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Proposal for FASTFORWARD Programs

DISCOVERY OF NEW DISEASES: A Proposal for a Comprehensive Rare Disease Research Program (MI-Genesis)

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PART I – EXECUTIVE SUMMARY

There are roughly 10,000 diseases afflicting humans, and most of these diseases are considered "*rare*" or "*orphan*" diseases. The Orphan Drug Act defines a rare disease as a disorder affecting fewer than 200,000 individuals in the United States. When added altogether, more than 25 million people or 8% of the US population suffers from a rare disease. The direct medical expenditures for these individuals in 2011 were estimated to be $286.6 billion with significantly higher social costs when the loss of wages and productivity are additionally factored. Specific therapies exist for only 250 of these diseases. Thus, rare diseases represent a significant fraction of our societal healthcare burden and in most cases there is substantial unmet medical need. In order to meet this need, NIH has prioritized research funding in rare diseases with new programs in translational medicine and the development of novel therapeutics.

The stated goals of the UMHS Strategic Research Plan include "*the identification of the right mechanism, with the right target, using the right therapy, for the right patient*". The most significant advances in the application of this model of translational medicine and much of the historically significant contributions of the University of Michigan Medical School faculty have been in the study of rare diseases. Noteworthy examples include the discovery of the basis of primary hyper-aldosteronism (Jerome Conn), the identification of the cystic fibrosis gene (Francis Collins), and the development and the use of zinc acetate for Wilson's disease (George Brewer). The U of M faculty members continue to focus and excel in the study of rare diseases as evidenced by the fact that funding for rare disease research is the basis for over one third of current NIH awards to the medical school.

Research in rare diseases has often resulted in novel insights into more common disorders and in some cases important disruptive approaches with highly significant impact for the population at large. A commonly cited example is the development of statins, a class of drugs that emerged from initial studies of the ultra-rare disorder known as familial hypercholesterolemia. The *genesis* of high impact, paradigm shifting medical progress is very commonly based in studies from academic centers on rare diseases. The recent development of *Next Generation Sequencing* has provided a powerful tool for elucidation of the molecular basis of rare disorders. With a cost nearing $1000 per individual exome, genetic analysis is moving to the front line of diagnosis, providing rapid identification of molecular defect and in many cases, insights into pathways to effective treatments. In order to capitalize on these new opportunities, NIH has made unprecedented commitments for rare disease research to be spent in the next 7 to 10 years. Due to the powerful platforms, and these recent NIH commitments, timing has never been better to focus on patients afflicted with rare or undiscovered diseases.

We propose the creation of a program in rare diseases that will address common challenges and needs of the University of Michigan medical community. This program will be open to and seek to engage all departments and disciplines within the UMHS through a horizontally and vertically integrated structure. The core mission of this program will be *to discover novel diseases, to elucidate new disease mechanisms, and to develop novel therapeutics for rare diseases*.

This mission will be addressed by the pursuit of the following aims:

- Support of the infrastructure for the clinical diagnosis, study, and treatment of rare diseases.
- The identification and support of core technologies in genomics, model organisms, and bioinformatics aimed at understanding the mechanisms of rare diseases to be followed by other platforms in the future.
- Enhancement of platforms that can be used for the development of novel therapeutics and their translational application to rare diseases.
- The education of the next generation of scientists and clinicians applying a mechanism-based approach to the diagnosis and treatment of human diseases.
- The active engagement of the community of affected patients, support groups, foundations, individual champions, and biotechnology and pharmaceutical companies to enhance research opportunities, to increase awareness, and to address the needs of patients with rare diseases.

Our program will be set both in the clinic and the laboratory. The ultimate goal will be a comprehensive program that will engage investigators from the basic and clinical sciences and leverage their expertise. The size of the proposed components and the creation of additional components will be scalable based on identified need, demand, and performance. In addition, synergistic alignments with programs being developed in parallel will be pursued. These will include patient registries, currently being developed through MICH-R, and drug discovery programs, under the current auspices of the Center for Chemical Genomics, Valteich Center, and Center for the Discovery of New Medicines. We envision a "virtuous cycle" of activities that will span all aspects of rare disease research. Based on identified areas of institutional need, short-term opportunities for

funding, and existing investigative strengths, the following six initiatives are proposed with an estimated annual budget of less than $5M/year.

