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Response to Request for Information: FY 2021-2025 Strategic Plan for the Office of Research Infrastructure Programs: Division of Comparative Medicine and Division of Construction and Instruments Programs

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The Genetics Society of America (GSA) represents more than 5,500 researchers who use genetics to understand fundamental biological processes. The research progress of a large majority of our members depends on resources supported by the Office of Research Infrastructure Programs (ORIP). Given the critical nature of these tools, we wish to emphasize the particular importance of maintaining this support for existing model organism resources and making new investments that accelerate the pace at which insights from model organisms can impact human health and medicine.

Model organism research has contributed major advances to our understanding of human biology, health, and disease

NIH has historically made strategic investments in model organisms that provide significant advantages for discovery in biomedicine. These include yeast, *Tetrahymena*, *Caenorhabditis elegans*, fruit flies, *Xenopus*, zebrafish, and mouse, among others. These investments have paid off in major advances in our fundamental understanding of living systems, health, and disease, as well as technological tools to further advance

biomedical research.

One measure of that success is that an overwhelming majority of Nobel Prizes in Physiology or Medicine in the past 30 years have been awarded for discoveries that relied substantially on work carried out in model organisms. Among many examples of such Nobel-winning contributions are the discovery of telomeres and telomerase in *Tetrahymena,* the demonstration of nuclear reprogramming in *Xenopus*, the discovery of RNAi in *C. elegans,* the discovery of the molecular mechanisms of autophagy in yeast, the discovery of the molecular mechanisms of circadian rhythm in *Drosophila,* the development of cancer immunotherapy in mouse, and many more.

The successes of model organisms underscore how basic science has repeatedly led to medical advances. For example, many highly medically significant genes, pathways, and processes were first identified or fully characterized in model organisms, typically based on studies that explored a fundamental question in biology—not a specific clinical problem. These include the Wnt, Hedgehog, BMP/TGFβ, and Toll signaling pathways, cell division cycle regulators, the SWI/SNF complex, the autophagy pathway, secretory pathway, programmed cell death, telomerase, histone acetylases, self-splicing RNA, microRNA, RNAi, DNA damage response pathways, and countless others.

Model organisms have been particularly vital for revealing the function of human genes. For example, mouse research has helped identify genes with pleiotropic properties, genes essential for embryo development, and genes with sexually dimorphic functional characteristics. This work is further enabled by new methods for genome editing and in vivo functional analysis of gene function.

In addition to their importance to basic science discovery, model organisms are poised to make unique and powerful contributions to the treatment and understanding of genetic diseases, particularly the identification of causative mutations and pathogenic mechanisms. Now that advances in sequencing technology are providing a flood of new disease-associated variants, many efforts around the world are engaged in using model organism-based pipelines to test the functional impacts of candidate variants and assist physicians working on diagnosis and treatment[1]. Additional medical applications are being generated from comparative studies of model organisms with disease-related organisms. Examples include studies of mosquito biology as an extension of work in *Drosophila*[2,3] and parasitic worm biology as an extension of work in *C. elegans*[4].

In addition, the long history of high-throughput phenotyping and screens in model organisms are now proving useful for in vivo drug screens[5]. Researchers are also developing methods for using model organisms to select optimal therapies tailored to individual patients[6].

Model organism research advances have been fueled by sustained support for community resources

As well as their inherent biological and methodological benefits, those models in which NIH has focused investment continue to be essential in no small part because of the enormous foundations of useful knowledge and reagents that have accumulated over decades.

These successes have hinged on community cooperation and the widespread sharing of reagents and data. Crucially, many thousands of strains and reagents are maintained and distributed by ORIP-funded repositories like the Bloomington *Drosophila* Stock Center, National *Xenopus* Resource, Zebrafish International Resource Center, the *Tetrahymena* Stock Center, the Mutant Mouse Resource and Research Centers, the Rodent Research and Resource Center, the *Caenorhabditis* Genetics Center, and several others.

