Analyzing the Policy Framework of Human-Relevant, Transformative Scientific Innovations

CENTER FOR CONTEMPORARY SCIENCES DISCOVERY FORUM SERIES

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CENTER FOR CONTEMPORARY SCIENCES

SUMMARY

On June 23, 2022, the Center for Contemporary Sciences (CCS) hosted its inaugural Discovery Forum. The event was an opportunity to analyze the policy framework underlying the most transformative scientific innovations of the decade. Emphasis was placed on new inventions enabled by advances in regenerative medicine, biomedical engineering, machine learning, and nanotechnology. This included applications like Organ-on-a-Chip, 3D-Bioprinting, and Micro-Physiological Systems (MPS), all poised to transform the healthcare industry. Numerous ideas for the legislative agenda needed to drive these disruptive technologies forward were examined, alongside the status of existing thresholds and barriers. The feasibility of implementing discerning policies focused on improving the drug development process, reducing the cost of medicine, streamlining biomedical research, and improving safety and toxicity testing was also evaluated. Experts from across the life sciences, biotech, academia, health agencies, and nonprofits participated in the forum. Leading animal welfare organizations also contributed valuable perspectives.

KEY TAKEAWAYS

- There is a growing recognition that animal models have poor predictive value in modeling human diseases. Today, disruptive technologies like Organ-Chip, Bioprinting, Artificial Intelligence, Nanofluidic, and related Micro-physiological Systems (MPS) are poised to shape pharmaceutical drug development, environmental toxicology testing, and biomedical research.
- Despite the significant technological innovations and the emerging application of MPS, large-scale policy efforts that challenge the status quo and have the potential to advance science and medicine, are still met with resistance, remain largely fragmented, and have yielded modest impact to date.
- Key challenges include the absence of serious investments in MPS by the federal government, a reluctance from regulatory agencies to replace animal models with MPS-based designs, an inherent bias for animal data from grantmaking organizations and scientific reviewers, and the lack of international standards for data acquisition, use and harmonization among MPS platforms.
- Forums like this one, that include multidisciplinary experts, are critical to bring fresh perspectives, refine existing ideas, spread much-needed awareness, and help design policies to promote disruptive technologies and their applications.

RECAP

The two-hour Discovery Forum was an opportunity for some of the leading experts in biotech, academia, and nonprofits, to engage in a wide-ranging discussion about current and future scientific technologies that are replacing animal testing and transforming the healthcare industry. Below are key highlights from the Forum. The Forum featured short presentations by speakers and lively discussions among panelists and participation from the audience.

FORUM SPEAKERS

JANE SHEN, PHARM D, PRESIDENT OF BIORG, INC

Dr. Shen discussed the importance of developing more accurate and personalized medicine for patients, noting that it takes 12 years and over $2 billion to develop drugs. Recognizing this dilemma, Dr. Shen, through her current work at BIORG, as well as collaborations with the Wake Forest Institute for Regenerative Medicine (WFIRM) team where she served as the Chief Strategy Officer, is developing and using Tumor-on-Chip models toward improving the treatment of cancer patients. The aim is to leverage innovative technologies and regenerative medicine approaches to provide patients with more accurate and personalized medicine. Dr. Shen's view is that these new technologies can be used not as a replacement, but in conjunction with existing models to facilitate safer, more precise, and more predictive medication for patients. Dr. Shen noted that there is a gap in precision medicine that can be minimized by implementation of these human-relevant technologies.

KATHLEEN CONLEE, VP, ANIMAL RESEARCH AT THE HUMANE SOCIETY OF THE UNITED STATES

Ms. Conlee presented on the importance of advancing science without the consequences of animal suffering. The organization has garnered support from many other high-level animal-focused organizations who support the Humane Society of the United States' (HSUS) initiatives. HSUS has been a leading advocate working to eliminate certain tests and practices commonly performed on animals, and pressing for the development, use, and regulatory acceptance of non-animal test methods. At the forefront of HSUS's work is the advancement of the 3 R's: replacement, reduction, and refinement of certain tests and practices involving animals in research.

HSUS has several campaigns to carry out its mission to reduce animals used in research. The "Be Cruelty Free" campaign focuses on reducing animal use in cosmetic testing. Other campaigns include finding sanctuaries for chimpanzees used in laboratories. The organization has also been a leader in the development of key federal legislation, such as the Humane Cosmetics Act, H.R. 6207/S. 3357, which prohibits animal testing in the evaluation of cosmetic products. This Act has been endorsed by more than 350 individual companies. As noted in Ms. Conlee's presentation, there are currently several other federal laws that impact animal research and testing, and the hope is that each one can contribute positively to the larger goal of advancing science without the use of animals. Although progress has been slow, Ms. Conlee emphasized that HSUS believes in the significance of perseverance and educating the public about the essentiality of shifting to non-animal test models.

