratory animals" which allow the sponsor to conclude "that it is reasonably safe to conduct" human trials). Indeed, the entire point of conducting animal studies—which the legal framework mandates—is that the results of those studies have some relevance to humans. That is, the framework assumes that if a drug is shown not to be toxic in animals, it is at least reasonably likely to be safe to conduct human trials."

"In the Remand Response, FDA acknowledged this linkage between animals and humans with the statement that "findings in animal toxicity studies are generally applicable to humans." Remand Resp. at FDA-11113. That is the rational connection that Vanda deems missing from the Remand Response**.** *And indeed, FDA is not free, legally speaking, to simply allow drug sponsors to proceed with human trials without adequate animal studies. While Vanda is correct that FDA does not explicitly support this statement with studies, the support is implicit in the legal framework and in common sense. If Vanda has a quarrel with animal studies and their predictive power for humans in general, its fire would be more appropriately aimed at the controlling statute and regulations, not at FDA's actions in this case.".* (Emphasis added)

The FFDCA has promoted the *status quo*, requiring traditional testing during preclinical studies, and creating an unreceptive environment that fails to encourage or support the development of modern and emerging test methods. The FDA itself has acted as if the FFDCA binds the FDA to

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[9] ***VANDA PHARMACEUTICALS, INC. v. FOOD AND DRUG ADMINISTRATION et al**, **No. 1:2019cv00301 - Document 50 (D.D.C. 2020),** MEMORANDUM OPINION. Signed by Judge John D. Bates on 1/31/2020. (lcjdb1) available at https://law.justia.com/cases/federal/district-courts/district-of-columbia/dcdce/1:2019cv00301/203979/50/

continue guiding sponsors away from making use of non-animal-based breakthrough testing methods.

If FDA has discretion to accept nonanimal data, the NIH, animal research facilities and pharmaceutical companies don't know about it, as evinced by statements from a range of contract research organizations.

Northern Biomedical Research conducts preclinical testing and describes the use of animals as mandatory:

"Current regulations require testing in animal models to identify any potential health or safety risks to the general public before any drug or therapy is brought to market. Thus, the use of animals in research is currently an essential and **mandatory** component of the drug discovery process…."[10]

Charles River says using animals for testing new treatments is required:

"Before any drug or therapy is brought to market, there are regulations requiring testing in animal models to identify any health or safety risks as well as effectiveness"[11]

Labcorp (formerly Covance) states new drugs must be tested on animals (citing FDA regulations).

"New drugs must be tested in animals before human clinical trials to ensure the safety of patients and volunteers."[12]

Pfizer says that animal data must be submitted to the FDA.

"Accordingly, before any potential medicine can be tested in, and subsequently approved for, humans, data from animal models must be submitted to the U.S. Federal Drug Administration (or its equivalent in other countries) to demonstrate its safety and efficacy."[13]

The National Institute for Allergy and Infectious Disease (NIAID) states controversial tests on beagles were conducted as required by the FDA.

NIAID said the contract for "preclinical pharmacology and toxicology services" was conducted "as required in animal models by the FDA, in compliance with Good Laboratory Practice (GLP) guidelines and in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) or its equivalent."[14]

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[10] Northern Biomedical Research https://nbrlab.com/about-us
[11] Charles River https://www.criver.com/about-us/about-us-overview/animals-research?region=3601
[12] Labcorp: https://drugdevelopment.labcorp.com/commitment/animal-welfare/why-animal-research.html
[13] Pfizer: https://www.pfizer.com/science/clinical-trials/integrity-and-transparency/animals-used-in-research
[14] Medpage Today, Fauci Blasted Over Puppy Research Claims, October 21, 2021, https://www.medpagetoday.com/special-reports/exclusives/95275

FDA Stonewalls on Detailed Legal Petitions Seeking Agency Support for the Proposition that Non-Animal Tests Are Permitted for Preclinical Trials.

Fifteen years ago, FDA received a thoroughly presented citizen petition specifically requesting a regulatory change to allow the use of data from non-animal methods. Three years later in response, FDA said it would issue draft guidance, but later moved decided not to do so. Seven years ago, another citizen petition seeking discretion to use such data was filed in 2015. While FDA provided two "interim responses," FDA has not yet provided a substantive response as required by 21 CFR 10.20(f).

Mandatory Alternatives Petition FDA-2007-P-0109– November 2007

1) A coalition of animal protection groups submitted the Mandatory Alternatives Petition in November 2007 to FDA, regarding the use of non-animal test methods. On May 20, 2010, FDA denied the Citizen Petition. The agency replied," FDA intends to issue a draft guidance to industry and to FDA staff regarding the use of NATMs." Despite that commitment, FDA internal documents show that FDA had an internal discussion on how to make a "legally defensible" response to the Petitioners, reneging on its commitment. In 2014, FDA wrote to Petitioners saying the agency would focus on "encouragement of the implementation of the principles of the 3Rs, to reduce, refine, and replace animal testing," and not issue guidance.

Modification of Regulations Petition Related to Animal Testing – FDA-2015-P-2820- July 2015

2) In July 2015, the Center for Responsible Science, with a series of other co-petitioners[15] requested that FDA modify existing regulations in Title 21 of the Code of Federal Regulations (CFR) that govern requirements for investigational new drug (IND) applications, investigational device exemptions (IDE), and new drug applications (NDAs). Filed July 2015.

Specifically, petitioners requested that Commissioner of the FDA amend certain regulations to establish and clarify that FDA will accept data from scientifically recognized modern and emerging test methods to support a drug or device investigational application. The requested amendments would broaden options in preclinical testing and will not require one type of testing over another. This clear signal will move product development forward by bringing written policy up to date with stated policy and science, and by paving the way for industry to develop and use emerging, superior technologies. Nearly seven years later, FDA has not provided a substantive response.

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[15] Asterand Bioscience, AxoSim, Empiriko, Friends of Cancer Research, Hurel Corp, In Vitro ADMET Laboratories, Invitro Cue, InVitro International, MatTek Corporation, National Organization for Rare Disorders, Safer Medicines Trust, United Spinal Association, 3D Biomatrix, Inc.)

Conclusion

We can apply human biology-based test methods to better predict how humans will respond to drugs in clinical trials. We are already on the verge of the next phase of modern drug development and allowing for the use of only animal models doesn't reflect 21st Century scientific advancement. H.R. 2565 and S. 2952 will be catalysts for this transition to modern science.

