IPC

STEM Friday 1

Animal Based Studies & Precision Medicine

Write 1 page discussing the ethical issues behind animal testing. Be sure to cite and refute or approve of quotes from the article. You must cite at least 2 quotes in order to receive full credit.

Make sure your handwriting is neat and legible! I cannot give you a grade if I can't read your writing!

Ideas

- **Are animal studies harmful to the animals**
- **Is it worth it to hurt animals if it helps humans**
- **Should animal studies be banned if they harm animals even if they help humans**
- **If animal studies are banned what would happen before human trials**

Chemistry

STEM Friday 1

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Ideas

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PRECISION MEDICINE

Animal-based studies will be essential for precision medicine

K. C. Kent Lloyd is a professor at the Department of Surgery, School of Medicine, and the Director of the Mouse Biology Program, University of California, Davis, 2795 Second Street, Suite 400, Davis, CA 95618, USA. Email: kclloyd@ucdavis.edu

Peter N. Robinson is a professor at Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany, and The Jackson Laboratory for Genomic Medicine, 10 Discovery Drive, Farmington, CT 06032, USA. Email: peter.robinson@jax.org

Calum A. MacRae is the Chief of cardiovascular medicine at Brigham and Women's Hospital and an associate professor of medicine at Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA. Email: camacrae@bics.bwh.harvard.edu

CREDITS: CHAERIN YOON (K.C.K.L.), TOMASZ ZEMOJTEL (P.N.R.), SUSAN R. SYMONDS (C.A.M.)

AT AN INSPIRING WHITE HOUSE CEREMONY ON 25 FEBRUARY 2016, PRESIDENT OBAMA celebrated the 1-year anniversary of the launch of the Precision Medicine Initiative (PMI), which promises to usher in a transformation of medical practice. A collaborative effort between government, academia, and industry, directed and led by the National Institutes of Health (NIH), the PMI envisages invoking an individual's molecular profile and other phenotypic descriptors combined with environmental exposures and lifestyle behaviors to guide therapies more targeted and cost-effective than current "one-size-fits-all" strategies. The extent to which massive amounts of genomic and other data can expose statistically relevant and clinically actionable results will be tested in a planned >1 million-person cohort. Although we very much support this audacious plan, it is important to note that no matter how large a cohort, statistical power will never be sufficient to address by data analysis alone every observation that emerges or to drive to mechanism each human finding. In this context, the PMI will benefit greatly from integrative informatics and innovative animal-based research and validation studies that leverage existing networks of biological knowledge to create a new taxonomy of disease and to accelerate the successful incorporation of precision medicine into mainstream clinical practice.

Francis Collins, the NIH Director, and his team have made tremendous progress in planning and preparing for the implementation of PMI during the last year since the official announcement of the vision for the PMI Cohort Program (www.nih.gov/news/health/sep2015/od-17.htm). This vision was informed by numerous public workshops of the PMI Working Group (completed September 2015) to resolve the challenges to building and launching a cohort with $130 million in funding opportunities awarded this year (www.nih.gov/precision-medicine-initiative-cohort-program/program-components). As part of these discussions, numerous elements, including genomics, electronic health records, participant-provided data, sensors, and mobile health technologies, have been proposed as essential to generate the data required to drive precision medicine. However, the critical role of experimental studies in genetic model organisms, for which there are enormous extant data sets that continue to accrue, has not been fully considered, especially in four areas that are key to the successful deployment of the PMI.

Gene variant interpretation. We are able to provide a confident interpretation of the clinical relevance for only a vanishingly small proportion of variants in human populations. Preclinical and coclinical studies using animal models strategically designed to reflect the genomic variation observed in cohort participants will be necessary to define downstream functional consequences and discriminate causal from correlative factors at relevant efficiency. New genome-editing technologies [for example, CRISPR (clustered regularly interspaced short palindromic repeats)] now enable the efficient derivation of precision disease models incorporating patient-specific genetic variants as a means of recapitulating essential aspects of human disease in zebrafish, mouse, rats, pigs, and other organisms. Indeed, the study of patient-derived avatars to define disease pathogenicity will fine-tune the diagnostic precision inherent in the PMI and accelerate the discovery of new therapeutic targets. The NIH can capitalize on recent technological advances in animal modeling by completing current efforts to functionally annotate key model organism genomes, such as the Knockout Mouse Project, which is part of the International Mouse Phenotyping Consortium (www.mousephenotype.org), and by expanding the nascent Pilot Center program in Precision Disease Modeling (http://grants.nih.gov/grants/guide/pa-files/PAR-14-280.html). Ultimately, disease penetrance, pleiotropy, and even higher-order gene-gene interactions will be accessible in such systems. Further, a commitment to the comprehensive investigation of variants found in traditionally underserved populations would contribute to inclusivity by clarifying the roles of variants that are rare or absent in majority ethnicities.

