



MAYO CLINIC

Handbook for MD-PhD Students

2017-2018

Kendall H. Lee, MD-PhD, *Program Director*
Scott Kaufmann, MD-PhD, *Associate Program Director*
Bruce Horazdovsky, PhD, *Associate Director of Student Affairs*
Lisa Schimmenti, MD, *Associate Director of Academic Affairs*
Pam McLean, PhD, *Assistant Director in Jacksonville, FL*
Joe Loftus, PhD, *Assistant Director in Scottsdale, AZ*
Robert T. Speary, *Program Administrator*
Lisa Hurley, *Program Coordinator*

[Table of Contents](#)

| | |
|-------------------------------------------------------|----|
| A Brief History of the Mayo Clinic MD-PhD program | 3 |
| Mission, Philosophy and Training | 4 |
| Program Administration | 5 |
| Overview of the MD-PhD Course of Study | 9 |
| Pre-clinical / Pre-thesis Phase (MS1-2) | 9 |
| Thesis Research Phase (GS1-GS3 or GS4) | 13 |
| Clinical Phase (MS3-MS4) | 18 |
| All phases | 19 |
| Facilities and Other Resources Available for Research | 21 |
| Mayo Clinic Resources Overview | 21 |
| Mayo Clinic Hybrid Clinical Research Centers | 22 |
| Mayo Clinic Core Facilities and Shared Resources | 24 |
| Other Shared Resources | 30 |

A BRIEF HISTORY OF THE MAYO CLINIC MD-PHD PROGRAM

Basic science research and graduate education at Mayo Clinic date to 1915, when Drs. William and Charles Mayo used the bulk of their life savings (\$1.5 million or \$36 million in today's dollars) to endow the Mayo Foundation for Education and Research. This initiated an educational program, initially in affiliation with the University of Minnesota that provided PhD training in biomedical sciences and led to the first awarded PhD degree in Biochemistry in 1917. Mayo Clinic School of Medicine (MCSOM) opened in 1972, also initially as a joint venture with the University of Minnesota, and granted its first MD degrees in 1977. In 1983, Mayo Foundation became an independent degree-granting institution accredited by the North Central Association of Colleges and Schools Commission on Institutions of Higher Education. A reorganization within the Mayo Foundation in 1989 led to the creation of MCSOM and Mayo Clinic Graduate School of Biomedical Sciences (MCGSBS) as they currently exist. Since then, approximately 46 new medical students, 36 new PhD students and 6 MD-PhD students have been admitted annually. Knowing that the competition for the very best students is keen, Mayo Clinic commits resources to fully support the tuition and stipend costs for all students. In the past 28 years, exceptionally strong Mayo Clinic support for education and research has allowed top students to be enrolled in the MD-PhD program, and a growing number of outstanding investigators to be recruited to the program's faculty. A strong integration between basic science and clinical and translational research has fostered the environment necessary to achieve our educational mission of training future leaders in biomedical research and academic medicine.

The Mayo Clinic Medical Scientist Training Program (MSTP) grant was first awarded by the National Institute of General Medical Sciences (NIGMS) in 2003 and renewed in 2008 and 2013. During the first fourteen years of support, our MSTP has continued to develop and mature.

The main strengths of our MD-PhD Program are:

- An enthusiastic training faculty of 71 mentors that provides extensive opportunities for cutting-edge interdisciplinary training in basic, translational, and clinical research,
- Outstanding current trainees who are passionate about the study of fundamental biological processes of relevance to human disease,
- A highly competitive applicant pool,
- An autonomous admissions process that enables selection of students based on their prior research experiences and demonstrated commitment to a career centered on biomedical research,
- An effective recruitment and retention plan to enhance student diversity with students who are from underrepresented groups or have a disability. We have a dedicated Associate Director and Executive Committee member, Dr. Bruce Horazdovsky, who leads this aspect of the Program,
- Integrated medical and graduate school curricula which permit students to complete three required graduate courses and two laboratory rotations during MS1 and MS2, facilitating a decrease in the time to degree,
- Programmatic features, including the *Selectives*, *Weekly Conferences*, *Annual Retreat*, *Clinical Experiences Program*, and *Clinical Re-Entry Course*, that respond to the specific needs of MD-PhD trainees, including integration of activities between current students and Program alumni,
- Strong institutional support for education, which enables us to fund our MD-PhD students throughout their medical and graduate training, providing exceptional flexibility in choosing thesis laboratories,

- Exceptional research resources that are accessible to our students and profoundly enhance their educational experience,
- Annual Individualized Development Plans (IDP) created for each student throughout the Program with the support of the Director, Associate and Assistant Directors. These IDPs, which are specific for each stage of training, include course and laboratory selection during MS1/MS2, progress toward degree and academic achievement during the graduate phase, re-entry to MS3 and residency selection/career guidance during MS4,
- A dedicated Director, 3 Associate Directors, 2 Assistant Directors, and outstanding administrative support for the Program. The Director (PI, Lee) and Associate Director (co-PI, Kaufmann) are MD-PhD clinician scientists and MSTP alumni (Yale and Johns Hopkins, respectively). Both have active clinical practices and research programs.

OUR MISSION, PHILOSOPHY AND TRAINING

The mission of the Mayo Clinic MD-PhD Program is to train talented and passionate students to be critical, productive physician scientists. Our main objective is to prepare you for academic careers in basic, translational and clinical research, focused on studying fundamental questions and translating basic discoveries into medical advances. The Program philosophy is that the skills required for this type of academic career are best developed in a basic research setting; however, the unique quality of the physician scientist is the ability to integrate basic studies with translational and clinical research to ultimately advance the practice of medicine. Therefore, in addition to providing strong education in medicine and intensive training in scientific inquiry, we will (i) train you to seek medical implications in even the most basic scientific discoveries; (ii) foster your innate curiosity so that you will be keen to take clinical questions back to the laboratory to look for new fundamental knowledge; and (iii) develop your leadership and collaborative skills so that you will be prepared to bridge basic and clinical research efforts as you pave the way for innovative solutions to medical problems.