The range of organizations – more than a dozen biotech and pharma companies, dozens of patient advocacy and medical organizations, and large numbers of animal welfare groups – collectively attest to the resonance of the reforms called for in this legislation.

It's time for FDA to update its Depression-era regulations and requirements for animal tests and to allow for nonclinical test models that are predictive of what will happen in humans in clinical trials. It's time for Congress and the FDA to unleash the power of science in overseeing U.S. drug development.

We hope that the committee will favorably report H.R. 2565 with amendments agreed upon by the bill's authors and fold the measure into the User Fee Amendments that you take up in 2022 and send on to the President to sign.

Wayne Pacelle is President of Animal Wellness Action and the Center for a Humane Economy.

Tamara Drake is Director of Research and Regulatory Policy for the Center for a Humane Economy

CENTER FOR A HUMANE ECONOMY

FDA MODERNIZATION ACT OF 2021 ENDORSEMENTS

Biotech & Pharmaceutical Companies:

AxoSim
Empiriko
Emulate
InVitro International
Obatala Sciences

SynVivo
Nortis Bio
BICO
CELLINK
MatTek

Visikol
SCIENION
Cellenion
Teva Pharmaceuticals

Medical Associations and Patient Advocacy Groups

National Medical Association
National Hispanic Medical Association
Histiocytosis Association
The VHL Alliance
Born a Hero Research Foundation
CHAMP1 Research Foundation
Lymphangiomatosis & Gorham's Disease Alliance
The International FPIES Association
International Pain Foundation
Beyond Celiac
United Leukodystrophy Foundation
Myositis Association
Reflex Sympathetic Dystrophy Syndrome Association
Allergy and Asthma Network
Nevus Outreach

CURED
National LGBT Cancer Network
A Cure in Sight
Cauda Equina Foundation
Gaucher Community Alliance
Rare and Undiagnosed Network
Marfan Foundation
International Autoimmune Encephalitis Society
Shwachman-Diamond Syndrome Foundation
NBIA Disorders Association
San Francisco AIDS Foundation
The LAM Foundation
The Gluten Intolerance Group
National Hemophilia Foundation

Organizations

All Creatures, WA
Animal Advocates of South-Central PA
Animal Protection League of NJ
Animal Wellness Action
Animal Wellness Foundation
Bailing out Benji
Beagle Freedom Project
Blind Spot Animal Sanctuary
Brother Wolf Animal Rescue
Center for a Humane Economy
Christian Animal Rights Association
Citizens for Alternatives to Animal Research
Coalition for NYC Animals, Inc.
Compassionate Bay
Dane 4 Dogs
Fair Start Movement
Forever Home Beagle Rescue
Friends of Animals
Georgia Pet Coalition
Green Mountain Animal Defenders
Humane Action Pittsburg
Jefferson County Humane Society, OH

Jewish Veg
Karma Rescue
Last Chance for Animals
League of Humane Voters NJ
Maine Animal Coalition
Marley's Mutts
Michelson Center for Public Policy
National Anti-Vivisection Society
New Life Animal Sanctuary
Pasado's Safe Haven
People for the Ethical Treatment of Animals
Phoenix Zones Initiative
Piedmont Farm Animal Refuge
Population Balance
Progressive Animal Welfare Society (PAWS)
Protect our Wildlife Vermont
Social Compassion in Legislation
SNAP – San Diego
Switch4Good
Their Turn
Voters for Animal Rights, NYC

Individuals of note

Dr. Neil Wilcox, former FDA, Senior Science Policy Officer, Office of Science, Office of the Commissioner and Science Policy Analyst

David Wiebers, M.D., Emeritus Professor of Neurology and Consultant Emeritus in Neurology and Epidemiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Dr. Paul Watkins, Director of the Institute for Drug Safety Sciences at the University of North Carolina, Chapel Hill.

Paul Locke, JD, DrPH, Johns Hopkins Bloomberg School of Public Health.

Dr. David Gortler, pharmacologist, pharmacist and an FDA and health care policy scholar at the Ethics and Public Policy Center Think Tank in Washington, D.C. He was a professor of pharmacology and biotechnology at the Yale University School of Medicine, where he also served at Yale's Bioethicist Center, and was an FDA Medical Officer who was later appointed by the White House to serve on the FDA's Senior Executive Leadership Team as senior advisor to the FDA Commissioner for drug safety, drug epidemiology, FDA science policy, and FDA regulatory affairs.

Amanda Proctor, BS-RRT, President & CEO, Medical Advisory, Scientific, & Review Board Member, Cardiopulmonary Science & Sleep Medicine, Cauda Equina Foundation

Dr. Daniel Krichbaum, Pharm D, Medical Advisory, Scientific, & Review Board Member, Co-Chief Medical Officer, Chief Science Officer, Cauda Equina Foundation

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Jason Hwang, MD, Medical Advisory, Scientific, & Review Board, Director of Radiology, Cauda Equina Foundation

Chuck Nitsch, PT, CEEAA, Medical Advisory, Scientific, & Review Board, Research Committee, Director of Physical Therapy, Cauda Equina Foundation.

Recent Relevant Publications on the FDA Modernization Act of 2021

Organ-Chips and Omics Advance Cancer Research

February 2, 2022

Aaron Hudson, PhD
Vice President, Global Marketing and Strategy, SCIEX

Scans and tests confirmed that I did in fact have lung cancer. I just couldn't believe it. I was devastated. For me, lung cancer was a death sentence; if you got lung cancer, you died, simple as that, and that's when I started to think—how am I going to tell my family, my kids?" said Jackie, the subject of a patient story posted by the Roy Castle Lung Cancer Foundation.[1] Lung and bronchus cancer is the third most common cancer in the United States, with an estimated 235,760 new cases diagnosed in 2021 and 131,880 deaths—accounting for 12.4% of all new cancer cases and 21.7% of all cancer deaths last year.[2] The five-year relative survival rate between 2011 and 2017 was 21.7%.[2]

Now, a team of researchers at multiple institutions around the world is taking a novel approach to unravel the mysteries of what causes certain cancers, namely those related to inflammation, such as some lung cancers. This groundbreaking research is being performed as a Cancer Grand Challenges research project, namely, STrOmal ReprograMming Cancer—or STORMing Cancer.[3,4] The team, which is led by Thea Tlsty, PhD, a professor of pathology at the University of California, San Francisco (UCSF), is applying a radical new approach to understanding the "nastiest of nasty" cancers. The approach relies on state-of-

the-art technologies—many of which are being developed by team members as they go along! Team members are focusing on four types of cancer—esophageal, stomach, colon, and lung—that are associated with chronic inflammation. Cancer cases that have been linked to chronic inflammation account for about 25% of all cancer cases and are estimated to cause 1.7 million deaths worldwide annually.[3]