PAUL LOCKE, DRPH, MPH, JD, ASSOCIATE PROFESSOR, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

Dr. Locke highlighted the importance of acknowledging the widening gap between the current science underlying disease and animal models used to study them. He suggested looking to innovative human-relevant technologies such as organoids and 3D models to better understand such diseases and to fill this space. Doing so could lead to better served patients and drug development. At the same time, Dr. Locke explained that these new technologies are not there yet.

One route to accelerate this pathway to new technologies is to make policy changes without modifying laws or regulations. One such policy change would be to encourage increased transparency at federal agencies, such as the National Institutes of Health (NIH), regarding how much of the budget is used for new technologies and methodologies and for what

diseases and conditions. For instance, through the appropriations process, it is essential to continue advocating for the NIH to increase funds allocated to new technology development. Current allocations are not sufficient to develop the technologies that will propel society into the future of health and medicine and help bridge the gaps in current research.

It would be beneficial for the grantmaking process to be oriented toward new technologies (via issuing a notice of special interest for new technologies), and to be more rigorous in requiring peer reviewers to assess applications which incorporate the use of such methodologies. With the development of Advanced Research Projects Agency for Health (ARPA-H), the hope is that there will be an increased implementation of, and budget for, advanced research projects to help accelerate and foster groundbreaking technologies, systems, and platforms for health and medicine. However, to be successful, this new agency must strictly adhere to its purpose—to proactively seek out innovations and alternatives to the status quo.

MONICA ENGEBRETSON, HEAD OF PUBLIC AFFAIRS NA AT CRUELTY FREE INTERNATIONAL

Ms. Engebretson emphasized the importance of prioritizing the development and use of non-animal methods and the importance of looking internationally to harmonize regulations and policies globally that support use of innovative test methods. In the United States, Cruelty Free International has been at the forefront of advancing legislation that highlights incentives for the use of non-animal testing methods and provides immediate welfare benefits to animals in research. One piece of legislation is the Hearts Act, H.R.4101. This act would amend the Health Research Extension Act of 1985 by establishing incentives for the use of nonanimal methods, while also requiring investigators to fully evaluate available non-animal methods using standardized guidelines. Additionally, research proposals would be reviewed by at least one person with expertise in non-animal research methods, and these proposal reviewers would have access to a reference librarian with expertise in evaluating the adequacy of the search methods used for alternatives.

However, even though researchers are asked to consider available alternatives, there are no criteria regarding what it means to "consider" alternative methods. In addition, in clarifying what constitutes a "consideration," there should be an incentive to receive additional grant money for research practices which incorporate the use of non-animal methods. Cruelty Free International is already increasing awareness of alternative test methods through their "Making Alternatives a Priority" (MAP) Campaign. The organization is also an avid proponent of the Companion Animal Release from Experiments Act, H.R.5726, otherwise known as the "CARE ACT." This legislation requires facilities that receive funding from the NIH to have adoption policies in place for dogs, cats, or rabbits no longer wanted for research. These

facilities must maintain records on the number of these animals 1) used by the research entity, 2) released for adoption, and 3) destroyed. Both the adoption policy and data on animals used in research must be publicly available on the research facility website. Going forward, the NIH should be clear in stating that an appropriate use for money in grant proposals is for adoptions of these lab animals and those that are surplus.

SEYOUM AYEHUNIE, PHD, CHIEF SCIENTIFIC OFFICER OF MATTEK LIFE SCIENCES

Dr. Ayehunie highlighted the importance of developing and investing in 3D models that can mimic human models. These include "physiologically relevant primary cell-based human 3D tissue models with high reproducibility, greater predictive power, and lower cost," which could simultaneously lead to the replacement or reduction of animal testing. MatTek, a BICO Company and a pioneer in combining technology, such as robotics, artificial intelligence, and 3D bioprinting with biology, has led the creation of 3D cell cultures and bioprinting of human tissues and organs for the medical, pharmaceutical, and cosmetic industries. The applications of MatTek's products are wide-ranging, spanning from organ tissues to models for body systems including ocular, reproductive, respiratory, and intestinal, the skin, and immune cells. Many of the models that have been developed were due to funding received from the NIH Small Business Programs.