MCSOM provides training for physicians but only limited training in research methodology. MCGSBS provides graduate level training in one of seven PhD tracks. The MD-PhD Program is distinct from the individual graduate programs in that you will receive the medical training of MCSOM and the basic science training of MCGSBS in one of the tracks to begin your journey to becoming a physician-scientist. In addition, the MD-PhD Program provides unique training activities (*MD-PhD Selectives, Weekly MD-PhD Conferences, an Annual Retreat, MD-PhD Clinical Re-entry Course and MD-PhD Day*) and provides unique career advising tailored to the training of physician-scientists. The MD-PhD Program also welcomes and provides a home for MCGSBS students who come to graduate school after receiving an MD degree elsewhere.

Participating Departments – As of July 2017, there are 71 MD-PhD training faculty that represent all 7 PhD graduate school tracks as well as 26 clinical and academic departments. The represented departments support research by a total of 561 postdoctoral fellows and 189 predoctoral students. Of these, MD-PhD training faculty currently serve as preceptors for 138 of the postdoctoral fellows and 146 of the predoctoral students. The broad range of departments that participate in the MD-PhD Program provide you with many and diverse opportunities for learning about human health and disease. Disease-related translational courses are offered by many of the departments and by the Mayo Clinic Center for Clinical and Translational Science (CCaTS). You have access to Grand Rounds from many departments, including Medicine, Neurology, Pediatrics, Neurosurgery, and Anesthesiology, as well as from the Center for Individualized Medicine, Center for the Science of Health Care Delivery, and the Center for Biomedical Discovery and CCaTS. In addition, during your PhD years, you will be immersed in a basic science community where the weekly seminar series is frequently focused on the molecular etiology and treatment of human disease, e.g., in the Departments of Biochemistry & Molecular Biology, Molecular Pharmacology,

Physiology & Biomedical Engineering, Neurobiology of Disease, Immunology, or Molecular Medicine.

Training Faculty - The MD-PhD training faculty are selected based on their past history of (or potential for) scientific and mentoring excellence, research productivity, and commitment to the training of MD-PhD students. The training faculty currently consists of 53 Full Professors, 10 Associate Professors, and 8 Assistant Professors, which include 40 PhD, 20 MD-PhD, and 11 MD scientists. Collectively, these faculty members have previously mentored 193 students to PhD degrees. Most members of our training faculty have extramural research support from a variety of sources, including federal agencies (mostly NIH), industry, and foundations. The average yearly grant support for participating faculty is \$848,101. Most faculty also have a significant history of student mentorship.

Mayo Clinic is been dedicated to the concept of “*people working together*” to achieve the best interest of the patient through clinical practice, research, and education. Accordingly, collaborative efforts are highly valued and our MD-PhD Program emphasizes collaborative, cross-disciplinary team science. Accordingly, many of the training faculty have joint projects and shared publications. In the last 5 years, 60 of our 71 participating faculty have co-authored at least one manuscript with another of our training faculty, resulting in a total of 47 joint publications. While the vast majority of you will pursue thesis projects in basic research laboratories, by the time of thesis completion many of you will participate in one or more projects that involve multiple laboratories or that will involve the interdisciplinary centers of research excellence such as the Mayo Clinic Cancer Center, Kogod Center on Aging, Mayo Clinic Center for Individualized Medicine or Mayo Clinic CCaTS.

Institutional Support – Mayo Clinic has made a continuing commitment to fully support the tuition and stipend costs for all PhD and MD-PhD students, throughout their medical and graduate training, providing exceptional flexibility to you in choosing thesis laboratories. Total Mayo Clinic research expenditures for 2016 were in excess of \$710 million. Of this total, \$420 million were from extramural sources, with \$290 million provided from intramural funds. Mayo Clinic also has 20 Federal Institutional Research training grants that are available to many of the MD-PhD training faculty in support of their research.

PROGRAM ADMINISTRATION

MD-PhD Executive Committee

The MD-PhD is administered by an Executive Committee (EC) that meets monthly to discuss student progress, to track program administration and to deal with routine problems. If you have a concern or topic you would like to discuss or to have discussed at an EC meeting, please feel free to contact one of the EC members:

Kendall H. Lee, MD-PhD, *Program Director*

lee.Kendall@mayo.edu; (77)4-7852

Scott H. Kaufmann, MD-PhD, Associate Program Director

kaufmann.scott@mayo.edu; (77)4-8950

Bruce Horazdovsky, PhD, Associate Director of Student Affairs

horazdovsky.Bruce@mayo.edu; (77)4-7951

Lisa Schimmenti, MD, Associate Director of Academic Affairs

schimmenti.Lisa@mayo.edu; (77)3-6294

Pam McLean, PhD, Assistant Director in Jacksonville, FL

mcLean.pamela@mayo.edu; (78)3-6692

Joe Loftus, PhD, Assistant Director in Scottsdale, AZ

loftus.joseph@mayo.edu; (79)1-6274

Robert T. Speary, Program Administrator

speary.robert@mayo.edu; (77)4-3163

Lisa Hurley, Program Coordinator
hurley.lisa@mayo.edu; (77)4-4356

MD-PhD Program Committee

The Program Committee includes 22 members of the MD-PhD training faculty chosen for their exceptionally strong commitment to the program. The committee also includes 2-3 MD-PhD student representatives, the Chair and Vice Chair of the MCSOM Admissions Committee, and additional Mayo clinicians chosen based on previous or current service on that Committee. The MD-PhD Program Committee has ultimate responsibility for the program, including selection of students, development of program policies and requirements, adjudication of problems or conflicts that arise, and support of the program itself.