Identifying common cancer pathways

Chronic inflammation, such as that resulting from chronic damage to the esophagus by stomach acid in gastroesophageal reflux disease (GERD), can result in abnormalities referred to as metaplasia in the esophageal tissue, recognized as a disease called Barrett's esophagus or metaplasia.[5] In some individuals, metaplasia tissue becomes even more abnormal, progressing to a precancerous state known as dysplasia.[5] Dysplasia tissue can then progress to cancer, for instance, in 10–15% of individuals with GERD, who then go on to develop esophageal cancer.[5]

To understand how chronic inflammation can lead to cancer, STORMing Cancer is examining the building blocks of tissues—specifically, the stromal and epithelial cells, as well as the surrounding extracellular matrix (ECM) and biochemical messengers—and the way they all interact with each other.[6]

Studies have shown that stromal cells can dictate how adjacent epithelial cells behave. Healthy epithelial cells transform into tumor-like cells when placed next to stromal cells that have been obtained from around a tumor. And vice versa: tumor cells behave like normal healthy epithelial cells when placed next to stromal cells from healthy tissue, despite maintaining an altered genotype.[6]

These studies indicate that the stroma is dominant and dynamic, as is the ECM by which the stroma mediates its effect on epithelial cells. To elucidate how healthy stromal cells and ECM can reprogram cancers into becoming healthy cells again, the global team is using multiple advanced methods in parallel to analyze biopsy and resection samples from individual patients with cancer and/or the associated chronic inflammatory condition (*Figure 1*).
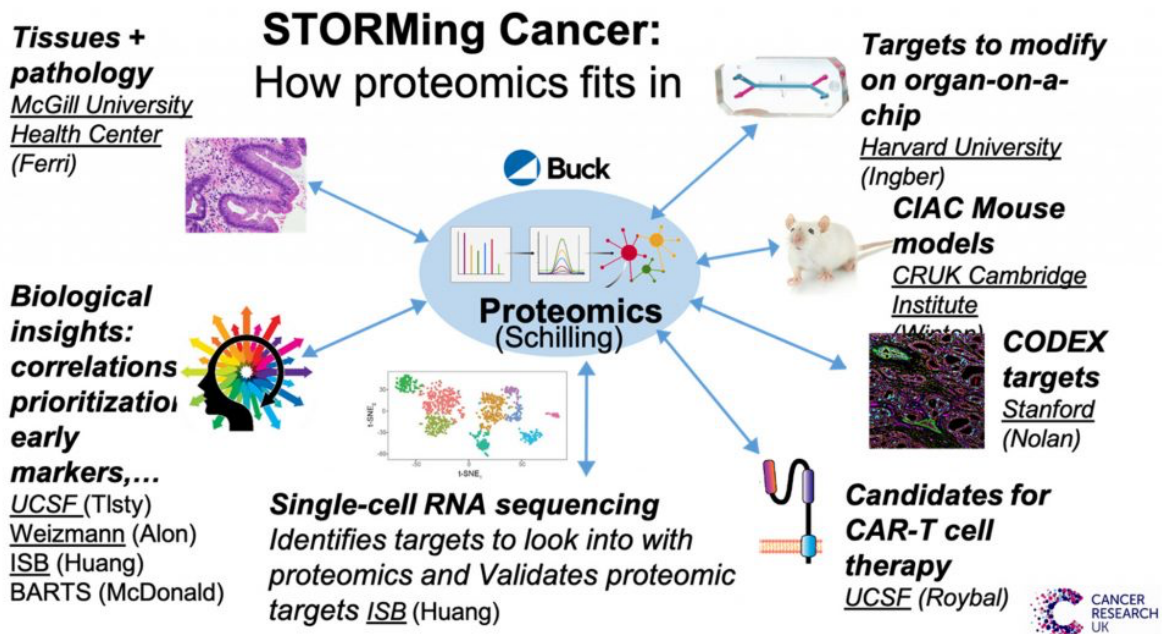
Figure 1. How the proteomics team fits in with the other multidisciplinary teams on the STORMing Cancer project. Cameron Wehrfritz, Buck Institute for Research on Aging

Cancer-on-chips for elucidating disease mechanisms

Donald E. Ingber, MD, PhD—a pioneer of organ-on-chip devices[7-13] and a co-founder of Emulate[14]—leads a group at the Wyss Institute at Harvard that is developing organ-on-chip devices that model inflammation-associated cancers. An organ-on-chip device from Emulate is about the size of an AA battery and composed of flexible polymer. It is a microengineered fluidic system that provides human cells with the dynamic environment needed to more faithfully replicate the body in three dimensions (*Figure 2*).
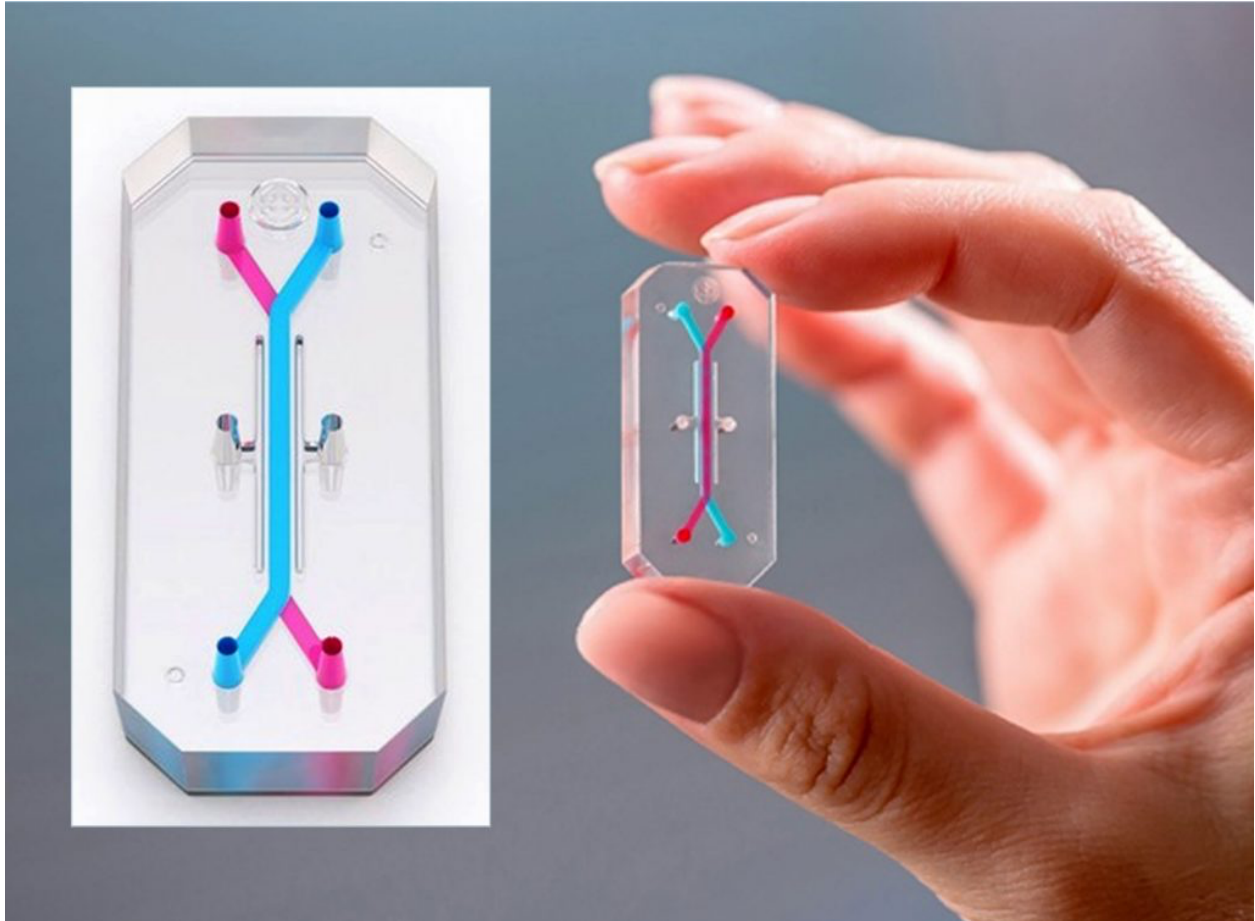
Figure 2. Emulate's Organ-Chip (Chip-S1) can be configured to emulate lung, liver, intestine, kidney, and brain. It can also be used as a platform to study a variety of diseases.

