The Jackson Laboratory
Leading the search for tomorrow's cures

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PREDICTIVE BIOLOGY FOR PREDICTIVE MEDICINE

The Genomic Prediction Gap

The sequencing of the first human genome in 2003 was an astonishing achievement. With the human blueprint in hand, scientists broadcasted the promise of predictive medicine: scientists would be able to decipher the genetic maps and predict disease risks and identify therapeutic targets. Since then, meteoric advances in sequencing and computing technology has resulted in amassing tens of millions of partially or fully sequenced human genomes worldwide. By now, scientists have cataloged more than 90,000 unique associations linking common DNA sequence variants to common diseases. While this trajectory has generated rich datasets and new innovations, it has not resulted in the cures for the common diseases like cancer, Alzheimer's or diabetes as was hoped for.

The big question is why? We believe this is because the original assumptions did not take into account the incredible genetic complexity underlying all human disease. Cancer, for example, is comprised of thousands of cancer subtypes, and every cancer is determined by thousands of mutations with no two tumors being genetically the same. Moreover, each mutation interacts with the others creating a complex network of downstream biochemical perturbations. Adding to this complexity is the overlay of intricate mechanisms controlling gene activity (i.e. gene expression and protein activity, happening at any given point in time, within the three-dimensional space of the cells in a tumor. Though everything begins with the genes, all health outcomes — the state of your health, the transition to disease, the subtype of disease and whether your body will be amenable or refractory to any given therapy — is completely dependent on structure of this complex genetic system. Originally, it was thought that a simple catalog of mutations would result in an address book for specific treatments: mutation A requires specifically treatment B. However, despite early successes, we now know this is not possible and that the ultimate solution to the cancer problem requires the ability to deconvolute the genetic complexity of a cancer.

This is the grand challenge we have chosen for The Jackson Laboratory: We seek to capture and understand the genetic complexity of any disease in order to **predict its outcomes**, and in the process, to identify unique vulnerabilities with which we can **craft new cures**.

PREDICTIVE BIOLOGY FOR PREDICTIVE MEDICINE

From weather prediction, to missile guidance systems, to personalized search engines and the mapping of our universe, each technological success came from the massive acquisition of precise datapoints used to create predictive computational models. This approach has not been exploited in medicine because of inadequacies in three arenas: limitations in data acquisition, the nascent nature of the computational models, and challenges in institutional organization. Unlike the ability of cosmologists to stream massive amounts of precise data from coordinated radiotelescopes, and observatories such as the Hubble Space Telescope, we cannot analyze the inner workings of a human being in the same manner. When computational models are created of an individual with a disease, there is no easy way to test whether this model will predict an outcome for a range of interventions. This limitation has blocked the creation of usable predictive models of complex disorders. Finally, unlike in astronomy where observatories are coordinated and linked together in data acquisition frameworks, biomedical institutions are still mainly managed as a collection of silos in the form of departments in universities.

At JAX we are working to break this logjam.

Our bold vision is to create an ecosystem in which we aggressively capture, digitalize and interrogate genomic, physiological and clinical data in humans and in the mouse as the experimental surrogate for the human condition. The computational models we can construct in the mouse can fill in the gaps in our understanding of the complex biology of human disease. We will use state-of-the-art artificial intelligence tools to learn from the datasets and generate de novo digital predictions. In the mouse, we can directly test whether these predictions are correct, and if not, we can iteratively improve the predictive capability. For example, we can look earlier at the predisease to disease transition; we can look in **all** tissues, internal and external, across the entire arc of aging; we can modulate environment, interventions, treatments and exposures to mimic what happens to humans; and, importantly, we can rapidly test and validate our findings and predictions in mice. Because we have tuned the mouse systems to the human disease, we can project the impact of our findings with precision to the human condition. The importance of our approach is that with mouse and cellular models of disease, we can delve in the fundamental complex biology underlying the human disorder rather than rely on clinical observation alone. In this manner, **JAX will provide the predictive biology to drive predictive medicine.**

JAX PREDICTIVE BIOLOGY AND THE CUBE INITIATIVE

At JAX, we have defined the necessary components for a powerful engine for predictive biology and predictive medicine.

THE ECOSYSTEM

- Deep experimental expertise in models of disease: murine (mice) and cellular models
- Genomic technologies
- Ability to capture and systematize massive datasets
- Tools to identify non-coding, *functionally conserved* regulatory elements and gene expression changes between human and mouse
- Perform genetic network analysis
- Ability to project mouse predictions onto human data, and vice versa
- The capability to create predictive models of disease biology
- Built to scale science and research.

At JAX, we are expanding our computational architecture and infrastructure using cloud computing, graph data models and modern workflow technologies to bring together human and mouse data, tools, and results for the creation of predictive models of disease.