| 2016-2017 MD-PhD Program Committee | |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Kendall H Lee, MD, PhD, Chair* | Pamela McLean, PhD* |
| Scott Kaufmann, MD, PhD, Vice Chair* | Timothy Nelson, MD, PhD* |
| Michael Ackerman, MD, PhD* | Y.S. Prakash, MD, PhD* |
| Garth Asay, MD* | Marina Ramirez Alvarado, PhD* |
| Daniel Billadeau, PhD* | Michael Romero, PhD* |
| Frank Brozovich, MD, PhD* | Stephen Russell, MD, PhD* |
| Gerardo Colon-Otero, MD* | Isobel Scarisbrick, PhD* |
| Bradley Erickson, MD, PhD* | Lisa Schimmenti, MD* |
| Molly Feely, MD* | Steven Sine, PhD* |
| Philip Fischer, MD* | Jerry Swanson, MD* |
| John Fryer, PhD* | Jan van Deursen, PhD* |
| Eddie Greene, MD* | Liewei Wang, MD, PhD* |
| Bruce Horazdovsky, PhD* | Jennifer Westendorf, PhD* |
| Diane Jelinek, PhD* | Michael Yaszemski, MD, PhD* |
| Ruth Johnson, MD* | Justin Maroun, Student Rep* |
| David Katzmann, PhD* | Erin Triplet, Student Rep* |
| Joseph Loftus, PhD* | Robert T. Speary |
| Carlos Mantilla, MD, PhD* | Lisa Hurley |
| *Voting member Current/previous member of MC Medical School Admissions Committee Mayo Clinic FL or AZ | |

Meet the MD-PhD Leadership

Dr. Kendall Lee joined the MD-PhD Executive Committee in 2017 and assumed the directorship of the program in 2017, succeeding Dr. Grazia Isaya, MD-PhD, whose 10-year leadership was instrumental in maintaining and expanding the Mayo Clinic MD-PhD Program. Dr. Lee received his MD and PhD degrees in Neurobiology from Yale University in 1998. He completed house staff training at Yale, Harvard, and Dartmouth Medical Schools before joining the Mayo Clinic in 2006. He is currently a consultant in the Department of Neurologic Surgery with a joint appointment in the Departments of Physiology & Biomedical Engineering and Physical Medicine & Rehabilitation.



Dr. Lee is recognized as a leader in the field of stereotactic and functional neurosurgery and neural engineering both nationally and internationally. He is the Director of the Mayo Clinic Neural Engineering Laboratories and has been successful in obtaining research support from both governmental sources and private foundations. He began his research career at Mayo Clinic with an NIH K08 award entitled, "Mechanism of Action of Deep Brain Stimulation." He is currently a PI or Co-PI on several research grants from the National Institutes of Health. Of particular note, he is a PI on an NIH U01 grant that was awarded as part of the **Brain Research through Advancing Innovative Neurotechnologies (BRAIN)** Initiative aimed at revolutionizing our understanding of the human brain and at uncovering new ways to treat, prevent, and cure brain disorders. This highly prestigious award identifies his laboratory as a national leader in the development of new technologies and novel approaches for large-scale recording and modulation in the nervous system.

Dr. Scott Kaufmann joined the MD-PhD Program Committee in 1996 and became Associate Director in 2003. Earlier in his career, Dr. Kaufmann completed training in the Johns Hopkins MSTP. After a residency in Internal Medicine and fellowship in Medical Oncology, he rose to the rank of Associate Professor of Pharmacology and Oncology at Hopkins before relocating to Mayo Clinic in 1994. His laboratory has, since its founding, investigated the biochemical basis for anticancer drug-induced apoptosis and the impact of various cellular alterations on drug resistance. Dr. Kaufmann's current work focuses extensively on the regulation of anticancer drug-induced apoptosis. He serves as principal investigator on several grants from the NIH and from several foundations.



Dr. Kaufmann teaches both medical students and graduate students. He takes the lead in teaching the pharmacology of anticancer drugs to first-year medical students in their Pharmacology course, and to second-year medical students in their Hematology course. He also serves as course director or co-director for two Molecular Pharmacology tutorials and he lectures in two additional graduate school courses. Since joining the Mayo Clinic, Dr. Kaufmann has also served on over 50 thesis advisory committees.

Dr. Bruce Horazdovsky joined the MD-PhD Executive Committee as an Associate Director in 2013. He received his PhD from Case Western Reserve University and completed postdoctoral training at the California Institute of Technology and the Howard Hughes Medical Institute at the University of California, San Diego. He was appointed to the Biochemistry faculty at the University of Texas Southwestern Medical Center in 1995 and moved his research group to the Mayo Clinic Department of Biochemistry and Molecular Biology in 2002. Dr. Horazdovsky focused his research efforts on regulated movement of receptors and other signaling proteins to and through the endocytic pathway, a process that has a direct impact on cellular homeostasis.



Since arriving at Mayo Clinic, Dr. Horazdovsky has also been engaged in the Mayo Clinic education mission. He is currently the Associate Dean of MCGSBS, Director of the Mayo Clinic Summer Undergraduate Research Fellowship (SURF) program, Director of both graduate school and medical school first year core curriculum courses, and Director of the Mayo Clinic Office of Research Postdoctoral Affairs. He has also served on over 30 PhD thesis advisory committees.

Dr. Horazdovsky has been a strong advocate of building a diverse and inclusive environment for students, postdoctoral research fellows and faculty at Mayo Clinic. He is part of an active recruiting team that has built long term relationships with institutions that meet the needs of students with diverse backgrounds. He has also been an active participant of Mayo Clinic's long-running NIH-supported NHLBI short-term research training program, Initiative for Maximizing Student Development (IMSD) and Post-Baccalaureate Research Education Program (PREP).

Dr. Lisa Schimmenti joined the MD-PhD Program Committee in 2016 and was named Associate Director for Academic Affairs in 2017. Dr. Schimmenti received her BA from Johns Hopkins and MD from the Albert Einstein College of Medicine. She completed a residency in pediatrics at Harbor-UCLA and entered fellowship training that was funded by an F32 award. Her first faculty position was at UCLA funded by a K08, followed by a faculty position at Minnesota where she was promoted to Associate Professor with tenure. At Minnesota, she held a subcontract to an R01, a March of Dimes award and an R01 to study the mechanism of *PAX2* pathogenic variants in human disease.