It contains two microchannels that can recreate an extracellular matrix, providing the scaffolding found in the body's cellular milieu. A flexible porous membrane between the channels allows the co-culture of distinct cell types and the study of phenomena at tissue-to-tissue interfaces. The channels are also designed to recreate the flow of blood and other fluids, providing biochemical surroundings that resemble those in vivo.

Using various analytical approaches, including atomic force microscopy, confocal imaging, cytokine analysis, and transcriptomics, Ingber and his team have identified mechanical and transcriptomic differences between healthy and cancerous cells as well as contributions of the stroma to epithelial cancer progression (personal communication).

These findings correlate with proteomic analyses performed by Birgit Schilling, PhD, and her team at the Buck Institute on pieces of the same patient samples. These analyses revealed robust proteomic signatures indicative of dramatic ECM

remodeling between normal and metaplasia stages.[6] Some of these changes persisted through dysplasia to full-blown cancer, whereas other changes were transient. (The transient changes occurred only during metaplasia and dysplasia, and then were lost at the tumor stage.[6])

The proteomic analyses were also performed using SWATH acquisition, which comprehensively detected and quantified every detectable peptide in the samples. Each analysis produced a multidimensional readout that was so thorough it was essentially a digital archive of the sample that could be reinterrogated later for new information, when no additional patient sample is available.

Thus, as the project progresses and new protein candidates are identified as potential markers for reprogramming precancerous or tumor cells, the team can return to the acquired data to check whether those proteins are detectable and, should they be detectable, whether their abundance differs between samples.[6]So far, one of the most important findings is that these proteomic signatures are found across the four cancer types and their associated chronic inflammatory states.[6] The next piece of the puzzle is to discover what distinguishes patients with chronic inflammation who go on to develop cancer from those who do not.[6]

Broadening horizons for translational research and drug development

The use of organ-on-chip platforms is expanding, with many research teams now developing their own models as well as using off-the-shelf options such as those produced by Emulate.[15] Organ-on-chip platforms are being used to model tissues such as vascular microvessels, intestinal tissue, and neural tissue, and diseases such as microvascular disease, and Crohn's disease, and Parkinson's disease.[15-19] Moreover, a bill to modernize the 1938 Federal Food Drug and Cosmetics Act (FFDCA) has been introduced to both houses of Congress.[20] The proposed FDA Modernization Act of 2021 aims to amend the mandate for animal testing during preclinical drug development by broadening the scope to accept evaluations of drug safety and efficacy using more advanced and humane technologies instead, where possible.[20,21] These technologies include organ-on-chip platforms. Once sufficient validation has been demonstrated, these platforms could pave the way for faster, more effective, and more humane drug development.[21]

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Disclaimer

Protecting Patients From Toxic Drugs Requires Modernization

This article includes research findings that are yet to be peer-reviewed. Results are therefore regarded as preliminary and should be interpreted as such. Find out about the role of the peer review process in research [here](#).

A chilly air blew into Tulsa, Oklahoma, in October of 1937, and with it came the usual wave of sore throats, colds and headaches. Eager to soothe their patients' discomfort, physicians turned to their growing arsenal of therapeutics where some found a raspberry-flavored concoction named Elixir Sulfanilamide. Before the snows of November had fallen, more than 100 people would die of acute poisoning brought on by this lethal elixir.

The Elixir Sulfanilamide disaster was a transformative moment in the American pharmaceutical industry[1]. Investigation found that the Elixir had undergone no prior testing to see if it was safe for consumption before it was distributed for use by the S.E. Massengill Company. One FDA agent described the company's drug development process as putting "drugs together, and if they don't explode,

they are placed on sale."[1] Public outcry from the incident motivated the U.S. Congress to act: They had to find a way to ensure that new drugs were safe.

In 1938, they enacted the Federal Food, Drug, and Cosmetics Act (FFDCA) which, among other stipulations, mandated that all new drugs be tested for toxicity in animals prior to human studies. At the time, researchers had few resources at their disposal with which drug toxicities could be tested. They could take it themselves, or they could give it to animals. In this light, it makes sense that the FFDCA required animal testing. But does this requirement make sense for the modern day?