The Undiagnosed Disease Program. This program will seek patients with unusual phenotypes involving multiple systems as a clinically based portal of entry for patients in whom a diagnosis has not been established. The interactive evaluation process for the patients will engage multiple clinical specialists, and coordinate discussions with basic researchers, including geneticists with the ultimate goal of establishing a diagnosis of an existing albeit rare disorder or of defining a novel clinical entity. The highly successful intramural program at the NIH inspires this initiative. The expansion of this program at the national level will be funded through the $146M appropriated from the Common Fund with the use of an RFA anticipated in late 2013. We propose to launch a University of Michigan-specific Undiagnosed Diseases Program immediately, with the expectation of successfully competing for this special funding opportunity and strengthen our traditional presence in rare diseases with a novel large-scale federal-funding mechanism.

Application of Genomic Sciences to Rare Diseases (Gen-Core). This component will develop a pipeline to interrogate the potential genetic basis for patients with rare disorders. This initiative will operate through the work of two overlapping committees. The "clinical" committee will be comprised of geneticists and informed physician scientists who will review projects for suitability and recommend appropriate sequencing strategies. The "variant" committee will be comprised of bioinformaticians and geneticists. They will review the interpreted data and provide consultation to the referring investigator regarding additional studies such as functional genomics or proof of principle experiments to firmly establish the genetic basis for candidate genes.

Model Organism Development for Rare Diseases. We propose the establishment of a state of the art zebrafish model organism program. This program will serve as a bridge between the genetic characterization of disease-causing mutations and the discovery of therapeutics for rare diseases. We envision that approximately half of the research questions to be addressed by this group will originate from the upstream work done by the Genomic Sciences group above.

Stem Cell modeling for Rare Diseases. Human embryonic and inducible pluripotent stem cell models generated at U of M have almost exclusively focused on rare disease models. The leadership of the existing programs in stem cell biology has proposed an alignment with the rare disease initiative for the enhanced development, maintenance and use of stem cell models for research on disease mechanisms and the development of novel therapeutics using these cell lines.

"Alpha" Initiatives in Rare Diseases. A select number of highly innovative projects with the potential to be the "genesis" of new mechanisms or novel therapeutics for rare diseases have been identified. We propose to provide catalytic funding for these high-risk, high-reward projects. Included are four proposals on allelic gene inactivation as the basis for autosomal dominant inheritance in rare diseases, the discovery of novel lysosomal storage disorders based on the characterization of newly identified lysosomal gene products, the identification of novel therapies using human embryonic stem cells from patients with muscular dystrophies, and the use of transcription activator-like effector nucleases for gene repair to cure juvenile lethal single gene defect conditions.

Rare Disease Concierge Service. This component is designed as an amalgamation of a business engagement center and a clinical research program. This service will connect patients with established diagnoses, biotechnology and pharmaceutical companies, foundations, and disease champions with U of M faculty involved in clinical care and research in specific rare diseases. This service is intended to engage, strengthen, build and market the rare disease expertise that exists at the UMHS with the goal of establishing UMHS as a preferred site for clinical care and research across a wide range of rare diseases. It is specifically intended to synergize with and bolster existing clinical research infrastructure or the clinical programs servicing rare diseases.

In summary, we propose a flexible and highly adaptable FastForward program focused on the discovery and study of rare diseases. This initiative will build on historical and current strengths within the University of Michigan Medical School to enhance and accelerate work in areas characterized by unmet medical need. By catalyzing new initiatives in basic and clinical sciences and by creating new partnerships in the public and private sectors, the financial model will be sustainable through the growth of traditional and new sources of funding. Finally, MI-Genesis is highly aligned with the central goal of the research strategic plan and will firmly establish the U of M as a prominent leader in the study of rare and orphan diseases.