At Minnesota, she was the Associate Director of the MSTP, where her efforts culminated in programs to enhance clinical skills, to develop relationships with physician-scientist mentors in their clinical practice and to develop a novel re-entry program from the graduate phase into the third year of medical training. She was also the co-course director for Science of Medical Practice, the first year medical school biochemistry and genetics course, a member of the medical school curriculum committee, and received the university's highest teaching award for her contributions. Dr. Schimmenti recently joined the staff at Mayo where she is Professor of Pediatrics. Her clinical practice focuses on the genetic management of deaf/hard of hearing children and her research laboratory focuses on pharmacologic therapy in zebrafish models of human hearing loss.

Dr. Pamela McLean joined the MD-PhD Program Committee in 2014 and was named Assistant Director for the MD-PhD program in Florida in 2017. Dr. McLean received her bachelor's degree from the University of Glasgow in the UK, and her PhD from Boston University. After completing a postdoctoral fellowship at Massachusetts General Hospital/Harvard Medical School, she was promoted to the rank of Assistant Professor, overseeing an independent research program funded by two R01 grants. In 2012 Dr. McLean was recruited to the Department of Neuroscience Research at Mayo Clinic in Jacksonville as an Associate Professor.



Dr. McLean's current research focuses on the role of protein misfolding and aggregation in Parkinson's disease and related neurodegenerative disorders. She serves as principle investigator on multiple grants and is a project PI on the NINDS/Mayo Clinic Udall Center for Excellence in Parkinson's disease Research.

Since arriving at Mayo Clinic, Dr. McLean has focused on educating the next generation of scientists. In 2013 Dr. McLean assumed the position of Director, Neurobiology of Disease (NBD) Track at Mayo Clinic Graduate School of Biomedical Sciences. The NBD track has approximately 20 pre-doctoral graduate students performing research towards the PhD degree at both the Rochester, Minnesota and Jacksonville, Florida Mayo Clinic campuses.

Since joining the Mayo Clinic, Dr. McLean has served on seven thesis advisory committees and currently has one pre-doctoral student in her laboratory.

Dr. Joseph Loftus joined the MD-PhD Program Committee in 2014 and was named Assistant Director and added to the Executive Committee in 2017. He received his PhD in Pharmacology from the University of Wisconsin–Madison and completed postdoctoral training in the Department of Immunology at The Research Institute of Scripps Clinic. He accepted a faculty position in 1991 as Assistant Member in the Department of Vascular Biology at Scripps where he studied the role of integrin adhesion receptors in hemostasis and thrombosis and participated in studies that were instrumental in defining the molecular basis for ligand recognition and specificity. Dr. Loftus moved to Mayo Clinic Arizona in 1996 where his NIH funded studies are focused on the role of adhesion receptor signaling pathways in the pathobiology of malignant glioblastoma multiforme (GBM). He is currently Professor of Biochemistry and Molecular Biology and serves as Co-Director of the Neuro-oncology Program in the Mayo Clinic Comprehensive Cancer Center and as Assistant Dean in Arizona for the Mayo Clinic Graduate School for Biomedical Sciences.



SUMMARY OF THE MD-PHD COURSE OF STUDY

Most of you will complete an integrated course of study consisting of 2 preclinical years along with completion of pre-thesis graduate school requirements, 4 graduate school years along with integrated opportunities for clinical rotation, and 1-2 final years of clinical training culminating in the MD degree and Step II of USMLE (See the Curricular Timeline on the page below). The goal is to complete the dual degree in 7 years, recognizing that some of you may take an extra year. To accomplish this, we are implementing a much more integrated MD-PhD Program which includes:

- A lab rotation schedule such that all rotations are completed by the end of MS2 (the third lab rotation is optional),
- Opportunities to complete Medical School clinical rotations during GS1-GS4 while performing PhD thesis research,
- MD-PhD specific core rotation requirements that streamline MS3-MS4 requirements. However, students are allowed to complete additional clinical rotations as individual interests and schedules allow,
- Enhanced Mentor and Thesis Committee training to ensure efficient progress to the PhD thesis defense.

Pre-clinical / Pre-thesis Phase (MS1-2)

You will typically complete both preclinical years of the MCSOM curriculum before your thesis research, thereby gaining a strong biomedical foundation for both the investigative and clinical aspects of your careers. The current MCSOM curriculum was developed in response to a 2004 vision statement from the Association of American Medical Colleges (AAMC) regarding the medical education system of the future. The recommendations of this committee prompted a critical analysis of the MCSOM curriculum. As part of that analysis, the MCSOM defined the following goals for its graduates:

- To become outstanding scholarly clinicians, scientists, and educators who place the needs of the patient first,
- To become compassionate physicians who value diversity and work toward social responsibility
- To become effective leaders and members of interdisciplinary teams who improve the processes and outcomes of healthcare,
- To become promoters of wellness in themselves, their patients, and their communities,
- To become creative thinkers who translate discovery into practice and advance medicine through innovation and education.

The MCSOM curriculum was revised in 2006 to meet these objectives. The preclinical curriculum now consists of nineteen didactic *Blocks* over a two-year period. The Blocks in the MS1 year include: 1 – Science of Healthcare Delivery part A, 2 – Biochemistry, Medical Genetics and Histology, 3 – Ethics, 4 – Anatomy, 5 – Science of Healthcare Delivery part B, 6 – Pathology and Immunology, 7 – Microbiology and Pharmacology, 8 – Neurosciences, 9 – Introductions to Psychiatry. The remaining blocks are organized by organ system and provide integrated introductions to the physiology, pathology, pathophysiology, and therapeutics of each major organ system, including Blocks: 10 – Circulation, 11 – Oxygen, 12 – Hematology, 13 – Musculoskeletal, 14 – Renal, 15 – Urinary Track, 16 – Endocrine, 17 – Gynecology, 18 – Nutrition and Digestion and 19 – Preclinical block.

