

**Department of Human Genetics
Mount Sinai School of Medicine
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The Departmental Roadmap

I. Introduction & Objectives:

The NIH recently published their “Roadmap for the 21st Century” (Science, 302:63-72, 2003). In this document 15 working groups laid out their view of the current and future state of biomedical science in the United States. Three major themes emerged from this effort that will guide NIH’s future intra- and extramural funding priorities over the next several years: “New Pathways to Discovery”, “Research Themes of the Future”, and “Reengineering of the Clinical Research Enterprise”.

“New Pathways to Discovery” refers to the investment in technologies that integrate information about complex biological systems, leading to an improved understanding of the molecular networks that comprise cells and tissues. Such technologies include the development of small molecule libraries, bioinformatics and computational biology, nanomedicine, and structural biology. “Research Themes of the Future” refers to the need for scientists to think “outside of the box”, and explore new interdisciplinary relationships. This will require dramatic cultural and organizational changes within the biomedical community, and there will be a special need to incorporate nontraditional teams of biological scientists, engineers, mathematicians, physical scientists, etc into working enterprises. “Reengineering of the Clinical Research Enterprise” refers to the need for academic clinical researchers to develop new partnerships among organized patient groups and community-based physicians. Emphasis will be placed on the development of new approaches that improve assessment of clinical outcomes, and on the development of regional, translational research centers. Expanded efforts also will be directed towards advanced training in clinical research, and developing and evaluating new drug treatments through clinical trials.

To address the NIH Roadmap and future NIH grant funding, the Chairman of the Department of Human Genetics, Dr. Robert J. Desnick, convened a committee on April 13th, 2004 to review the NIH Roadmap and to generate a Roadmap for the Department that will guide future research and educational planning in genetics and genomics sciences, and to identify appropriate recruitments. The committee members included Edward H. Schuchman, Ph.D., Committee Chair, Robert J. Desnick, Ph.D., M.D., Margaret McGovern, M.D., Ph.D., Kurt Hirschhorn, M.D., Bruce Gelb, M.D., David Bishop, Ph.D., Yiannis Ioannou, Ph.D., and Rong Wang, Ph.D. The committee met on several occasions and solicited input from all faculty, fellows and students. An initial draft of this document was sent to all faculty, fellows and students for review and comment.

II. Overview of Basic Research Activities:

A. Major Research Programs:

Since its inception, basic research in the Department of Human Genetics has focused on four main themes: 1) studies of inherited metabolic diseases, 2) generation and characterization of animal

models of human genetic diseases, 3) genomics and gene discovery, and 4) treatment of genetic diseases. Our faculty has had substantial success in each of these areas (see attached list of "Departmental Firsts"). For example, using biochemical and molecular genetic technology, our faculty have cloned the genes encoding six lysosomal enzymes and five of the nine genes for heme biosynthesis, identified causative mutations in human patients with various genetic diseases, developed methods to efficiently produce their recombinant proteins, and made transgenic and knock-out/knock-in mice to evaluate various therapeutic modalities. Our successful development and evaluation of enzyme therapy for Fabry disease, approved in Europe in 2001 and by the FDA in 2003, exemplifies our ability to translate basic research into clinical practice. Moreover, our efforts to develop and evaluate novel therapeutic strategies have resulted in a translational pipeline, including current preclinical and clinical studies of enzyme replacement, pharmacologic chaperones, and gene transfer for specific genetic diseases. We also have developed partnerships with the private sector based on our basic research discoveries, and licensed our intellectual property for the development and clinical evaluation of new therapies. These include a long-term partnership with the Genzyme Corporation and the recent founding of a new biopharmaceutical company, Amicus Therapeutics.

During the last decade, our faculty also has been successful in using genomics and gene discovery technology. Using positional cloning strategies we have mapped the disease loci for 14 diseases and identified the causative genes in 12 of these disorders. Efforts to understand the pathophysiology of these disorders is being studied in mouse models, and therapeutic endeavors for several diseases are currently under development. In addition, new molecular-based diagnostic tests have been developed for these diseases. However, despite these successes, we also recognize the need to expand in the area of genomics and gene discovery, particularly in the identification of the causative or predisposing/susceptibility genes for common diseases (see below).

The Roadmap Committee reviewed our current strengths and limitations, and in particular our strengths of translating basic research into clinically relevant diagnostics and therapeutics. The Committee made a series of recommendations for the recruitment of new faculty and the initiation of new themes to advance our current efforts in view of current research trends and the NIH Roadmap. These recommendations are presented below.

