Beyond Animal Experimentation – A Proposal for the *Model Human* Initiative

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Executive Summary: Non-human animals ('animals') have served as a long-standing model for biomedical research in the United States. Though used in studies that are both basic and applied in nature, animal experimentation as a whole is justified as a means toward informing human health (Akhtar 2015). However, despite the pervasive use of animals in research today – ~500 million predicted in the US (Ferdowsian and Gluck 2015) – mounting evidence demonstrates the lack of predictive utility of animal models for human disease, therapeutic response, and toxicity. Above all, approximately 90% of compounds entering clinical trials following successful animal-based studies fail to produce the equivalent response in a human population (Hay et al. 2014; Garner et al. 2017; van der Worp et al. 2010). Though there are a number of factors that contribute to this high failure rate, our increased understanding of the effects of human-to-human variation (*i.e.* intra-species variation) on therapeutic response – underscoring the field of precision medicine – suggests that unavoidable interspecies variation fundamental to animal models will prove an even greater obstacle toward medical progress in the modern era. Herein, I call on the National Institutes of Health (NIH) to expand upon its efforts to improve the translatability of pre-clinical research through the establishment of the *Model Human* initiative, which, through the recognition of the limitation of animal experimentation to understand human biology, promotes the development of innovative technologies to supplant animal models, as well as fosters the growth of university infrastructure to couple advanced epidemiological human data to the discovery of biological mechanism and therapeutic intervention.

I. The failure of animal models

Animal experimentation has been conducted in some form or another for thousands of years; but, our modern conception of animals as models of human biology can be attributed to 19th century physiologist Claude Bernard who presumed that "experiments on animals are entirely conclusive for the toxicology and hygiene of man (Hajar 2011)." Of course, it cannot be denied that animal experimentation has led to insights beneficial to biomedical progress: past experimentation focused on understanding gross anatomy and function has been largely translatable between species, and more recent studies have revealed fundamental principles of biological systems that serve to incite biomedical advances. However, the utility of these models has not kept pace with our understanding of, and approach toward, human disease at the cellular and molecular level. This is evidenced primarily by the extraordinarily high rate of failure (~90%) (Hay et al. 2014; Garner et al. 2017; van der Worp et al. 2010) of therapeutics in clinical trials, which had previously succeeded in pre-clinical animal studies. Of course, this failure rate severely hinders our efforts to improve societal health: not only is the time to discovery of a beneficial compound prolonged, but these failures account for 73% of the cost of bringing a drug to market (Garner 2014). It is important to note here that the total failure rate is likely much higher than reported because the statistics can only account for those compounds that succeeded in animal studies and subsequently failed

in human patients. It fails to account for the missed opportunities of compounds unsuccessful in animals that would have been successful in humans, of which there is anecdotal evidence (Akhtar 2015).

Systematic meta-analyses of the congruence of animal studies with clinical results underscore the dismal predictive utility of animal models evident in the high failure rate of clinical trials; but, they also better flesh out the shortcomings of pre-clinical studies in terms of weaknesses in experimental protocol and weaknesses intrinsic to animal models (van der Worp et al. 2010; Perel et al. 2007; Pound, Ebrahim, and Sandercock 2004; Pandora Pound 2014; Roberts et al. 2002). Certainly, methodological failings – improper randomization, small sample size, unintended bias, over interpretation, and publication bias toward positive results – contribute to the failure of clinical trials and need to be addressed (van der Worp et al. 2010; Garner et al. 2017; Garner 2014). However, even given ideal experimental conditions, a lack of generalizability of results in animals to human patients occur due to existing disparities between species (van der Worp et al. 2010). This latter point becomes particularly pertinent with the growing recognition of the impact of intra-species differences on disease pathology and treatment, serving as the impetus for our investment in precision medicine (National Research Council 2011).