Each block contains a clinical component (“clinical integration”) that provides clinical experiences directly related to topics covered in the classroom. The “basic doctoring” and “advanced doctoring” themes provide a graded experience in clinical history taking and physical examination over the MS1 and MS2 years. In addition to Blocks, there are four themes—Basic Science Foundations, Improving the Public’s Health, Clinical Experiences, and Principles of Pharmacology and Therapeutics—that are represented throughout the curriculum. This curriculum was introduced with an explicit intention to decrease the amount of time in lecture and enhance active learning. Thus, while formal classroom lectures still play a role, the curriculum focuses more extensively on laboratory, small-group, and problem-based strategies. Moreover, building on the notion that future physicians learn best when they have actually seen a patient who illustrates the pathophysiological principle under discussion, the new curriculum includes several half-days per week (especially in MS2) seeing patients in the specialty area associated with the organ block under discussion. Thus, by the end of MS2, you will have developed an extensive foundation in human biology as well as substantial clinical skills.

Between these 2- to 6-week didactic Blocks are 1-week Selectives (27 weeks in total over the first 2 years), which provide MS1 and MS2 students with the ability to pursue a variety of interests, including career exploration, additional “shadowing” experience, service learning, or volunteer work. The MCSOM Director of the Selectives Program works with students to identify opportunities for Selectives that best fit their career interests. While MD-PhD students participate in some of these activities, we use one 1-week selective each year for the *Selective on Survival Skills for the Physician-Scientist*. In addition, MD-PhD students are encouraged to use one or more Selectives to become familiar with a lab (e.g., before the start of a rotation) or to develop in-depth knowledge of their mentor’s field (e.g. by writing a review article) once they have chosen their thesis laboratory.

Mayo Clinic MD-PhD Program Curricular Timeline – 2017

| | July | August | September | October | November | December | January | February | March | April | May | June |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------|----------|---------|----------|-------|-------|-----------------------|---------------------------|
| Year I | Lab Rotation #1 | Medical School Curriculum Year 1: Clinical Integrations, Basic Doctoring, Senior Sages (Geriatrics) | | | | | | | | | | Lab Rotation #2 |
| | MGS Course: Core 6000 Responsible Conduct of Research MGS Course: Core 6150 Genome Biology | MD-PhD Selective: Grant Writing | Coursework: Science of Healthcare Delivery, Anatomy, Ethics, Pathology and Immunology, Microbiology and Pharmacology, Neuroscience, Psychiatry Selectives* | | | | | | | | | MD-PhD Retreat (mid June) |
| Ongoing Activities: Weekly MD-PhD conferences, Bi-weekly meetings with PhD track directors and MD-PhD faculty for lab selection. | | | | | | | | | | | | |
| Year II | Medical School Curriculum Year 2: Advanced Doctoring, Autopsy | | | | | | | | | | | |
| | | MD-PhD Selective: Critical Reading Skills | Coursework: Circulation, Oxygen, Hematology, Renal, Gynecology, Urinary Tract, Endocrine, Nutrition & Digestion USMLE Board Review Course Selectives* | | | | | | | | USMLE Step 1 | Lab Rotation #3 (opt) |
| Ongoing Activities: Weekly MD-PhD conferences, Bi-weekly meetings with PhD track directors and MD-PhD faculty for lab selection. | | | | | | | | | | | | |
| Year III | Lab Rotation #3 (opt) | Graduate School Coursework: 3-4 didactic courses in Core curriculum and track of specialization. Comprehensive written qualifying exam in late Year III. Thesis research. Apply for extramural funding. | | | | | | | | | | MD-PhD Retreat (mid June) |
| | Ongoing Activities: Journal clubs, Seminar series, Continuing clinical education opportunities. | | | | | | | | | | | |
| Year IV | Graduate School Coursework: Tutorials and journal clubs in track of specialization. Oral qualifying exam late in Year III or early in Year IV. Thesis Research. Apply for extramural funding | | | | | | | | | | | |
| | | | | | | | | | | | | MD-PhD Retreat (mid June) |
| Ongoing Activities: Journal clubs, Seminar series, Continuing clinical education opportunities. | | | | | | | | | | | | |
| Year V & VI | Thesis Research Thesis preparation and Thesis defense | | | | | | | | | | MD-PhD Reentry course | MD-PhD Retreat (mid June) |
| | | | | | | | | | | | | Pre-clinical Block |
| Ongoing Activities: Journal clubs, Seminar series, Continuing clinical education opportunities. | | | | | | | | | | | | |
| Year VII | Medical School Year 3: Required clerkships (Family Medicine, Internal Medicine, Neurology, Obstetrics/Gynecology, Pediatrics, Psychiatry, Surgery) Evidence-Based Medicine, Didactic Intersession, Senior Sages (Geriatrics) | | | | | | | | | | | |
| | | | | | | | | | | | | MD-PhD Retreat (mid June) |
| Ongoing Activities: Weekly MD-PhD conferences. | | | | | | | | | | | | |
| Year VIII | Medical School Year 4: Required clerkships: Emergency Medicine, Medicine Subinternship Clinical Electives, Residency Boot Camp, Didactic Intersession, Residency Interviews USMLE Step 2 taken by December 1 | | | | | | | | | | | |
| | | | | | | | | | | | | MD-PhD Retreat (mid June) |
| Ongoing Activities: Weekly MD-PhD conferences. | | | | | | | | | | | | Graduation |
| Notes and Legend: | | | | | | | | | | | | |
| To facilitate description of this curriculum, we designate the first two years as MS1 and MS2, the PhD thesis years as GS1-GS3 (or GS1-GS4) and the predominantly clinical clerkship year(s) as MS3 and MS4. | | | | | | | | | | | | |
| * Selectives: Dedicated 1-2 weeks blocks during MS1 and MS2 that enable the student to experience the self-directed approach behind the design of the medical curriculum, emphasizing personal responsibility for the learning experience. | | | | | | | | | | | | |

Additional MD-PhD-specific activities during the Pre-clinical / Pre-Thesis Phase (MS1-MS2)

Laboratory Rotations and Choice of PhD Thesis Advisor:

Laboratory Rotations: You are expected to complete two research rotations, with a third rotation as optional. Most students complete these research rotations during the summers before the start of MS1 and MS2. If you have performed research at Mayo Clinic before entering the MD-PhD Program you can receive credit for one rotation and if you have picked a laboratory you will not be required to do further rotations. You will have an option to complete a third research rotation after taking USMLE Part 1 if you require an additional rotation to choose your PhD thesis mentor. Rotations are encouraged, but not required, at all three sites: Rochester, Scottsdale and Jacksonville. Mayo Graduate School and the MD-PhD Program will cover all expenses associated with a rotation away from your starting site.