B. Recommendations for Basic Research:

1. Focus on Neurodegenerative Diseases: Many inborn errors of metabolism have severe and debilitating CNS disease, but the underlying pathophysiology of the neurologic involvement in these disorders is poorly understood. Such understanding would guide the development of new therapeutics to treat these diseases. While our Department has been extremely successful in the study of metabolic disorders and has created several mouse models with neurological phenotypes similar to their human counterparts, additional expertise in neurobiology and CNS therapy is needed to advance studies of neurological pathogenesis and facilitate the development of effective CNS-directed therapies. Such recruitment should recognize the neurobiology strengths in other Departments and should recruit expert faculty who would complement existing Sinai expertise. This is an important direction for our future research in this era of neurobiology.

Thus, the Roadmap Committee recommends that a major, new research direction be focused on the investigation of brain disease in inherited metabolic diseases, and the development and evaluation of new CNS-directed therapeutic strategies for these disorders. For example, such therapeutic strategies may include: intracranial stem cell transplantation, gene therapy, and the development of small

molecule therapeutics, such as pharmacologic chaperones. To accomplish these goals, the Committee recommends recruitment of a faculty member with expertise in neurogenetics and/or neuroscience, with the expectation that such an individual would bring a unique and independent research program to the Department. Clearly, such an individual would also augment the substantial strengths in neurosciences and neurodegenerative disease that already exists at Mount Sinai. While the specific research program of such a faculty recruit may span several areas, it is essential that s/he have a strong background in neuroscience and animal models, and be willing to actively participate in ongoing Departmental and Institutional research programs.

2. *Genomics and Gene Discovery:* Although our past efforts in the identification of disease genes have focused primarily on Mendelian disorders, the Committee recognizes that we are at a unique moment in history since the genomes of man and a variety of model organisms have been sequenced, and novel expression assays and proteomics techniques have been developed, providing the tools needed for the genetic analysis of common disorders. Clearly, the genetic analysis of such complex traits will represent a major research focus in Human Genetics in the 21st century. Thus, it is important to advance our capabilities in the area of complex traits.

The Departmental Roadmap Committee recommends that our gene discovery program be augmented by new faculty in the area of genetic epidemiology. Genetic epidemiologists are essential for the gene discovery efforts in the Department, as well as in the Institution. Thus, this is a high priority for immediate recruitment. Genetic epidemiologists are needed to provide the necessary expertise in computational biology required for the genetic analysis of complex disorders. The Roadmap Committee recommends that a search committee be established immediately to recruit a team of two genetic epidemiologist/statisticians (previously called population geneticists), a senior, more experienced investigator who is theoretical and can design novel methodologies, and a second investigator who would provide service to Institutional investigators.

3. *Pharmacogenetics:* Pharmacogenetics refers to common genetic variations that alter drug metabolism. This is a rapidly expanding field that has been dramatically bolstered by the Human Genome Project and new molecular technologies, and has recently become a major focus of research in the public and private sectors. In fact, this area represents a rich opportunity for the Departmental Faculty to interact with Clinical Faculty throughout the Institution in order to identify and develop assays for commonly used drugs that will be of particular value to the patient populations served by Mount Sinai. Therefore, the Roadmap Committee recommends that an expert, senior (if possible) pharmacogeneticist be recruited to establish a research and clinical program in the Department. Such an individual may be studying the genetics of drug metabolism in cancer, cardiovascular and/or neurodegenerative diseases, since these represent important areas of strength at Mount Sinai with large, ongoing clinical and basic research programs. Also, it is well recognized that aging individuals require special consideration in drug dose. Thus, the geriatric community may be an important target for such research and clinical studies. Such an individual would clearly add a new dimension to our Department, but also could augment many existing research programs throughout the Institution.

4. *Cutting Edge Research Themes:* The field of genetics and genomics is rapidly advancing and new areas of research are always being uncovered. In particular, translational areas such as reproductive genetics and molecular cytogenetics, as well as the rapidly growing and important field of epigenetics, promise to be important research themes over the next five years. Therefore, the

Committee recommends that the Department carefully monitor developments in these areas and, if resources become available, recruit around these themes.