Such resources have propelled the rapid progress of model organism research. Centralized resources not only provide obvious efficiencies of scale and allow coordination across distributed labs, but they also encourage transparency, standardization, and replication. Because of their adoption of best practices, including standardized protocols and procedures, these resources are essential to fulfilling the NIH mission of promoting rigor and reproducibility in research.

Stock centers also lower the barrier of entry for researchers and educators new to a particular system. NIH support for stock centers keeps model organisms accessible to the widest range of researchers, including those in underrepresented or underserved communities. They also serve as important hubs of expertise.

Overall, consistent support for centralized stock centers and other resources has increased the efficiency, speed, and reliability of the field and maximized NIH's return on investment.

GSA recognizes that new investments will be needed as technical advances like CRISPR

gene editing stimulate more widespread use of additional organisms and new analytical approaches. Examples include the growing mosquito research community and the development of an encyclopedia of gene function in the mouse research community. GSA supports new strategic investments and emphasizes that these should not come at the expense of existing critical resources. We also note that well-established models remain essential for cost-effective development of tools that can then be applied to emerging models. Any loss of support for established model organism stock centers in particular would be devastating to ongoing and future progress not only in understanding basic biology but also in accelerating advances in genomic and precision medicine.

Return on investment in stock centers depends on consistent funding for databases

The data generated by the major model organism communities are systematically curated and made freely available through databases such as the *Saccharomyces* Genome Database, WormBase, FlyBase, Xenbase, ZFIN, Tetrahymena genome database (TGD), and Mouse Genome Informatics. These databases function side-by-side with the corresponding resource centers, providing the biological information and organization essential to ensuring efficient use of maintained stocks and reagents.

GSA notes that NIH and other funding for these databases has decreased and become less certain in recent years. GSA supports the goal of increasing integration of the model organism databases via the Alliance of Genome Resources. However, if overall support for these critical resources drops, further progress of the field will suffer, as will the research return on investment in stock centers. Note that in considering the role of new informatics resources to integrate data, ORIP should recognize that success in this area would depend on the stability, reliability, accessibility, and richness of existing databases.

Increased collaboration between research communities and cross-model validation can help improve the rigor and reproducibility of animal models of human health and disease

In cases where model organisms are used to make clinical predictions, such as in drug screens and genetic variant testing, tests of the validity of the disease model in question

may be needed. Cross-model validation of predictions is a particularly useful tool for establishing the generalizability of conclusions. Indeed, using multiple in vivo models to probe different aspects of a clinical question is becoming increasingly common. This takes maximal advantage of the fact that different models have complementary strengths and tools.

As a "hub" organization, GSA has long recognized the importance of bringing together communities that work with different model systems to share insights and multiply the impact of their research. We encourage ORIP to invest in resources that make it easier for researchers to work with multiple models, understand and use data from other systems, and collaborate across research communities. These investments from ORIP can and do have multiplicative effects.

Thank you for the opportunity to submit comments for this strategic plan. ORIP's support has been a key contributor to the success of model organism research and no doubt its future investments will continue to advance human health and medicine.

Submitted by the Genetics Society of America President Denise J. Montell

Additional community statements

C. elegans

The *C. elegans* research community – over 1400 laboratories across the globe, half of which are in the US – continues to contribute to technology and biology with lasting impact on human disease, as recognized by multiple Nobel and Lasker awards. The *C. elegans* genome project was the first for a multicellular organism, and it served as the forerunner of the human genome project. *C. elegans* developmental anatomy is defined at single cell resolution, and it is now complemented by a molecular atlas made possible by advances in single cell RNA-sequencing, again a first for a multicellular organism. The development of tools for dissemination and systems-level functional analysis have accompanied these technological milestones. Fluorescently tagged protein technology, a mainstay of modern cell biology, was pioneered in the worm.

Biological contributions include numerous discoveries of conserved molecular and

cellular mechanisms such as microRNAs and RNAi, cell death, cell polarity, and signal transduction pathways. *C. elegans* researchers continue to contribute to these and many additional broad areas such as neurobiology, behavior, aging, pathogenesis, immunity, evolution, as well as cellular, tissue and organ systems. These studies define organismal, cellular and molecular mechanisms important for understanding human disease, since identical or analogous mechanisms occur in higher organisms.