Process of picking a rotation and thesis mentor: At the time that you were invited to Mayo for an interview, you were asked to review faculty research descriptions and list potential faculty of interest, and initial meetings with faculty were based on those lists. Additional meetings were arranged for your second-look visit in March or April. These meetings often resulted in decisions about your first rotations.

To provide an additional mechanism for exposing you to the MD-PhD faculty, the MS1 and MS2 students organize a twice monthly pizza lunch designed to provide exposure to potential mentors. Each year the inaugural speakers are the Program Directors from the seven PhD tracks, each of whom presents an overview of research opportunities within the respective tracks. Additional sessions are used to invite individual potential mentors who are asked to present a chalk talk describing the ongoing research and potential future opportunities in his/her lab. These sessions provide you with an opportunity to meet additional training faculty.

Finally, the Director, Associate, and Assistant Directors are always available to provide input into the choice of rotations and thesis mentors. The directors will attend the Weekly Conferences which will provide opportunities for you to interact with them informally. They have “open door” policies and are available for private consultation at any time. If you experience any problems during a rotation, it is very important that you talk with the program director immediately.

Genome Biology (Core 6150): To provide an introduction to MCGSBS and provide you with a head start on meeting the course requirements for the PhD, we have arranged the schedules in MCSOM and MCGSBS so that you can enroll in the Genome Biology graduate school core course during MS1 Blocks 1-3. This course is directed by Dr. Horazdovsky (Associate Program Director) and complements the concurrent MCSOM biochemistry/genetics Block (taught at a more fundamental level). Core 6150 explores the organization and function of the genome with an emphasis on the features that are critical for the regulation of gene expression in mammalian systems. Topics include genome packaging and replication, transcription, RNA processing, noncoding RNA function, translation, and protein processing. The course is primarily a “concept” course but has been expanded to include introductory lectures on quantitative analysis of genome-wide data sets, specific gene expression profiles, as well as extensive paper review sessions in which lecturers lead a paper discussion and analyze primary data with students. You have the option to test out of this course by taking an exam provided and graded by the course director to prove mastery of the material.

MD-PhD Selectives: This feature stems from an integrated effort between the MD-PhD Program and MCSOM to provide unique educational experiences for MS1 and MS2 students in the context of the MCSOM curriculum. As indicated above, the MCSOM curriculum includes 27 weeks of Selectives which provide medical students with the ability to engage in a variety of activities, including career exploration, additional “shadowing,” service learning, or volunteer work. You are

encouraged to use part of this selective time to get a start on a future rotation or begin literature review that will facilitate your PhD thesis research. In addition, each year the MD-PhD Program provides one selective tailored specifically to the needs and interests of MD-PhD students. Although required for MD-PhD students in MS1 and MS2, the course is also open to more advanced students upon request. A selective in Bioinformatics was first offered in the winter of 2007; this selective was very timely and became the foundation for a new course “*Introduction to Bioinformatics*” that is now one of the advanced courses offered each year by MCGSBS to all interested PhD and MD-PhD students. Selectives in the following years have focused on grant writing skills, clinical trial design, or critical reading skills. The “*Introduction to Grant Writing*” course is organized by the Director and is offered in even years. The “*Critical Reading Skills for MD-PhD Scientists*” course has been organized by the Associate Directors and includes sessions on evaluating published and unpublished data as well as reconciling conflicting claims in the published literature, using recent publications as examples. Each *Selective* undergoes MCGSBS evaluation and approval so that MS1 and MS2 students participating in these courses earn graduate school credit (1 credit per selective).

Transition to PhD Thesis work in the Graduate School: We have found that the educational and “cultural” differences between the medical school and the graduate school can be quite a profound transition process. Special efforts are made to assist you with this transition. In the winter or spring quarter of each year, this upcoming transition is a topic for discussion at one of the *Career Development Talks*. To further aid you in the transition from the highly structured MCSOM curriculum to the more self-directed PhD program, the Executive Committee and several advanced students will meet with MS2 students after they complete USMLE Step 1 in June each year. The goal of this meeting is to openly acknowledge and focus on the transition process with input from students who have recently made the transition.

Thesis Research Phase (GS1-GS3 or GS4)

Graduate Studies: Upon successful completion of USMLE Step 1, expected by July 1 after MS2, you will transition to MCGSBS and thesis research. If you have not yet selected a thesis mentor by this time, you will complete a third research rotation during the summer before the beginning of the MCGSBS academic year. With rare exceptions, you will have chosen a thesis advisor and a PhD track by the end of that summer, in consultation with the Director, Associate and Assistant Directors. Frequently, these decisions are made during MS2.

PhD tracks: You will select your PhD thesis advisor (and thesis advisory committee members) from among the MCGSBS faculty. These faculty participate in seven multi-disciplinary PhD tracks, including:

Biochemistry and Molecular Biology (BMB) (D.J. Katzmann, PhD, Program Director) This program has 87 faculty with laboratories engaged in three main concentrations: Biochemistry & Structural Biology, Cell Biology & Genetics, and Cancer Biology. Students learn to conduct biomedical research by use of *in vitro* experimental systems, human disease specimens, and an array of model organisms, including mouse, zebrafish, *Drosophila* and yeast, with the vast majority of projects directly related to human disease.