Toxicity and the questionable value of animal testing

Studies done shortly after the Elixir Sulfanilamide disaster showed that diethylene glycol – the solvent used in the elixir – had a rapid and sometimes lethal effect on the kidneys. Had the Massengill Company tested the safety of their product in animals, they would have seen this.[2]

One of the values of using animal models is their complexity. Unlike traditional cell culture, living organisms consist of heterogeneous and interconnected tissues. The transit of a drug through one organ may modify it, alter its pharmacological properties, and thus change how the drug behaves in another organ. Such dynamics are hard to replicate *in vitro*.

There is no doubt that animal models have contributed to major advances in medicine and have contributed to safe and effective drugs making it to market. However, animal testing also has significant drawbacks and its continued use as a mandatory part of drug screening may be doing more harm than good.

Credit: Pixabay

A growing body of evidence suggests that animal models are seriously lacking in both sensitivity and specificity when it comes to predicting drug toxicity in humans.[3-5] A 2014 study analyzing the effects of 2,366 drugs in both animals and humans found that "tests on animals (specifically rat, mouse and rabbit models) are highly inconsistent predictors of toxic responses in humans and are little better than what would result merely by chance."[6] A 2008 review found similar results, concluding that animal models predicting drug toxicity in humans may have sensitivity and specificity values below 70%.[4]

The cost of poor specificity and selectivity is too often passed onto the patient. A review of 578 discontinued and withdrawn drugs in Europe and the United States showed that nearly half halted distribution due to post-approval toxicity.[7]Similarly, a 2012 analysis of 93 post-approval drugs with serious toxicity effects found that only 19% of them showed indications of toxicity in animal studies.[8]

These data points are just a few out of many that suggest preclinical toxicity screening of therapeutics in animals is less than reliable.[3-5] Just how unreliable it is, though, is unknown owing to a lack of consistency among studies, the lack of negative data reporting, and inherent difficulties in gathering data in a field where patents and intellectual property are common.

Use of an unreliable model in therapeutic development has logistical costs as well. Housing and caring for laboratory animals is an extremely resource intensive process, requiring time, facilities, and personnel among many other investments. Additionally, resources spent advancing a toxic therapeutic into the clinic are often not recoverable. Lastly, working through inefficient or ineffective preclinical models can cost valuable time that prevents patients from getting the therapeutics they so desperately need.

Looking back to the Elixir Sulfanilamide disaster, the FFDCA was enacted to protect patients and prevent the unnecessary loss of life due to poor drug development practices. It is incumbent on us to honor that intention by continually reevaluating and updating our drug development process as new technologies are developed.

Modernizing drug screening with organ-chip technology

In the 80 years since the FFDCA was enacted, several technological advancements have taken place. We now have the ability to culture primary human cells in dynamic, human-relevant environments that are amenable to controlled experimentation. This allows researchers to more precisely evaluate how a drug will behave in specific organs.
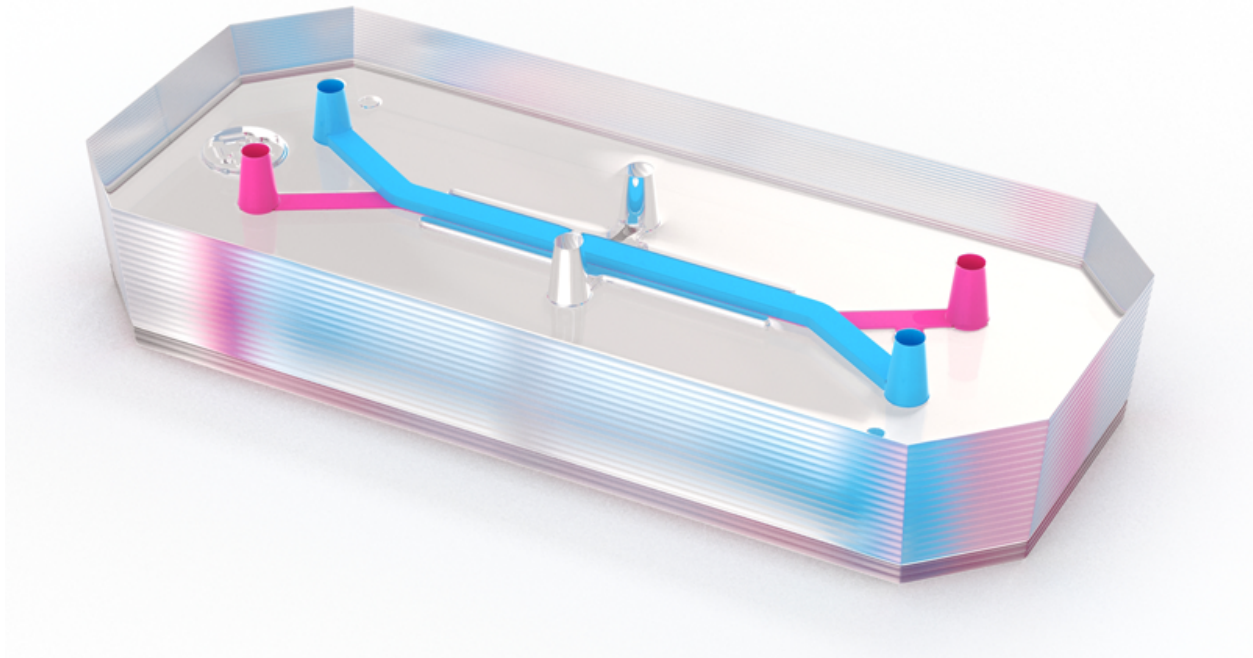
Credit: Emulate

Organ-chips are a good example of this. These microengineered three-dimensional cell culture systems allow researchers to recreate tissue-specific environments, such as what cells may experience in the human liver, for example. Human cells grown in organ-chips closely mimic *in vivo* cells both in behavior and in gene expression profiles. And, importantly, organ-chips may predict human drug toxicity with greater specificity and selectivity relative to contemporary models.

In a recent preprint published on *bioRxiv*, researchers analyzed 780 liver-chips for their ability to predict drug-induced liver injury caused by 27 known hepatotoxic and non-hepatotoxic small molecules.[9] They found that liver-chips far outperform current models, showing an 80% sensitivity and 100% specificity in predicting drug toxicity. By correcting for protein binding, sensitivity could be increased to 87%. Notably, the hepatotoxic drugs used in this study had all cleared animal tests during preclinical evaluation, indicating the liver-chip's superior ability to identify how human cells are likely to respond to toxic compounds. What's more, an economic value analysis suggests that this improved performance translates into billions of dollars in productivity value.

In light of the growing body of evidence casting doubt on the continued value of preclinical animal testing, we must consider replacing animal testing with superior models like organ-chips. The efficiency and accuracy of organ-chips suggests they should be adopted as a decision-making tool in preclinical drug screening, one that speeds up the drug development process while also reducing the number of toxic drugs that reach the patient's bedside.