C. New Technologies & Expansion of Core Facilities:

In the NIH Roadmap, there was a clear understanding that substantial resources must be designated for new technology development. Initiatives will be made to fund core facilities providing such technologies to large groups of researchers, rather than to individual scientists. Within the Department, we have a tradition of developing such core facilities, and plan to expand and augment these existing programs with new equipment and/or expertise. Currently, the Department has dedicated cores for DNA Sequencing & Genotyping, Animal Pathology, Microscopy, and Mass Spectroscopy & Proteomics. These Cores have obtained substantial NIH funding and service researchers throughout the Institution. These Cores will need to be maintained, updated and expanded as our research enterprise grows. Our specific plans for each of these core facilities is described briefly below:

a. DNA Sequencing & Genotyping Core:

Overview: Currently, the DNACore in the Department of Human Genetics provides 1) automated DNA sequencing, 2) oligonucleotide synthesis and purification, 3) loss of heterozygosity (LOH) analyses, 4) linkage analysis for Mendelian traits by whole genome genotyping, 5) rapid mutation or SNP screening by denaturing HPLC (DHPLC), and software discounts for limited DNA sequence analysis packages as briefly outlined below:

DNA Sequencing: At present, the DNACore provides for the DNA sequencing needs of MSSM researchers. Our current throughput of about 50,000 sequences per year is easily managed on our two ABI 3700 96 capillary array instruments. We anticipate a continued increase in resequencing as investigators screen for mutations in human diseases, generate recombinant constructs requiring sequence validation, and pursue comparative genomics in other organisms. The DNACore's recent acquisition of a Beckman Biomek FX robotic workstation obtained by a equipment grant from the NIH (NCRR), will facilitate high-throughput genomics. The robotic will speed the accurate preparation of cycle sequencing reactions, automated dye terminator removal, determine DNA concentrations, and normalize samples for optimal read-length and quality.

Oligonucleotide Synthesis and Purification: The DNACore can synthesize up to 12 oligonucleotides per day on its ABI 394 DNA synthesizer and companion Savant OligoPrep for automated deprotection and lyophilization. This service is primarily used by investigators who need faster turnaround time than possible from commercial vendors or who need special services such as modified oligos and oligo purification. We have an HPLC system for rapid purification of large quantities of oligonucleotides.

LOH and Linkage Analyses: The DNACore supports LOH and linkage studies and by analysis of microsatellite markers on ABI 3100 and ABI 377 sequencers.

Mutation/SNP Screening: The DNACore provides mutation and SNP screening using a Transgenomic WAVE™ denaturing high-performance liquid chromatography (DHPLC) instrument with a 192 tube autosampler. This instrument is particularly useful in mutation identification, SNP

discovery, and analysis of candidate genes in target populations as it is nearly as sensitive as sequencing, but about 1/5th the cost.

Bioinformatics: The DNACore and the Department of Human Genetics also supports Bioinformatics initiatives through its sponsorship of the GCG suite of programs, discount distribution of the Accelrys MacVector and DS Gene programs, and access to linkage analysis software on the DNACore SunSparc 20 server.

Future Goals of the DNACore: The DNACore foresees the need for investments in new technology to support the research endeavors of Departmental and Institutional Investigators, particularly in genomics, proteomics, and bioinformatics in the following areas.

Gene Association Studies: In the next five years, the genetic analysis of complex traits will become a greater focus of research, and therefore, there will be a need for high-throughput SNP analyses for association studies. Several expensive technologies are available; the equipment investment will be \$100,000 - \$500,000. The DNACore is well-positioned to be able to achieve the high-throughput sample preparation and handling required by these technologies due to the recent acquisition of a Beckman-Coulter Biomek robotic liquid handler with both 96 tip and variable span 8 heads.

Proteomics: In addition, the Biomek FX will support high-throughput proteomics endeavors, particularly in concert with the Beckman 2D profiler and Mass spec instruments in the Department of Human Genetics.

Bioinformatics

The DNACore SUN Sparc20 server is at the end of its lifetime and it is planned to be replaced by an Apple X-Server. This server is rapidly becoming a favorite in the science community, since a super computer cluster of X-servers was recently found to be the third fastest computer in the world. All of the currently used linkage programs are now compiled and supported on the X-server.

b. Mass Spectroscopy/ Proteomics Core: Proteomics encompasses systematic studies of the identity, changing abundance, distribution, modifications, interactions, structure and function of large sets of proteins, as well as their involvement in disease. Since multiple proteins can be obtained from each gene, there are more proteins in the human proteome than the 30,000–40,000 genes estimated for the genome. As a technology, proteomics provides tools to study proteins in more comprehensive and systematic ways. It can be used as an analytical means to discover biomarkers of human disease, potentially identify new targets for drug discovery, and elucidate molecular mechanisms of disease pathology.

