Interview

Genomics and personalized medicine: a perspective

Dr Desnick is Professor and Chairman of the Department of Genetics and Genomic Sciences and Associate Dean for Genome-Based Research at The Mount Sinai School of Medicine (NY, USA) and Physician-in-Chief of the Department of Medical Genetics and Genomics at the Mount Sinai Hospital (NY, USA). In 1977 he joined the faculty of The Mount Sinai School of Medicine as the Arthur J and Nellie Z Cohen Professor of Pediatrics and Genetics, and as Chief of the Division of Medical and Molecular Genetics. In 1993 he became the first Chairman of the Department of Genetics and Genomic Sciences at The Mount Sinai School of Medicine. Dr Desnick's research interests include molecular and biochemical genetics. He has published over 600 research papers and chapters, including nine edited books. He is Board Certified in clinical, biochemical and molecular genetics by the American Board of Medical Genetics (MD, USA) and is a Fellow of the American Academy of Pediatrics (IL, USA). He has been the recipient of various fellowships and awards and is a past Chair of the American Association of Medical Colleges (DC, USA), a Fellow of the American Academy for the Advancement of Science (DC, USA) and a member of the Institute of Medicine of the National Academy of Sciences (DC, USA).

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You are currently Professor and Chairman of the Department of Genetics and Genomic Sciences and Associate Dean for Genome-Based Research at the Mount Sinai School of Medicine in New York City. What led to your interest in human genetics?

As a college undergraduate, I was a humanities major, enjoying the classics and later Western literature, and a biology minor. I had no particular science focus until I took an introductory genetics course given by Professor Sheldon Reed, the Harvard-trained geneticist who coined the term 'genetic counseling' and who was a pioneer in human behavioral genetics. His course introduced the field of genetics to me, and introduced me to human genetics in particular. After attending a series of courses in biochemical, molecular and population genetics, I decided to pursue a PhD degree in human genetics. Realizing that I knew little human biology, I became an MD/PhD student, and pursued both degrees simultaneously.

Your group is involved in several areas of genetic research ranging from molecular genetics to pharmacogenomics. Can you briefly discuss the different projects that you are involved with?

My research in human metabolic diseases originally focused on Fabry disease, an X-linked lysosomal storage disease caused by the deficient activity of α -galactosidase A (α -Gal A). My laboratory had outstanding students and post-doctorates, and together we purified and sequenced the human enzyme, cloned its cDNA and gene, and learned how to overexpress it and other recombinant lysosomal enzymes so that they were selectively secreted. We made the first α -Gal A knock-out and transgenic mice, and used the mouse models to evaluate enzyme and gene replacement therapy for Fabry disease. These studies led to the European Medicines Agency (EMA) and US FDA approval of recombinant enzyme replacement therapy (ERT) for Fabry disease. Together with Professor Edward Schuchman (Mount

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Sinai School of Medicine, NY, USA), we subsequently developed an ERT for Niemann–Pick B disease (now in clinical trials) and with Dr Jim Fan (Mount Sinai School of Medicine), we developed the concept of ‘pharmacologic chaperone therapy’ to rescue misfolded/mistranslated enzymes or proteins with small molecules. Jim Fan and I were the scientific founders of Amicus Therapeutics (NJ, USA), a NASDAQ-listed biotechnology company that is carrying out clinical trials to evaluate pharmacologic chaperone therapies for various inherited metabolic disorders. My interests have also focused on gene discovery, and currently, projects are underway to find the causative predisposing genes for several Mendelian and common diseases. Together with Professor David Bishop (Mount Sinai School of Medicine), we are pursuing translational studies of the human porphyrias, the inborn errors of heme biosynthesis, and are investigating gene and stem-cell replacement for their treatment. Finally, we have an important effort in the area of pharmacogenetics and pharmacogenomics, and are participating in patient trials to establish clinical validity for genotype-guided dosing.

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What, in your opinion, is the most exciting research that your department is currently carrying out?

There are many exciting projects underway, as this is an exceptional time in genetic medicine with the sequenced human genome and a full toolbox to translate basic findings into clinical practice. Currently, efforts in the department are focused on various human diseases, specifically, studies to identify their causative or predisposing genes, understand their pathogenesis and develop new therapies. Research by the departmental faculty ranges from basic genetic studies of human cancer predisposition, a new morbid obesity gene, new methods to prolong human egg and embryo viability, microRNAs and immunologic disorders, and the role of copy number variation (CNV) in various diseases, through to clinical trials evaluating new treatments for genetic disorders, including the clinical validation of pharmacogenetic guided-dosing for various drugs.

The department is also responsible for some important research breakthroughs. Can you briefly discuss these milestones?

Our department now has over 50 full-time faculty members and they have achieved numerous research accomplishments over the years. Among these are the development of the mixed lymphocyte culture reaction and description of early chromosomal disorders (e.g., studied by Hirschhorn), identification of the enzyme and/or genetic defects causing several Mendelian diseases (e.g., studied by R Desnick, B Gelb, E Schuchman, D Bishop, T Tukel, L Ozelius, G Diaz, J Martignetti, Y Ioannou and E Jabs), the identification of the predisposing gene alterations in cancers and common diseases (e.g., studied by J Martignetti, G Narla and I Peter) and the development and application of new diagnostics and therapeutics (e.g., studied by L Edelmann, R Kornreich, R Desnick, E Schuchman, J Fan and others). For lysosomal diseases, our method of overexpressing/secreting lysosomal enzymes facilitated the development and evaluation of recombinant ERT, and now, treatments have been approved and are available for patients with six lysosomal diseases.

A lot of your research involves pharmacogenomics. How far do you think we are from achieving personalized healthcare?

Although personalized medicine is in its infancy, pharmacogenetics is likely to have a real impact on individualized healthcare soon. Recognizing that biochemical geneticists have expertise in both genetics and metabolism, I am encouraging the biochemical genetics community to work in pharmacogenetics and pharmacogenomics. Therefore, we established a biochemical genetics/pharmacogenetics group at The Mount Sinai School of Medicine, and now have several pharmacogenetics projects underway, including participation in the National Heart Lung and Blood Institute (NHLBI)-sponsored warfarin clinical trial. If we can demonstrate the clinical- and cost-effectiveness of pharmacogenetic testing for drug selection, personalized dosing will become a reality.

What, in your opinion, are some of the major barriers that prevent personalized healthcare from being achieved?

I am optimistic that personalized healthcare will become a reality, as data are rapidly accruing on predisposing common, rare and CNVs for common diseases. Expression and CNV arrays will permit more tumor-specific diagnostic profiling and personalized cancer therapies. However, these advances can lead to overstated claims for personalized medicine, which must be tempered with reality. Personalized genetic risk assessment is being advanced prematurely to the public, as there are limited indications that present findings are going to impact or change current medical practice. We have to minimize the hype and focus on the diagnostic and therapeutic realities, so that patients and physicians can appreciate, and benefit from, personalized healthcare. Pharmacogenetics/pharmacogenomics and cancer array profiling are corner stones of personalized medical practice, that once shown to be clinically cost-effective, will become readily accepted by physicians and patients.

Where do you think your research efforts will be focused over the next 5 years?

Our research efforts will use the new genomic techniques to identify predisposing genes for improved diagnostics and therapeutics for rare and common diseases. In addition, we are expanding our pharmacogenetics/pharmacogenomics research program. It has never been a better time to translate basic findings to the bedside and to be able to predict, prevent, avoid and/or minimize disease through the application of personalized medicine.

Financial & competing interests disclosure

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