Towards a safer, efficient and more humane future

Animal testing has played an important and significant role in the evolution of medicine. However, our technological and medical expertise has advanced over the past 80 years. With these advancements, it is increasingly recognized that our narrow reliance on animal testing for preclinical drug screening comes at a significant cost.

Fortunately, steps are being taken to modernize drug development. In 2021, a bipartisan congressional committee proposed the FDA Modernization Act of 2021 – an amendment to the FFDCA that broadens the scope of acceptable preclinical models for drug development, enabling researchers to test a drug's safety and efficacy using more advanced and humane methods, including organ-chips.

By adopting technology like organ-chips, we make the drug development process safer, more efficient and more humane.

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Tackling Life's Toughest AI Challenge

January 5, 2022

By Isaac Bentwich, MD, and Amir Bein, PhD

Isaac Bentwich, MD
Founder and CEO, Quris

Drug development and regulation is undergoing a quiet revolution. As discussed in the December 2021issue of *GEN*, the European Parliament resolution to phase out animal testing has been followed by a similar initiative in the United States, the FDA Modernization Act of 2021. If this bill becomes law, it will remove an 80-year-old statute that mandates reliance on animal studies. The stage is now set for a transformation of how we discover, develop, and regulate drugs, and a new class of artificial intelligence technologies is an important part of this transformation.

According to Nobel laureate Aaron Ciechanover, MD, DSc, "One of the main problems in drug development is the model that we are using—the mouse. The mouse is not human, so there is no wonder that 92% of drugs that are successful in mice are failing in clinical trials in humans."

Amir Bein, PhD

Vice President, Biology, Quris

To effectively predict human efficacy and safety, we need to find a new drug development path, one that avoids the faulty reliance on mice. If we don't, we will never solve the drug safety prediction problem.

The challenge

Drug development has become unbearably slow and expensive. It costs over $2.6 billion per drug, and it takes 12–15 years to bring a drug to the market. A big part of the cost stems from the difficulty in predicting which drug candidates will safely work in humans. A stunning 89% of drug candidates that successfully pass animal testing fail in clinical trials (Van Norman GA. *J. Am. Coll. Cardiol. Basic Transl. Sci.* 2019; 4: 845–854)—trials that cost hundreds of millions of dollars.

Let that percentage sink in: Animal testing is so ineffective at predicting drug safety and efficacy in humans, that it is in fact simply wrong close to 90% of the time. A paradigm shift is needed to move basic research, big pharma, and regulatory agencies to a more efficient drug development system.

"We are at the tipping point of the modernization of drug discovery," notes Robert S. Langer, ScD, a co-founder of Moderna, a lauded Institute Professor at the Massachusetts Institute of Technology, and the most cited engineer in history.

AI is transforming pharma

So, what does the future hold? How can we better predict which drugs will work safely in humans? How do we break free of the faulty reliance on animal testing? We can apply artificial intelligence (AI). It is now emerging as a disruptor of the pharma industry, with AI-pharma companies—several of them young companies with multibillion-dollar valuations—improving various aspects of drug discovery and development. These companies have already shown significant, measurable savings and impact in different parts of the pharma value-creation chain, from drug discovery and development to clinical testing and development to marketing.

AI-pharma processes and companies may be divided into two broad classes. A first class of AI-pharma may be termed "early stage" or "chemical level" AI. This class, which is characterized by the use of various forms of AI in drug discovery, includes companies such as Isomorphic Laboratories (a Google-Alphabet spinout), Recursion ($2.8B), Exscientia ($2.4B), Insitro ($2.5B), XtalPi ($2B), ImmunAI ($1.4B), BenevolentAI ($1B), and Insilico Medicine ($1B). Companies in this class use AI and powerful bioinformatics to invent new molecules, accelerate discovery, improve the quality of new drug leads, find new targets for a disease, find drug candidates that have better molecule-target fit, repurpose existing drugs, and improve our understanding of the mechanisms of action of drug candidates so as to better anticipate and avoid off-target side effects.

A second class of AI-pharma may be termed "late stage" or "clinical level" AI. Here, powerful AI is used to optimize drug utilization and personalization of drugs that have already attained regulatory approval. Tempus ($8B) is an excellent example of this class of AI-pharma companies.

Both these classes of AI-pharma started out relying on existing biology data, with the emphasis now moving more toward generating cutting-edge biology-at-scale data, which is more informative and actionable. Data from single-cell genomics, epigenetics, proteomics, metabolomics, and immune profiling, as well as from protein-folding prediction studies (such as those performed by Google's revolutionary DeepMind system), can be analyzed by machine learning. As leading AI-pharma companies have shown, this is effective in significantly improving and accelerating many processes in drug discovery, as well as in post-regulatory utilization of existing drugs.

**The next frontier: Bio-AI clinical prediction**

And yet, with all this impressive progress, a major AI challenge remains largely unaddressed: how to predict which drug candidates will work safely in the

human body. Think of it this way: chemical-level AI processes accelerate drug discovery and may deliver more qualitative, better understood drug candidates, but each new molecule or target still has to be tested to assess its actual effect in the human body.

Currently, this means testing of a drug candidate begins with traditional in vitro lab assays (traditional 2D tissue cultures and other in vitro assays). If that goes well, testing progresses to animal models. Unfortunately, tests that rely on mice and rat models are consistently 89% wrong in predicting if a drug candidate is safe and efficacious in the human body, which brings us back to square one. Current AI platforms do not adequately address this problem.

A new class of AI-pharma called Clinical Prediction AI focuses on predicting which drug candidates will work safely and efficaciously in humans. A major difficulty in addressing this challenge is the data itself. Most of the above rely on biology-at-scale in vitro data used or generated by traditional tissue culture approaches. While easily accessible and no doubt informative, the data and resulting insights are nonetheless extremely poor in their predictiveness of clinical safety and efficacy in the human body.