Biomedical Engineering and Physiology (BMEP) (C. Mantilla, MD, PhD, Program Director) This program has 80 faculty with laboratories engaged in four main concentrations. Current areas of research in each concentration include: Biomedical Imaging: Physics of medical imaging, medical radiation physics, biological imaging, functional MRI, MR elastography, cardiovascular MRI, radiation therapy physics, 3D micro CT, focused ultrasound treatment, 3D ultrasound, image-guided surgery, virtual endoscopy, 3D visualization, image processing, display and analysis; Biomechanics:

Functional anatomy, mechanical loading response, polymer scaffold design, device and instrumentation design, gait analysis, muscle modeling, rehabilitation engineering, surgical procedure analysis, patient outcome studies; Molecular Biophysics: Structural biology, molecular basis for and function of receptors and ion channels, structural basis of protein elasticity, structure and function of metalloproteins, microscopy image analysis; Physiology: Systems biology, computational biology, regenerative biology, ion channel regulation, intracellular signaling, regulation of blood pressure and flow, renal transport, cardiovascular mechanics, respiratory mechanics and ventilation, vascular endothelial cells, hypertension, neurovascular interaction, smooth muscle, cardiac muscle, calcium regulation, and functional stimulation. The BMEP track is funded in part by an institutional training grant (T32 HL105355-06) from the NIH.

Clinical and Translational Science (CTS) (A.J. Windebank, MD, S.C. Ekker, PhD, Program co-Directors) This program has 79 faculty and covers the full spectrum of clinical and translational science with emphasis on population-based translational science, patient-based translational science and laboratory-based translational science. The program emphasizes a broad base of didactic coursework that prepares graduates to translate research discoveries into health improvement for the patient and the community. This is coupled with an in-depth and transdisciplinary research project that may be focused in any area of biomedical, human or population research. The CTS track is funded by a TL1 grant (TL1 TR00137-10) from the NIH.

Immunology (IMM) (K. Hedin, PhD, Program Director) This program has 31 faculty engaged in the following areas of research: Molecular basis of immune recognition, cellular activation, development of immune cells, lymphocyte differentiation and effector functions; immunobiology of immune cells; animal models of human diseases; pathophysiology and molecular basis of human disease; and development of therapeutic strategies to manipulate immune regulatory and effector mechanisms in disease. The IMM track is funded in part by an institutional graduate training grant (T32 AI07425-21) from the NIH.

Molecular Pharmacology and Experimental Therapeutics (MPET) (R.M. Weinshilboum, MD, and Liewei Wang, MD, PhD, Program co-Directors) This program provides students with an interdisciplinary education spanning the disciplines of pharmacology, biochemistry, molecular biology, cell biology, structural biology, and pharmacogenomics. A highly interactive, multidisciplinary group of 29 faculty members performs basic and translational research to define the biological, genetic and physiological processes that underlie drug response phenotypes, and to apply those findings to the active development of more effective therapeutics. The MPET track is funded in part by an institutional graduate training grant (T32 GM08685-19) from the NIH.

Neurobiology of Disease (NBD) (P.J. McLean, PhD, Program Director) This program has 46 faculty members with primary interests in neurobiological processes related to human disease. Faculty members are drawn from all basic science disciplines and encompass a wide range of research interests, including: neural engineering; autoimmune diseases affecting the nervous system; calcium regulation and signaling; computational analysis and neural networks; growth factor-mediated signal transduction and cell death; mechanisms of vesicular transport in exocytosis and endocytosis; molecular biology and biophysics of membrane receptors and channels; molecular genetics and mechanisms of neurodegenerative disease; molecular mechanisms of pain; molecular mechanisms of addiction and psychiatric disorders; neural development and regeneration; receptor pharmacology; and three-dimensional imaging of nervous system structure and function.

Virology and Gene Therapy (VGT) (Yasuhiro Ikeda, DVM, PhD, Program Director) This track includes 20 faculty members who take advantage of the outstanding research in virology and molecular medicine at Mayo Clinic to promote gene and virus therapy (oncolysis), and their application to the clinic in a timely and responsible manner. Current areas of research include: molecular mechanisms of viral replication, virus-cell interactions, viral pathology and immunopathology, virotherapy and immune-based therapies for cancer, targeted viral vectors, gene

therapy of cardiovascular diseases, gene therapy of hematological malignancies and solid tumors, and xenotransplantation.

In addition to the seven graduate tracks described above, a new inter-track training program has been developed. The **Regenerative Sciences Training Program (RSTP)** at Mayo Clinic was initiated in 2017 and is supported by the Mayo Clinic Center for Regenerative Medicine. The RSTP is designed to equip the next generation of leaders with the skills necessary for the discovery, translation, and application of regenerative medical therapies. The planned curriculum will augment current track educational offerings to improve students' understanding of regenerative technologies and their applications, and in product development, regulation, and use of regenerative medical solutions that are needed to drive the development of new regenerative therapies. RSTP will add 3-4 new PhD student slots per year until a planned steady-state cohort 15-16 PhD students is reached. Students will be selected from the existing graduate track cohorts and each student will remain associated with their primary graduate track. Each RSTP-funded PhD student or MD-PhD student will receive up to 4 years of stipend and travel support beginning in Year 2 of their PhD training. All MCGSBS MD-PhD and PhD students will be welcome to participate in RSTP courses, workshops, seminars, journal clubs, and other innovative educational activities designed to enhance students' breadth of knowledge and career connections in the areas of regenerative science and medicine.

In addition to these PhD tracks and the RSTP (each of which has a weekly visiting faculty seminar series and a weekly "Works in Progress" series where students are expected to present annually), there are numerous inter-departmental centers (e.g., Cancer Center, Kogod Center on Aging, Regenerative Medicine, Individualized Medicine) that can provide you with additional training activities such as seminar series, symposia, special conferences and retreats that enhance the learning opportunities for MD-PhD students.