II. The age of precision medicine

Precision medicine – the customization of healthcare practices/products for individual patients – stems from the finding that both the pathology of a disease and the response to treatment can vary from person to person. These intra-species differences emerge due to the fact that biological beings are complex systems of hierarchical, but interacting, parts: small differences in any one of these parts can result in large changes in the system as a whole (R. Greek, Menache, and Rice 2012). Precision medicine, in theory, should account for the influences of biological differences – genomic and epigenomic – as well as environmental factors (All of Us, National Institutes of Health). The current All of Us research program initiated by the NIH exemplifies this philosophy in its pursuit to collect data from more than one million individuals to understand the contribution of environment, lifestyle, and biology on health and disease. Given the magnitude of effect of intra-species differences, it is not unexpected that animal models, with much greater differences that span species, are poor predictors of human disease biology. In fact, interspecies differences in necessary pharmacokinetic pathways have been noted (R. Greek, Menache, and Rice 2012).

What's more, studies conducted on relatively homogenous populations of animals lacking environmental and life history variation cannot properly model the highly heterogeneous human population, or even populations of their wild counterparts (Abolins et al. 2017). With this in mind, epidemiological insight gained from research programs like that of *All of Us,* is indispensable for understanding human health and disease. When coupled with advances in biomedical research to add mechanistic understanding, we can better translate these findings into preventative and/or therapeutic measures. This requires moving beyond animal models toward a means of biological discovery with greater relevance to the human population.

III. The *Model Human* Initiative

The NIH has worked to address the failure of animal models to predict human drug response and disease biology and has made progress toward developing animal alternatives through funding efforts, collaborative initiatives, and organizational changes. Most notable among these efforts is the creation of a new institute, The National Center for Advancing Translational Sciences (NCATS), to address the bottlenecks obstructing the translation of preclinical studies to human therapeutics (Collins 2011). Among the many goals of the institute is the development of toxicity and efficacy models that surpass animal models in their predictive capabilities. While the actions of the NIH thus far are a sure sign of progress, they only go so far as to implement change at the translational end of biomedical research, leaving intact the remainder of our system (most notably basic research), which still largely regards animal experimentation as a necessary prerequisite to biomedical advances. In contrast, the *Model Human* Initiative will span institutes and stages of research – from basic discovery to clinical application – to form a new biomedical research landscape shaped by the awareness that human (disease) biology is best understood with human-based models. As such, the central goal of the initiative is to phase out the use of

animal models at all stages of research in favor of human-based models that are more informative of human biology and predictive of outcome in clinical trials.

i. Implementation

Importantly, the *Model Human* Initiative proceeds from an understanding of the contribution of animal experimentation to biomedical progress; it thus does not call for a complete and immediate elimination of all animal experimentation. Rather, the initiative aims to couple the knowledge gained from precision medicine to advances in basic biomedical discovery to create human-based models that (1) greatly reduce animal experimentation and (2) result in a scientific enterprise better equipped to confront human disease.

Preliminary phases of the initiative will focus on tool development and university infrastructure so that data derived from precision medicine research programs can be effectively implemented in biomedical discovery. To this end, the initiative will provide granting mechanisms at the level of the university, as well as individual labs and small businesses. Funding at the university level will be used to generate core research centers and collaborative efforts that focus on building university capabilities to translate correlative human epidemiological data to causative biological mechanism. Funding at the lab level will invest in techniques aimed toward non-animal models for basic biological discovery. This includes, but is not limited to, genome and epigenome engineering, advanced culture systems, organoid development and tissue engineering, and *in silico* modeling of complex biological systems. Though challenges toward developing these new techniques exist (*e.g.* recapitulating complex immune function *in vitro*), it should not be forgotten that we are currently up against obstacles and limitations inherent to animal experimentation. Each of these techniques, thus, holds the potential to uncover health-relevant biological mechanisms that could not otherwise have been revealed via animal experimentation.