To be successful, Clinical Prediction AI requires data be generated that captures novel biology and that is highly predictive of the clinical safety and efficacy of drugs in the human body. Miniaturized "Organ on Chip" technologies, especially those that interconnect multiple organ models, provide data that is highly predictive of pharmacokinetics (Herland et al. *Nat. Biomed. Eng.* 2020; 4: 421–436) and pharmacodynamics in the human body. However, in their current form, these technologies are unsuited to the task of quickly and inexpensively conducting thousands and, ultimately, millions of experiments and thereby training a robust AI platform.
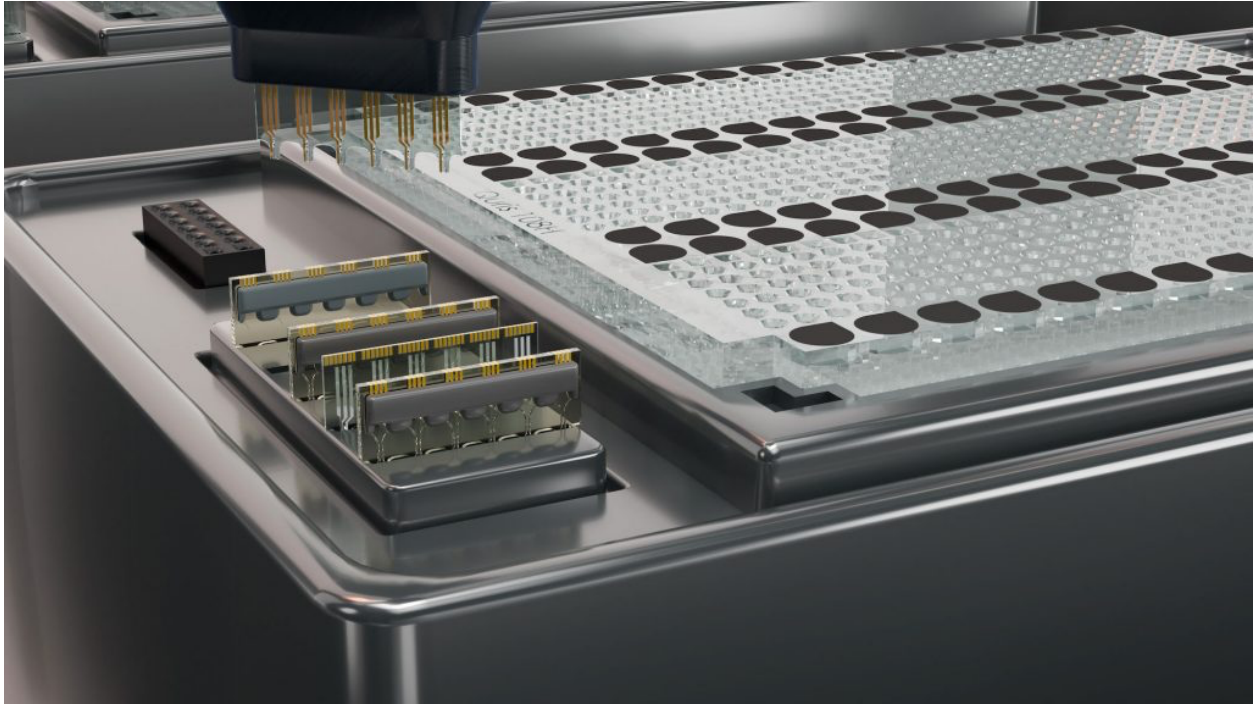
Quris has developed the AI Chip-on-Chip, an automated platform that can test thousands of drugs on miniaturized, stem-cell-derived Patients-on-a-Chip. The platform incorporates nanosensors that continuously monitor patient cells, or miniaturized organs, to collect data about their responses to potential drugs. Ultimately, the data is analyzed using AI to predict how well the drugs will fare in clinical trials.

To significantly improve drug prediction capabilities, a completely new, holistic approach is needed. We can deliver on the real promise of Clinical Prediction AI only if we start by testing known safe and unsafe drugs on a robust humanized in vitro system, comprised of miniaturized patients-on-a-chip within an automated high-throughput platform. Automatically generated data then needs to be classified and used to continuously retrain the machine learning algorithm to generate high-fidelity predictions of clinical safety and efficacy.

Clinical Prediction AI is complementary to, and synergistic with, other AI-pharma approaches. It supports chemical-level AI drug discovery by identifying drug candidates early on that are likely to be safe and effective in the human body, and it works well with clinical-level AI by helping personalize drugs. Together, these different AI approaches will help transform drug development, steer its regulation, and change (or eliminate) the role of animal testing.

Isaac Bentwich, MD, is the founder and CEO of Quris, and Amir Bein, PhD, serves as vice president of biology at the company.

https://www.forbes.com/sites/forbestechcouncil/2021/12/20/the-fda-modernization-act-can-leverage-technology-to-accelerate-drug-discovery-and-save-millions-of-animals/?sh=18a478901cc0

Erik Gatenholm

Forbes Councils Member

Forbes Technology Council

COUNCIL POST| Membership (Fee-Based)

The FDA Modernization Act Can Leverage Technology To Accelerate Drug Discovery And Save Millions Of Animals

Erik Gatenholm10:30am EST

Innovation

Erik Gatenholm is the CEO and co-founder of BICO, a leading bio convergence company.

getty

What if I told you that the United States, the world's leading developer of drugs and cosmetics, still relies on regulations from the 1930s to ensure the safety of new products?

It's true. In 1938, Congress passed the U.S. Federal Food, Drug, and Cosmetic Act. This act mandates that new drugs and cosmetics be tested on animals before entering clinical trials and approved for use in humans. Since then, billions of

dogs, primates, rabbits and mice have been unnecessarily experimented on, tortured and killed. In fact, a study published by the National Center for Biotechnology Information (NCBI) found that more than 115 million animals are used each year in biomedical research.

The legislation was passed 20 years before the first modern blood tests, 40 years before modern computers and 60 years before the human genome was mapped. Now, we have all of these tools and so many more to evaluate and ensure the safety of cosmetics and drug candidates before they reach human trials.

Worldwide, other countries are beginning to change the way they test. The European Union outlawed animal testing for cosmetics in 2013 and is implementing measures for pharmaceuticals. This year, Mexico did the same for cosmetics and banned imports of products tested on animals worldwide, meaning U.S.-developed products forced to test on animals will lose market access.

New advancements in computer modeling, tissue engineering and other bio-convergence technologies have made the need to test on animals obsolete. Because of this, Senators Cory Booker and Rand Paul recently introduced the bipartisan FDA Modernization Act, which would remove the mandate on animal testing. The legislation would give drug and cosmetic developers the choice on whether or not they want to test on animals.

As noted in the study published by NCBI, animal testing is not an effective measure of whether a drug is dangerous to humans — and drug developers know this. The National Center for Advancing Translational Sciences has found that more than 95% of drugs that pass animal testing fail in human trials for either being ineffective or unsafe.