Two newer initiatives have direct human disease relevance: human disease genetics, human parasites. The worm is beginning to serve as a powerful source of phenolog-based analysis of human disease variants. This field has emerged thanks to the convergence of increasingly accurate identification of human disease-causing genetic variants with the ease of *C. elegans* genome editing, the high degree of gene conservation between humans and worm, and the rich history and relative ease of phenotypic analyses. Facile screens using classic unbiased genetic approaches, RNAi, or chemicals can be brought to bear on pathways within which human disease genes function to identify and advance new therapeutic avenues. The *C. elegans* community is also contributing to the investigation of evolutionarily related nematode parasites, with genome and other information now accessible within WormBase, the main *C. elegans* database. Both of these initiatives will require expanded resources.

The past and future success of these contributions to human disease from the *C. elegans* community would not be possible without community resources and the abiding spirit of data sharing that they reflect. These include many extant resources including the stock center and main genetics database WormBase, as well as future resources, such as omics data tools, comprehensive databases for human gene function in *C. elegans*, comparative anatomical resources for parasites, and the development of tools, reporters and platforms for high-throughput screening.

Contributed by E. Jane Hubbard, Acting President of the International C. elegans *Board.*

Ciliates

Ciliated protozoa have a rich history and future for making transformative biological discoveries. By the late 1930s Tracy Sonneborn developed advanced Paramecium genetics to dissect the relationship between the cytoplasm and nucleus (cytoplasmic inheritance). Discoveries made in his laboratory have been further studied to uncover

mechanisms underlying epigenetic regulation, programmed DNA rearrangements, endosymbiosis, and biological self-assembly. Over 80 years later, the phenomena described motivate new scientists to make dramatic advances. Through the application of biochemical and molecular approaches, three investigators who started their research by using *Tetrahymena* were awarded the Nobel Prize for their foundational discoveries: Tom Cech in 1989 (Chemistry) for the discovery of self-splicing RNA from *Tetrahymena* and Elizabeth Blackburn and Carol Greider in 2009 (Physiology or Medicine) for their work on telomeres and telomerase, both of which were first discovered in *Tetrahymena*. More recently, David Allis was awarded the Breakthrough Prize in Life Sciences in 2015, and the Albert Lasker award in 2018, for the discovery of covalent modifications to histone proteins and their critical role in disease, work that he began by using *Tetrahymena*. Characteristics of ciliated protozoa have catalyzed new thinking and innovative research approaches to create unique opportunities to gain mechanistic insight into fundamental and important biological questions. Recent examples of novel insights include the role of the Piwi protein and non-coding RNAs in the epigenetic regulation of programmed chromosome rearrangements to control transposable elements, the function of post-translational tubulin modification in cytoskeletal function, the importance of whole genome duplications in genome evolution, the structure of ribosomes and telomerase, and the coordination of cell signaling pathways in cell patterning and morphogenesis. These broad discoveries highlight future directions for ciliate research, and many more that are yet to be identified.

The transformative discoveries highlighted above were often first reported at Ciliate Molecular Biology Conferences. Communication and collaboration across the community are vital to the coordinated advancement of ciliate and general biological research. The community of ciliate researchers is dispersed throughout the world. The Ciliate Listserv email group resulted from the need for improved communication and has been used to advertise meetings and important community developments. Moreover, the creation of a community-elected advisory committee in 2011, *Tetrahymena* Research Advisory Committee (TetRA), has focused on the development and support of community-based research initiatives and infrastructure. Previous Ciliate meetings have catalyzed community efforts to sequence *Tetrahymena* and *Paramecium* genomes, generate whole genome microarray gene expression data, and spur community genome annotation projects to ensure these resources essential to ciliate research are available online (TGD

and ParameciumDB). The *Tetrahymena* Stock Center is a key asset necessary to sustained ciliate research by supporting the dissemination of reagents, strains and expertise. It provides essential infrastructure to coordinate efforts of a small and geographically distributed research community and serves as a crucial conduit for researchers new to using these organisms. Importantly, the stock center also engages in outreach to K-12 science teachers, including those with very limited resources. Additionally, the stock center provides support to the four-year and community college community, thus facilitating the cultivation of future biologist and ciliate researchers. The community relies on all these resources for continued advancement in biological and biomedical research endeavors.