A cultural of scientific integration

The scale of the operations requires that all component parts work well together and are integrated without dampening individual brilliance or initiative. At JAX, our "One JAX" theme has created a culture of coordination and collaboration ideally suited for this predictive biology challenge. As a flat, nonprofit research organization, we can cross disciplines easily, with the intellectual heft one finds in academia without divisive departmental lines. We can stay true to our long-term strategies.

A focus on human disease

To maximize our impact on human health, and to provide focus to our work, we will center on human disease and its pathobiology, rather than on general biology. To achieve the quickest impact, the selection of the diseases we attack is dictated by societal need, internal expertise and the level of understanding of that disorder in humans. To date, our focus has been on neurodegeneration, neurosensory degeneration, cancer and aging.

The commitment to engage the wider scientific community

No single institution can achieve the goal of predictive biology and predictive medicine alone. The optimal model is institutional excellence that is highly connected with global like-minded institutions through formal consortia, less formal interactive networks, and information portals for data sharing. JAX is uniquely suited for this challenge given our history and our operational structure. We are the global center for genetic information for the experimental mouse. Our distribution network delivers over 3 million mouse models to 20,000 institutions world-wide; we are one of seven basic NCI-designated cancer centers, one of three centers for precision genetics, and one of six Shock centers for the basic biology of aging (Mouse Genome Informatics, *www.informatics.jax.org*).

PROOF OF CONCEPT FOR PRECISION BIOLOGY: THE CUBE INITIATIVE

In mid-2019, after enunciating the principles of predictive biology for predictive medicine, The Jackson Laboratory launched The Cube Initiative. This two-year initiative is a bold proof of concept project that tests our ecosystem, our culture, and our resolve on a single disease entity: Type 2 diabetes. Type 2 Diabetes is a common disease with high morbidity, affecting 500+ million people worldwide and growing, and costing $327 billion in the U.S. alone in 2017. The problem concerns nations across the globe and also accentuates dementia and liver disease. Much is known about the genetics of the human disorder with more than 230 genetic variants associated with T2D, but these are mainly statistical associations; how they function, and interact together, remains unsolved. Our most recent work has shown that our mouse models of the disease mimic, at the genetic level, the complex interactions implied by the human data. Our goal is to unlock the genetic and biological complexity of T2D, so that we can make predictions to uncover unique biomedical solutions that can be translated into the clinic. Already, over 130 senior scientists at JAX are participating in this collective effort contributing their individual expertise. The platform we are assembling is an innovative digital accelerator that will fully integrate cross-species genomic and biological phenotypic data. Working with collaborators at the University of Wisconsin-Madison, Northeastern University, Vanderbilt University, Harvard University and Fudan University in Shanghai, China, JAX scientists and computational and technological staff is testing our ability to scale like never before.

This proof of concept explores efficient approaches to achieve the optimal predictive biology ecosystem. Future Cube projects can be launched in aging and inflammation (Immunoaging Cube), neurodegenerative disorders (Neuro Cube) and cancer (Cancer Cube), all consistent with our expertise and internal focus.

DRIVING JAX PREDICTIVE BIOLOGY: SCALE AND DIGITAL INTEGRATION

At The Jackson Laboratory, predictive biology is our future. It is the aspirational goal that will exploit our deep expertise in models of disease, complex genetics and functional genomics, and computational biology. We also know that we will need to expand and harden several scientific domains in order for us to achieve the **depth and scale necessary to actualize the ideal predictive biology ecosystem.** They are:

The BioCERN concept

The future of discovery using animal models will rely not on small laboratories manned by students working with inadequate infrastructure for advanced exploration, but highly qualified, highly scaled operations run by professional experts. We propose to significantly reconstruct and expand our animal experimental space to achieve the most contemporary and most efficient discovery pipeline for mouse models in the world. In high energy physics, individual universities no longer run their own particle accelerators but rely on large, professionally run structures such as the Large Hadron Collider operated at CERN, the European Organization for Nuclear Research. The most important questions in physics can only be answered by experiments performed by platforms such as the LHC. We believe that JAX is the only organization in the world that can create and operate such an infrastructure for biology. We want to create the BioCERN for predictive biology and precision medicine.

Artificial Intelligence and Data Sciences Initiative

JAX has a powerful and robust infrastructure for genomics and computational biology that empowers our current science. The next challenge is to manage datasets that are even larger by orders of magnitude. It is only at that level that we will be able to create computational (in silico) models of disease that approach being predictive. Therefore, we propose to dramatically expand our data sciences capabilities augmented by artificial intelligence expertise.

Cellular Engineering

The greatest advance in genetics since the sequencing of the human genome has been the discovery of approaches to engineer individual genomes in a facile manner. Not only are these tools necessary to assess and prove the impact of single base changes in complex biological systems, but they provide new therapies through cell-based treatments. Artificial tissues created by reconstituting engineered cells can one day regenerate diseased organs. JAX has these tools but we must expand and deepen these skills in scale to achieve our predictive biology goals and to have an impact on precision medicine.

By Madeleine Braun, Ph.D., and Edison Liu, M.D.