Dr. Ayehunie stated that although MatTek's models have been used internationally (i.e., in the European Union), and are widely accepted, validation of these models is complicated and time-consuming. For example, it took almost 11 years for a skin irritation model developed by the group to be validated. This is in part, due to the translational problems that exist between animal and human models. For example, drugs that pass animal models often fail in clinical trials. But using bioengineered tissue models, where one can look at a microenvironment of that of a human, MatTek has seen, at least in toxicity studies, high predictions that such drugs are problematic in human tissues, too, which could give some indication of preclinical phase results. Even with such technological advances, a "gold standard" of tissue models and microphysiological systems must still be developed. As Dr. Ayehunie emphasized, the models must be high throughput, cost effective, and highly predictive of human responses. Lastly, there is a need to develop more complex tissue models. The burden is on us, Dr. Ayehunie argued, to work together to describe how these new and innovative models can address those things that animal models cannot.

AYSHA AKHTAR, MD, MPH, CEO AND CO-FOUNDER OF THE CENTER FOR CONTEMPORARY SCIENCES

Dr. Akhtar highlighted the importance of investing in human-relevant technologies and discussed the education and policy initiatives that CCS has been involved in to help advance

these technologies. For example, CCS has been an avid advocate and lead scientific support of the FDA Modernization Act of 2022. This bill would amend the 1938 Federal Food Drug and Cosmetics Act, which previously required all drugs must be tested on animals, by replacing the word "animal" with "non-clinical." This modification does not take away the option of using animal testing but allows for more innovative testing technology to be used in place of traditional animal testing methods.

The effort to expand the type of testing options a drug developer could use has been a slow process, often with advocates and researchers taking on the issue paper by paper, guidance by guidance. The passage of the Bill in the House (as an inclusion in a larger package of FDA reforms) in May of 2022 is a victory and gives this legislation a better chance of being passed in the Senate later this year. The hope is for this bill to become law. If enacted, the law will help level the playing field by allowing non-animal human-relevant testing methods in the drug development and research space. There is still the need for further validation of non-animal testing methods. With further validation, researchers and pharmaceutical companies may be more confident to use these alternative methods and include them in their applications to the FDA. By doing so, there may be a greater chance these technologies will be accepted by larger entities, which could shift funding. Since research tends to go where the funding goes, shifting these funding mechanisms to create a pathway for investment in these innovative technologies is essential.

Forum Q&A

Below are the key highlights from the Q&A session. Topics have been compiled into thematic groups for brevity.

Investment and Transparency:

Q: How can we shift the funding mechanisms and work together to create some process/pathway to encourage more funding of innovative technologies? Does this shift need to happen internally within the NIH, or can it happen externally through appropriations?

A: All participants are in favor of more funding being directed to MPS. But the issue is having a strategic plan in place before we have the funding. If we do not have a plan about how we are going to use this funding effectively to move things forward, we will miss an opportunity. Although many discussions have taken place about the

different technologies available, we need to continue to work on validation and regulatory acceptance of the models. As Dr. Locke emphasized, the first step in this process is to show that investment in innovative technologies pays off over a 5-10-year period. After gathering data on how human-relevant models will make communities healthier, provide better drugs/medicine, and improve public health, bigger forces, like Congress, can be approached. Overall, we must make the case that shifting the funding to these innovative, human-relevant models would take us to a better place as a society. Additionally, the NIH basic budget for 2022 is $42 billion but the proposed budget for 2023 is $62.5 billion. How much of this money is actually allocated to new technology development to help bridge those gaps in current research? $2 million? $5 million? It is not enough. According to Dr. Locke, the minimum amount needed is $100 million. It is through the appropriations process that we may be able to ramp up the amounts being devoted to the technologies that will lead us into the future.

Q: What is the mechanism for transparency of the NIH? How do we really effect change on the practical level? And is this change incremental or one huge shift?

A: Overall, the NIH tries to do a fair amount in terms of transparency. However, as several expert participants noted, it can be difficult, as a researcher, to access data and get a clear idea of what NIH is doing outside of what is published. As members of the public, and taxpayers, we are invested in how our money is being allocated for research (and deserve to know where the money is going). So as researchers and as members of the public, any of us should be able to know if the NIH is planning to fund new technology, where, how, and for what diseases/health areas. Using appropriations to increase funding is another way to show there is a desire for increased funding for these new technologies. As Dr. Locke mentioned, legislative measures could be passed to require increased transparency of the NIH. And as Dr. Akhtar reiterated, research goes where the funding goes! An increase in visibility for New Approach Methodologies (NAMS) would call for the NIH and FDA to step up and increase resources directed for this type of research.

Quality Control, Validation, and Refinement

Q: We need to prioritize resources and what we develop. Should we condition based on diseases? Or is there another way?