Contributed by the TetRA Board.

Drosophila

Please see separately submitted statement contributed by Hugo Bellen, Vice-President of the Genetics Society of America, as well as an independent submission by the *Drosophila* Board of Directors.

Mouse

The laboratory mouse remains the leading model for understanding basic mammalian biology and pathophysiology, making the mouse essential for translational research. With conservation of gene structure and function, the mouse acts as a mammalian avatar for experiments, incorporating inbred backgrounds to hold constant the genome while manipulating individual genes to understand function and pathways. Landmark innovations in genome sequencing and genome editing technologies are further increasing the pace of knowledge. The ability to see the biology through the lens of the mouse, which adds depth and perspective as well as a testing ground for therapeutics, is an unprecedented convergence of resources and technology that will accelerate advances in human health and medicine. Looking past the immediate horizon of Mendelian disorders, somatic cell editing, and gene replacement strategies, the mouse has great untapped potential in terms of resources related to genetic diversity and

environmental exposures that will better inform more complex diseases.

Nearly half of the protein-coding genome is considered "dark", where in vivo function of individual genes remains unknown. NIH is the flagship of an international collaboration using the mouse to understand the function of every human orthologous gene in the mouse genome. However, at current levels of funding, the effort will fall far short, leaving ~9000 genes unstudied. This is commensurate with the Human Genome Project leaving half the number of chromosomes unsequenced. It is essential that this effort to functionally annotate the genome proceeds until the genome is completed, and the mice and phenotyping data made fully available and accessible to the research community.

Contributed by K.C. Kent Lloyd, Director of the Mutant Mouse Resource and Research Center (MMRRC) at the University of California, Davis and Cat Lutz, Director of the MMRRC at the Jackson Laboratory.

Xenopus

The International *Xenopus* Board joins with The Genetic Society of America in stressing the critical importance of model organism-driven research and the need for ORIP support of facilities and resources essential to this research.

Xenopus continues to be one of the most commonly utilized model animals as a consequence of its unique experimental advantages, cost effectiveness, and close evolutionary relationship with mammals. Studies using *Xenopus* have made countless fundamental contributions to diverse areas of biomedical research including neurobiology, physiology, molecular biology, cell biology, and developmental biology. Recent advances in high throughput DNA sequencing, genome editing, proteomics, and pharmacological screening are particularly well suited to *Xenopus*, enabling rapid functional genomics and human disease modeling at a systems level. The ORIP funded National *Xenopus* Resource (NXR) is an absolutely essential resource for the *Xenopus* community in the United States and Canada. It serves as a crucial repository and distribution center for genetic stocks. Having this resource has reduced the burden for

individual labs to maintain stocks, and because it serves as a centralized repository for these stocks it allows their rapid distribution to the broader community, driving research progress. Importantly, the NXR continues to generate new transgenic and knockout lines and generates custom transgenic and knockout animals on a fee-for-service basis. This allows investigators to obtain lines invaluable to their research in a fast and effective manner, without diverting resources to establish the requisite techniques in their own laboratories. Through workshops and other mechanisms, it also plays an increasingly indispensable role in the dissemination of technical expertise, particularly in genomics, genome editing, and imaging. Continued support of the NXR is essential to the ongoing success and growth of research using *Xenopus* in North America, and to maximizing the impact of the >$100 million annual investment that the NIH makes in research utilizing *Xenopus*.