There is a growing need to further enhance our existing Mass Spectrometry/Proteomics Core to serve better both basic and clinical research. The Mass Spectrometry/Proteomics Core in the Department currently provides state-of-the art proteomic analysis. The core has 2D-gel electrophoresis equipment, an Applied Biosystems Voyager-DE STR matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF-MS), a Thermo Finnigan LCQ electrospray ionization ion trap mass spectrometer (ESI-IT-MS), and a new Applied Biosystems QSTAR Hybrid LC/MS/MS quadrupole TOF mass spectrometer. The goal of the core is to remain state-of-the-art in proteomics and protein analysis. To that end, additional equipment is needed, including a 2-

dimensional protein chromatography system, a 2-dimensional fluorescence differential gel system for quantitative proteomic research, as well as the next generation of mass spectrometers.

c. Animal Pathology Core: Our Animal Pathology Core is a Departmental facility equipped with two dissecting microscopes, a paraffin embedding station, microtome and cryostat. Departmental staff members are trained in the use of this equipment, and can prepare tissue sections for routine, light microscopic analysis, as well as *in situ* hybridization. Having such a facility on site has greatly enhanced our translational research projects using animal models, and we anticipate that the need for this facility will increase over the next five years as more translational research is undertaken. Thus, the Committee recommends that this facility be expanded by purchasing one additional light microscope and a second embedding station for histological analysis. In addition, the Committee feels that this core may be of considerable service to the Institution at large since many investigators routinely working with rodent models do not have access to equipment needed to prepare materials for histological analysis. Thus, discussions should be undertaken with the Dean of Research to investigate whether these services should be offered outside of the Department on a fee-for-service basis.

d. Microscopy Core: Our Microscopy Core currently has a Nikon Eclipse fluorescence microscope equipped with a deconvolution software package. To expand this Core, the Roadmap Committee recommends that we purchase a confocal microscopy system capable of exciting in the UV range so that fluorochromes we are currently unable to use with our current system can be utilized. This system needs to be equipped with software and hardware that would allow for calcium, pH and other cellular function indicator measurements. In addition, it is critical that the system is equipped to carry out fluorescence resonance emission transfer (FRET) analyses.

III. Clinical Research and Patient Care Activities:

A. Overview of Activities:

As noted above, an important strength of our Department is translational research, leading to the development of several therapeutics that have been or will be evaluated in clinical trials. In addition, the Department provides comprehensive genetic services from preconception to late-adulthood. These programs include the Reproductive Genetics Program, the Program for Inherited Metabolic Diseases, The Comprehensive Diagnosis and Treatment Program for Gaucher, Fabry, and Niemann-Pick Diseases, the Clinical Genetics Program, the Center for Jewish Genetic Diseases, the Cardiovascular Genetics Program, and the Cancer Genetics Counseling Program. There also are three busy CLIA-certified laboratories in the Department providing sophisticated genetic diagnoses and therapeutic monitoring: Molecular Genetics, Biochemical Genetics, and Cytogenetics.

We anticipate that these clinical activities will continue to grow with the development of therapies for inherited metabolic diseases, requiring clinical trials to evaluate their safety and efficacy. Already, the Department is a national leader in this area. Similarly, there will be new and improved molecular diagnostics for additional Mendelian disorders and for predisposition/susceptibility genes for common diseases. Also, it is expected that genetic screening and counseling programs will expand, and that pharmacogenetic testing will become a reality.

B. Recommendations for Clinical Research:

To maintain and expand our position of leadership in Clinical Genetics, the Roadmap Committee recognizes the need to support our clinicians and clinical programs. To this end, the Roadmap Committee makes the following recommendations:

1. *Organization of Clinical Research and Patient Care for Inherited Metabolic Diseases:* The current disease-specific paradigm governing clinical research in the Department should be changed to a more centralized clinical program with disease-specific experts. In this way, there will be more effective use of resources and staff, and patient coverage will be shared. The structure of the clinical research and clinical trial programs should be reviewed with the aim of centralized coordination, especially when possible for routine patient care, as well as for the conduct of clinical trials.

2. *Biochemical Genetics Recruitment:* A new Associate or Full Professor with federal funding in the area of inborn errors of metabolism should be recruited to coordinate the Clinical Biochemical Genetics Program. This individual will oversee and expand the clinical, clinical research, and diagnostic activities, and provide leadership for the programs devoted to the care and investigation of metabolic disorders.