While many forward-looking pharmaceutical companies realize that animal testing isn't effective, the current law forces them to conduct these inhumane experiments against their will. In fact, to develop one new pharmaceutical or cosmetic product, hundreds of animals need to be tested on and euthanized.

The FDA Modernization Act would allow us to use tools like 3-D bioprinting to fabricate a miniature "organ on a chip" that contains real human cells and functions similarly to an organ in a person's body — and we could test new drugs on that, providing a much more physiologically relevant analysis than if we were to test on a mouse. The same goes for skin care products; cell-culturing methods

have become so advanced that we are now able to [grow human skin](#) in a petri dish to better determine toxicity compared to testing on a live rabbit.

I believe this is a good first step in bringing our pharmaceutical regulation firmly into the 21st century. This bill would not only save billions of animal lives over the years, but it would also enable us to create safer products faster and ensure the United States remains a competitive country in which to develop new drugs and cosmetics.

https://www.genengnews.com/commentary/point-of-view/welcome-alternatives-to-animal-testing/

Welcome Alternatives to Animal Testing

December 3, 2021

By Gary Michelson, MD, and Aysha Akhtar, MD

Gary K. Michelson, MD

With strong bipartisan support, Senate leaders on October 7 introduced the FDA Modernization Act of 2021 to revise a depression-era statute that requires animal testing for new drugs.[1] This follows action by the European Parliament in September to adopt a resolution—by a vote of 667 to 4—to phase out animal testing.

This is great news for public health as it marks a major milestone in transforming the biomedical sciences to embrace testing platforms that are more innovative

and relevant to human health than the animal testing platforms that have been delivering disappointing results for decades.

Aysha Akhtar, MD

The public expects the FDA and pharmaceutical companies to deploy first-rate science to develop and approve treatments for millions of Americans suffering from diseases. But a 1938 federal law is hamstringing drug developers and throwing up roadblocks that drive up costs, delay treatments, leave the afflicted without life-saving therapies, and churn through animals used in testing.

We are in desperate need of a reboot when it comes to drug development.

An outdated approach

Since its enactment in 1938, the Federal Food Drug and Cosmetics Act (FFDCA) has required data for safety and efficacy from animal tests for all new drugs and vaccines. But this 80-year-old statute has not caught up with the science.

Whatever role animal testing may have played in the past, we now know that it is extremely poor in predicting the safety and effectiveness of drugs and vaccines for humans. For example, in 2003, Elan Pharmaceuticals was forced to terminate a Phase II trial when an investigational Alzheimer's vaccine was found to cause brain swelling in humans.[2] No significant adverse effects were detected in genetically modified mice or nonhuman primates.

In another example, in 2006, six volunteers who were injected with an immunomodulatory drug, TGN 1412, suffered severe adverse reactions resulting from a life-threatening cytokine storm that led to catastrophic systemic organ

failure.[3] TGN 1412 had been tested in mice, rabbits, rats, and nonhuman primates with no ill effects.[4]

Recently, the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee concluded that animal models are "problematic" in assessing the safety risks of gene therapies derived from adeno-associated virus (AAV) vectors.[5] There have been severe adverse events in AAV vector clinical trials, including acute liver failure and encephalopathy, in children.[6]

Time and again, drugs and vaccines that proved promising in animal tests failed when tried in humans. At least 172 drugs that showed promise in animals for the treatment of Alzheimer's disease failed in humans,[7] as did 150 drugs tested successfully in animals for inflammatory diseases.[8] More than 114 therapies for stroke tested in animals failed in human trials.[9]

More than 700 human trials of potential HIV/AIDS vaccines have been conducted, all of which gave encouraging results in animals, including monkeys and chimpanzees.[10] Yet not one has worked in humans.

A recent Phase IIb trial of Johnson & Johnson's HIV/AIDS vaccine didn't work,[11] even though animal data had shown high efficacy.[12]

Even worse, we have no idea how many drugs and vaccines that didn't work in animals would have proven to be lifesaving for humans. But we now know that animal tests often fail to model human diseases adequately and can provide highly misleading information.

For example, cyclosporine, a drug widely and successfully used to treat autoimmune disorders and prevent organ transplant rejection, was delayed because of animal tests.[13] How many potential cures were thrown out because of unreliable animal testing?

Overall, 90–95% of drugs found to be safe and effective in animal tests fail during human clinical trials, primarily because of toxicities not predicted by animal tests or because of lack of efficacy.[14]

Taking us in the wrong direction and throwing away possible cures because of misleading animal tests are just some of the problems with our present drug development paradigm. It is also painfully slow and expensive. It takes 10–15 years to develop a new drug, only for most of them to fail. The cost to bring a new

drug to market is $1–6 billion, which is passed on to consumers in the form of higher prices.[15]

New methods

Bioprinted organ models, organ-on-a-chip models, "virtual humans," and artificial intelligence applications have been developed to predict human responses to new drugs more accurately and more quickly. The benefit these methods offer is that they are based on human biology.

Recognizing the need for better models for human diseases, the Biomedical Advanced Research and Development Authority issued awards in September for human vaccine organ-chips[16] and lung-chips[17] for COVID-19 research.

Despite these signs of progress, because of the 1938 law, the FDA continues to operate with a straitjacket, compelling researchers to rely on animal testing, no matter how unreliable, when evaluating new drug submissions.

Fortunately, key Democrats and Republicans have joined together. The FDA Modernization Act would lift the requirement for animal testing and allow the FDA to authorize the best testing methods, whether animal or non-animal, to determine the safety and efficacy of a new drug. This measure will enable greater innovation in medical research and allow for the methods most likely to predict human outcomes.

The use of human biology–based test methods would better predict how humans will respond to drugs and vaccines in clinical trials and speed delivery of medicines to patients. Drug sponsors would have more options for testing the safety and efficacy of drugs, cut time to market in half,[18] and reduce costs as much as fivefold.

A call to action

As physicians, we know that people come to medical professionals desperate for life-saving treatments. During the SARS-CoV-2 crisis, we as a nation realized that a protracted, bureaucratic, and inaccurate drug and vaccine approval process must be revamped. Thus, government and scientists brought urgency to the pandemic response, cut through organizational red tape, and developed successful vaccines in less than a year. We must bring this commitment and innovation to other drug development programs and get cures and treatments to those who desperately need them.

The FDA Modernization Act will free the FDA to allow for the best science to address the diseases that afflict us. This is an essential reform, and the Congress and the Biden administration should pursue it with the same urgency they are bringing to the fight against SARS-CoV-2.

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