Similarly, the importance of Xenbase.org, the *Xenopus* model organism bioinformatic database, cannot be over-emphasized. Xenbase is an essential web-accessible resource that integrates the diverse genomic, expression and functional data available from *Xenopus* research. Comparative functional genomics between humans and model organisms has led to a wealth of discoveries, and databases such as Xenbase are essential to translate this vast body of data into a meaningful biological synthesis. Xenbase enhances the value of *Xenopus* data through high quality curation, data integration, providing bioinformatics tools optimized for *Xenopus* experiments, and linking *Xenopus* data to human genes. Xenbase also plays an indispensable role in making *Xenopus* data accessible to the broader biomedical community through data sharing with NCBI, UniProtK and Ensembl. Xenbase is the single most important clearinghouse for *Xenopus* data. It provides high quality annotation, tools specific for *Xenopus* research, and integrates diverse data types in a way not available at any other single database. For example, Xenbase inter-relates *Xenopus* genomic, epigenetic, mRNA and protein sequence data, with gene expression and gene function, as well as physical reagents such as antibodies, morpholinos and transgenic lines. Organism-specific genomic databases are critical for modern biology, and Xenbase is essential for all research that uses *Xenopus*, and plays a major role in supporting and driving the success of research projects across the entire *Xenopus* community.

Contributed by Carole LaBonne, President of the International Xenopus *Board.*

Zebrafish

We write in support of GSA's response to the ORIP RFI regarding its strategic plan and to convey the importance of supporting infrastructure to model organism stock centers and databases to maximize scientific advances in the mission of the NIH.

Model organisms have served as key avenues for the discovery of basic processes of biology, organism development, physiology, homeostatic mechanisms, to mention a few. Model organisms serve as essential conduits to disease gene discovery, understanding mechanisms of disease etiology, and as a consequence the design to therapeutics. The zebrafish vertebrate model has become a powerful genetic model for vertebrate development, physiology, and disease, with remarkable concordance between zebrafish disease gene phenotypes and their human counterparts. Each organism has its special qualities that provide unique scientific attributes to research and unique advances to our scientific knowledge. The translucency of the zebrafish embryo and larva make it ideal for real-time imaging of tissue-level, cellular, and subcellular processes to reveal key biological events, not evident in fixed or single timepoint analyses. The ability to perform large-scale forward genetic screens in the zebrafish is another of its valued features. Its reduced complexity to mammals, relative low cost, ease of husbandry and experimental manipulation further strengthen it as a model.

ORIP has the important function to provide the infrastructure to maintain the animal resources available to the scientific community. ORIP's support of the Zebrafish International Resource Center (ZIRC) is vital to this organism's success and the success of the scientific enterprise broadly. It serves as the main repository of zebrafish strains and other reagents, including a large fraction of the 20,000 mutant gene alleles generated by the Sanger Centre. ZIRC provides these many mutant, transgenic, and wild-type strains to researchers throughout the United States and world on a daily basis. Importantly, ZIRC rapidly distributes strains upon request, which allows the rapid advancement of scientific discovery. Support of the ZIRC database with its integration to ZFIN, the Zebrafish Information Network, is also essential to ZIRC's mission to deliver zebrafish resources to the scientific community.

ZIRC has also spear-headed the generation of highly efficient sperm freezing and in

vitro fertilization recovery methods in the zebrafish, allowing them to freeze the vast majority of lines, and recovering them on request. Investment in ZIRC to lead the zebrafish community in such methods and additionally in husbandry development is important, as well as in distributing this knowledge through in-person training and online resources.

ZIRC and the other model organism stock centers provide an invaluable resource to the scientific community long-term by maintaining zebrafish strains and other resources, beyond the lifespan of any individual laboratory. Zebrafish research will continue to expand to fill gaps in knowledge, including in gene-environment interactions, neural circuitry and behavior, regenerative mechanisms, and disease modeling. ORIPs support of the infrastructure, improvements of methodologies, and dissemination of that knowledge through online resources and training of the next generation of researchers is important in ORIPs next strategic plan.

Contributed by Mary Mullins, Past President, International Zebrafish Society

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