3. *Genetic Testing and Counseling:* The NIH Ethical, Legal and Social Implications (ELSI) Branch of the Human Genome Project has identified clinical research programs directed at studying the quality assurance and clinical issues associated with genetic testing, as well as the design and development of genetic counseling models for predisposition testing, as two important areas for the next decade. Our faculty already has substantial expertise in these areas, and has obtained external funding to support these activities. The Roadmap Committee recommends that these activities be expanded further in order to enhance our efforts to continue to attract competitive funding through the ELSI mechanism.

4. *Diagnostic Laboratories:* The diagnostic menu in our clinical laboratories should be expanded to include the porphyrias and other genetic disorders. Also, the molecular diagnostic laboratory should develop pharmacogenetic tests that will be useful to Mount Sinai's physicians. In addition, it is recommended that the operational infrastructure and marketing of the clinical laboratories be upgraded to maintain our competitiveness and accommodate this expanded menu.

IV. Educational Activities:

A. Overview of Activities:

Education is a major priority in the NIH roadmap, particularly in the area of clinical research. This will be supported by increased federal funding for training and other educational grants. We currently participate in graduate education both for predoctoral PhD and MD/PhD (MSTP) students in the Mount Sinai Graduate School of Biological Sciences, as well as in the training of MS students in our Departmental-based training program in Genetic Counseling. We also train medical students through the Medical Genetics Course offered in the second year of Medical School and in a number of first and third year electives. Our postdoctoral training programs include an ACGME-approved Residency in Medical Genetics, the first approved program in the country, and a combined program in Medical Genetics and Pediatrics. In addition, the Department sponsors postdoctoral programs that lead to American Board of Medical Genetics eligibility in Cytogenetics, Biochemical Genetics and Molecular Genetics. Our pre-doctoral students, as well as Ph.D. and M.D. postdoctoral fellows, have

been partially supported for over 30 years with an NIH training grant in Mental Retardation and Developmental Disabilities.

Department faculty also have had leadership roles in developing the clinical research education infrastructure of the Institution including securing funding through the NIH K30 mechanism, and the establishment of a Masters Degree in Clinical Research now offered through the graduate school. We have also worked collaboratively with the Cancer Prevention group on their training grant.

B. Recommendations for Educational Activities:

The Committee recommends that the Department focus on enhancing the basic and clinical educational resources for the training of our graduate and postgraduate students. Specific recommendations include the following:

1. *Predoctoral and Postdoctoral Training in Human Genetics:* A major priority for our Department will be to expand recruitment and programs for our NIH training grant in Mental Retardation and Developmental Disabilities. These improvements will enhance our efforts to renew our grant and to increase our funding.

2. *MD Clinical Genetics Training:* The training of internists in genetics is critical to the integration of new genetic knowledge into the clinical research and care of patient with complex disorders such as cardiovascular disease and cancer. Therefore, a joint residency training program should be established with Internal Medicine, particularly because combined Genetics/Internal Medicine training programs have been approved by both boards.

3. *Cancer Genetics Training Program:* A training program for physicians in cooperation with the Cancer Prevention and Control group should be established and funding obtained to train physicians who can combine genetic expertise with the skills of behavioral medicine. These individuals will be uniquely qualified to create the testing, screening and counseling models for susceptibility genes, and also will be trained in epidemiology and surveillance methods that will allow them to compete for CDC and other federal funding.

4. *Post-Graduate Training:* There is a critical need for post-graduate education in genetics, particularly for public health professionals and physicians who care for adults. We are uniquely positioned through our long-standing, collaborative research relationship with the CDC to participate in the development of these programs, and expect that substantial funding will be available for curriculum development and pilot studies. Therefore, an annual postgraduate CME program focusing on various themes (e.g., Recent Advances, Cancer Genetics, Reproductive Genetics, Therapy of Genetic Diseases, etc.) in Medical Genetics should be given at Mount Sinai.

V. Executive Summary:

In summary, the Department of Human Genetics Roadmap Committee recommends the following actions:

- Recruitment of a basic research faculty member in the area of neurogenetics and/or neurosciences

- Recruitment of two genetic epidemiologists, one to perform primary, basic research and the other to provide Institutional service
- Recruitment of a faculty member in the area of pharmacogenomics
- Recruitment of a clinical biochemical geneticist to supervise and coordinate all clinical research and clinical activities in our inherited metabolic diseases program
- Improvement and expansion of our core facilities to enhance services to the Department and Institution
- Expansion of our cancer genetics program, with increased interactions with the Cancer Prevention and Control group and establishment of a Cancer Genetics training program
- Increased efforts to obtain training grants for our predoctoral, PhD and MD postdoctoral, and fellowship programs
- Establishment of a joint Residency training program in genetics and internal medicine