While these avenues of research currently receive some NIH support, the *Model Human* Initiative will greatly expand upon these efforts with increased investment in projects that develop, validate, and/or utilize these novel techniques. In addition, systematic analyses of the biological relevance of animal models and/or their alternatives to human health and disease will be funded. Via the increased investment in animal alternatives, the *Model Human* Initiative importantly sets, for the first time, an NIH-wide goal to supplant animal experimentation with novel techniques that can better represent human biology. This shift in perspective holds the power to reshape future research priorities at the level of the university and lab; but, even more importantly, the symbolic nature of this new NIH goal coupled with the outcomes produced by initial investments of the initiative will help garner the confidence in animal alternatives necessary to change standards used by publications to judge the quality of research and by regulatory bodies for approval of therapeutics for public use – each of which represents a powerful component of the scientific enterprise that reinforces the use of animals in biomedical research.

ii. Stakeholder analysis

The *Model Human* Initiative seeks an additional ~100M/year of investment over the next 10 years for the preliminary phases, on par with other recent NIH initiatives (National Institutes of Health, Underwood). Once completed, additional funding, as well as the diversion of funds from animal experimentation, to these new model systems is anticipated. During the preliminary phases, though, no diversion of funds is expected. Thus, universities and labs only serve to benefit from additional funding. Similarly, current policies enforced by government regulatory bodies, as well as the business practices of independent entities that breed and supply research animals will not be immediately affected; however, as new model systems take hold, the practices of each of these stakeholders will likely shift in line with the changing research culture. Finally, in any discussion of public health, the primary stakeholders are the citizens. Given the current failure of animal models to produce effective treatments, it is an imperative of the research community to work toward better alternatives, which is the ultimate goal of the *Model Human* Initiative.

III. Conclusion—the US as a scientific and moral leader

The scientific enterprise is distinguished by two key qualities: (1) a focus on evidence-based decision making, and (2) a forward-looking vision that

emphasizes the role of scientific innovation to drive human progress. The continued reliance on animal experimentation to combat human disease, however, does not fully embrace these qualities. In fact, future investment into animal experimentation, without the goals outlined in the *Model Human* Initiative as an impetus, could serve to divert funds from more novel and effective means of addressing human health problems. Of tremendous importance to scientific progress is the tenet that past necessity does not predict future necessity. Thus, without disregarding the role animal experimentation has played in biomedical progress up to this point, we can envision a future research program composed of systems and techniques that far surpass the utility of animals.

Though this memorandum focuses on the scientific rationale for moving beyond animal-based studies for the benefit of human health – an argument that holds sufficient weight to spur change – it should not go unwritten that the question of animal experimentation is not solely scientific in nature. In addition to the growing awareness of the scientific community to the futility of animals as models of human disease, is a growing recognition of animal sentience and, in particular, the capacity of animals to suffer, both in response to physical pain, as well as stress derived from housing, handling, and other routine practices (Lahvis 2017; Sorge et al. 2014; Akhtar 2015; Sneddon et al. 2014; DeGrazia 2014). Thus, in addition to the scientific imperative outlined throughout, there exists a moral imperative to work toward a scientific enterprise that eliminates animal experimentation (R. Greek and Greek 2010). Already, in 2010, the EU commission released a directive recognizing the "intrinsic value" of animals, and calling for a "final goal of full replacement of procedures on live animals … as soon as it is scientifically possible to do so (Office 2010)."

In the US, as throughout the world, the animal experimentation debate has been fraught with extremist views. Though this is most often attributed to animal protectionists, an opposing and unwavering stance is often taken by scientists and science supporters (Matthews 2008). This leads to the impression that the removal of animals from biomedical research would not only obstruct medical progress, but also science itself. The *Model Human* Initiative quashes this debate, regarding the elimination of animal-based studies as a mark of scientific progress. Emphasizing the leadership role of the NIH to establish goals that guide the future of science both within the US and abroad, the *Model Human* Initiative upholds the US as both a scientific and moral leader.

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