A: Ideally there would be a technology platform that is agnostic and can be applied to all disease conditions. However, as Dr. Shen shared in her presentation, it is beneficial to assess which areas have the most immediate need and application for these new technologies. Look where the diagnoses are time-sensitive and where we cannot afford to waste time experimenting with drugs that may not work. For example, in oncology there is the ability to tissue engineer, use an organoid, take a

tumor from the patient, and be able to provide personalized answers and medication. CCS indicated that some applications of MPS and complex in vitro systems are farther along than others (e.g., predictive toxicology). Significant and credible work is being done there, so strengthening those 'beachheads' based on a prioritization scheme is a feasible approach.

Q: What about validation? What should we be doing to improve the validation process? Are there fixes we can focus on now, so it is still scientifically rigorous, but it is faster and less expensive?

A: As Dr. Shen reiterated, the Covid-19 pandemic forced us to do things we normally would not do, and we are ok. We did not have to go through 12 years, $2 billion dollars for clinical trials. She also posited, if we invested more money up front, there is a possibility of cutting this timeframe down to 6 years. We need safer, more accurate drugs up front, even pre-clinical, before you go into humans. To this point, Dr. Ayehunie noted that the preclinical phase as it is now 4-6 years. If this can be reduced by even 5-10%, there is a reduction of $100 million from pharma, which is a great advantage. Although some agencies and businesses cite that the cost of using a non-animal method is a burden, it is the case that human trials are extremely expensive. As Dr. Ayehunie emphasized, even though there has been great progress in technological advancements, we are still trying to obtain a "gold standard" of tissue models and microphysiological systems. And these models must have high throughput, be cost effective, and highly predictive of human responses, which is challenging to do. However, as CCS pointed out regarding the issue of standardization, the NIH, and federal agencies as well as the private sector have tools, centers, and mechanisms to spark innovation on a larger scale. Expertise exists to develop common data elements or language for these emerging systems, and we started seeing much-needed efforts on that front.

Reviewer Bias

Q: Is there is a process to educate institutional review boards (IRB), granting agencies, scientific reviewers, and the research community in general and reduce the bias towards animal experimentation? How can one change the erroneous notion that because a given drug was successful in the animal testing stage, it would have a better chance in being successful in the therapeutic phase in humans?

A: Dr. Shen noted that the FDA uses very firm language which requires two animal studies prior to advancing to clinical trials. And those physicians and researchers have been trained to look for animal models. This is a narrative of the NIH, and most grants given by regulatory bodies are looking for traditional animal models. Dr. Shen also emphasized that prior to even getting to the level of an IRB of a health system o

review for a patient taking investigational products, we must educate our regulators of the emerging new technologies that could supplement/augment animal models. As several experts expressed, while there is a desire to be innovative. But when it comes down to applying for regulatory submissions/applications, everyone goes back to what is known and what has been traditionally relied upon in terms of research models. There is an assumption that if a company submits something unknown, it is a pain point and will not be considered. We need to change this narrative.

Q: The healthcare industry has largely been removed from this conversation. Does anyone have thoughts on how we can bring them into these conversations?

A: One persuasive hook might be for economic reasons such as emphasizing the frequent costs from side effects/adverse effects from medications. Dr. Shen suggested another way to involve the healthcare industry in the conversation is by utilizing payer groups. These groups, like Blue Cross and Aetna , are those that are leading or governing insurance policies and have authority in determining decision triaging protocol for healthcare providers and systems. The incentive that these new technologies could provide less costly and more personalized treatment options for patients, and therefore less hospitalizations and less complications, would be a convincing angle for these groups. CCS noted that recent studies using Organ-Chips technologies are making strong arguments for productivity gains in the billions if these technologies are included in the R&D process at the preclinical stages.

On The Wishlist

Q: In the ideal world, how would things be different?

A: Every drug company should incorporate or otherwise be required to add a new alternative technology to their research and development process. All experts agreed that we must normalize alternative methods, even if that means that animal data is still submitted. But in addition to a traditional submission, researchers and biotech or pharmaceutical companies would be required to be innovative and submit something alternative. There must be a record included showing that an alternative test method was used as well and that there was an effort made to incorporate a New Approach Methodology (NAMS). Make it a requirement every biotech and pharmaceutical company, in addition to the traditional submission, are required to be innovative and submit something alternative. Dr. Shen also shared that she has already been part of round tables with pharmaceutical companies that head innovation of these new technologies. Ms. Conlee also added the advantage of taking a state-by-state approach. Unless listed as a federal requirement, a state, like California, could preclude the use of certain animals in research (in California, dogs had been used for toxicity testing).

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