Incorporating "-omic" data. Effectively linking the unprecedented amounts of genomic, metabolomic, and other -omic data with environmental, behavioral, and lifestyle information

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to identify potentially actionable results will be a distinguishing mark of the PMI's effectiveness. Current and ongoing genome-wide animal studies that have successfully accomplished this linkage (*1*) can serve as models for the PMI to use in the harmonization of data acquisition and handling protocols, standardization of statistical and curation strategies, identification and integration of critical metadata, and facilitation of public data access. Integrative computational analysis of genomes from multiple species can be used to inform the interpretation of human exome or genome data (*2*). Model organisms offer the opportunity to perform system-level investigations of the effects of genetic variants, environmental exposures, or candidate therapeutic strategies on physiological and pathophysiological -omics networks in multiple tissues in a way that would be impossible in human studies.

Environmental exposures. The environment influences human health in myriad, poorly understood ways. Humans are exposed to tens of thousands of environmental agents across their life span. Although the effects of certain factors, such as persistent pollutant exposure, ionizing radiation, and smoking, are relatively well understood, the biomedical community is just beginning to grapple with the question of how to relate the totality of environmental exposures of an individual with corresponding health outcomes. The PMI plans to collect a wide variety of high-level environmental information, such as air quality, geographic location, seasonal events, and other individual-associated data, as a means of revealing heretofore unrecognized interactions between genes and the environment that are linked to human health. Animal models have long been used to investigate environmental exposures ranging from radiation, cigarette smoke, to dietary emulsifiers and are likely to remain an essential resource for the clarification of the role of environmental influences in the development of disease. In addition, some model organisms offer investigation on a scale that enables empiric testing of large numbers of potential gene-environment interactions, including formal phenotype-driven drug discovery (*3*). Coincidentally, animals themselves are another major source of environmental exposure data not yet considered but highly relevant to the PMI. The PMI will offer an unprecedented amount of exposure data that is almost certain to lead to the identification of numerous potentially actionable correlations between specific environmental exposures and health outcomes. Animal models will be needed to provide quick and accurate assessment of the scientific validity of such gene-environment correlations.

Integrative in vivo modeling. With study sizes quickly expanding to more than 1 million in the PMI, a necessary ingredient for the in vivo modeling that will maximize the pace and value of translational research will be the expansion of the phenotypic repertoire in humans and model organisms. Without more granular phenotypes, it will be difficult to deconvolute the complexity of the human genome in health or disease. New phenotypes, moving from human to model or vice versa, will generate resources that enable information from model organism studies to be integrated with data from human medicine to generate biological insights of clinical importance. Incorporating computational reasoning and semantic mapping efforts to enable phenotype comparisons between species, such as those implemented by the Monarch Initiative, will bridge and narrow the current knowledge gap and maximize the potential of cohort data (*4*). Computational cross-species phenotype mapping has been successfully used to empower the identification of genes associated with rare Mendelian diseases (*5*), and future efforts will be needed to develop comparable resources for all disease entities. New computable bedside phenotypes, cross-species by intent, would facilitate the prospective integration of a wealth of extant and emerging data from animal models, while also aligning discovery genetics, translation, and care redesign. Indeed, to unveil connections between human and animal health, the PMI provides a unique opportunity for synergistic interactions between the medical and veterinary professions, working together to advance understanding in health and disease that benefits all species.

As an example of the utility of animal models for identifying targets for precision therapies, we look to studies in rare disorders, such as fibrodysplasia ossificans progressiva (FOP), a disease characterized by soft tissue ossification leading to respiratory failure. The FOP diagnosis was based initially on clinical symptoms alone until the discovery of a causative mutation in the gene encoding the type I activin A receptor (ACVR1) in all affected patients. Mouse models established activation of ACVR1 and recurrent mechanical stimuli as the mechanism for ossification, and drug screening in zebrafish led to preclinical testing of novel pathway modifiers and the emergence of promising therapeutic targets (*6*) successfully tested

in mice (*7*). Combining mechanistic insights with therapeutic discovery in model organisms will be critical to fully realizing the potential for PMI, where defining the pathogenicity of genomic data and cost-effective discovery of precision therapies require paradigm shifts.

Precision medicine is transitioning from traditional and next-generation approaches to clinical practice. Although overcoming barriers to health disparities and access to care remain and should not be overlooked (*8*), enthusiasm is palpable for the promise of PMI as the foundation for a new research paradigm that builds a comprehensive scientific knowledge base for precision medicine that is fully integrated with clinical care. With recent announcements of the first NIH awards to establish the infrastructure and to launch processes for enrolling and capturing data on more than 1 million persons, now is the time for creative approaches to maximize the long-term impact of the PMI, leveraging previous investments in organismal biology and genomics while setting precision medicine off on a successful trajectory from its inception. The impact of the PMI will be greatly accelerated if we systematically integrate model organisms from the outset, developing computational and experimental frameworks for the efficient validation at scale of potentially actionable findings from the PMI.

–K. C. Kent Lloyd, Peter N. Robinson and Calum A. MacRae

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