The MCGSBS Curriculum: The choice of graduate program track dictates the track-specific course requirements that will be expected of the students. With the exception of the BMEP track, which has its own course requirements, the MCGSBS tracks have a coordinated Core Curriculum. Because MD-PhD students acquire scientific knowledge through both the MD and PhD curricula, compromises have been struck to minimize the amount of time you will spend in didactic courses without sacrificing the full knowledge base that you need. Required Core courses for MD-PhD students are:

- Core 6150 Genome Biology (3 cr.) – completed during MS1 as described above
- Core 6000 Responsible Conduct of Research (1 cr.) – completed during MS1
- Core 6100 Chemical Principles of Biological Systems (3 cr., all tracks except BMEP) – completed in GS1
- Core 6300 Molecular Biophysics (3 cr., required for BMEP) – completed during GS1

Importantly, you have the option to test out of Core 6150 and 6100 by taking an exam offered by the course director to assess prior mastery of the material and many MD-PhD students have tested out.

Any core courses beyond these four (e.g., Molecular & Cellular Biology, Molecular Pharmacology & Receptor Signaling) are only required on a track-specific basis. In an effort to keep the course requirements manageable and facilitate engagement in research, MCGSBS has dropped the requirement of a specific number of course credits for MD-PhD students and instead allows the individual tracks to set the track-specific expectations. Moreover, you are encouraged to test out of all courses for which you can demonstrate prior mastery. Typically, students have tested out of 3-4 didactic courses (including Core 6150 and 6100 or 6300) and then taken 3-4 advanced topic courses that are based on discussion of the scientific literature.

Qualifying Exams: Qualifying exams in the various PhD tracks are similar and involve (i) a written

comprehensive examination, typically immediately after GS1; (ii) an oral examination within a few months of passing the written examination; and (iii) completion and defense of a thesis proposal.

Thesis Advisory Committees (TAC): You are encouraged to formulate your TAC within 6 months of picking your thesis laboratory (i.e., by December of GS1) in order to obtain input from committee members and accelerate the thesis project. You will need to submit your proposed TAC to the MCGSBS for approval by the end of GS1 at the latest. Your TAC must consist of a minimum of five faculty members, including at least two from your chosen PhD track, with the thesis advisor as chair. Your TAC should also contain the MD-PhD Program Director or an Associate or Assistant Director. MCGSBS strongly encourages the inclusion of an external examiner, i.e., a recognized authority on the thesis topic from another institution.

Once formulated, your TAC will play several key roles in the thesis research process by providing critical feedback on scientific progress, by providing access to technologies and reagents that complement the expertise available in the thesis laboratory, and by playing a key role in monitoring your progress by meeting with you at least every six months and reviewing the written progress report that is submitted to MCGSBS after each TAC meeting.

Tracking Progress: The MD-PhD Executive Committee will monitor your progress towards completion of thesis research in several ways:

- The MD-PhD Executive Committee formally reviews MCGSBS transcripts of all MD-PhD students and written Thesis Advisory Committee reports as well as annual written progress reports provided by each thesis mentor and student. Particular attention is paid to i) students' and mentors' estimates of thesis completion date; ii) progress in completing track requirements; and iii) discoveries and publications listed in those reports.
- Each student in the graduate school portion of the program will present a poster or a talk at the MD-PhD Annual Retreat, which gives the Directors and faculty an opportunity to judge the students' progress first-hand.
- The MD-PhD Administrator Robert Speary also serves as administrator for MCGSBS, and will facilitate communication between the MCGSBS and the MD-PhD Program when performance or personal issues impact the progress of MD-PhD students.
- The Director, or an Associate or Assistant Director, will serve as a member on all MD-PhD student thesis committees, which provides first-hand knowledge of progress.

Thesis Completion: The focus of the MD-PhD program is research training. You are required to complete a thesis that, in the eyes of your Thesis Advisory Committee, represents a significant, original contribution to scientific knowledge. The final decision regarding the timing of thesis completion and defense is negotiated between you, your thesis mentor and Thesis Advisory Committee. MCGSBS has adopted the explicit requirement of a first-author research publication prior to degree completion. However, your mentor and the MD-PhD faculty will counsel you that your record of discovery and publication is the basis for your applications for future research training (Physician Scientist Training Programs and postdoctoral fellowships) and should strongly encourage you to publish more than this minimal requirement and to work thoughtfully at the development of your professional resume.

Training in Quantitative Biology: There is an ongoing effort on behalf of the MCGSBS faculty to ensure that all students receive appropriate quantitative graduate training via introductory, intermediate and advanced courses with progressively increasing emphasis on specific quantitative methods in molecular biology, biochemistry and structural biology. You will have the opportunity to take several courses that help satisfy this requirement as described below:

- 1) Core 6150 Genome Biology (3 cr.): Described in greater detail in the Preclinical Section above, this course includes quantitative analysis of genome-wide data sets and specific gene expression profiles.
- 2) Core 6100 Chemical Principles of Biological Systems (3 cr.): This course, which is required of all MD-PhD students (except Biomedical Engineering track students) during GS1, not only provides an introduction to fundamental principles of biomacromolecular structure and function, but also provides a survey of quantitative methods in the determination of molecular structures, the analysis of biomolecular interactions, and the biophysical principles underlying diverse cellular processes. Sections of the course that specifically focus on quantitative methods include: macromolecular structure determination, thermodynamic principles of protein folding and misfolding, enzyme catalysis and kinetics, membrane biophysics, and bioenergetics.

Additional intermediate and advanced courses with extensive quantitative content include:

| | | |
|------|------|---------------------------------------------------------------------|
| BMB | 6000 | Biological Macromolecules |
| BMB | 6030 | Data Analysis and Mathematical Modeling in Biomedical Research |
| BMB | 6040 | Fractals and Chaos in Biosciences |
| BMB | 6050 | Biological Kinetics |
| BMB | 6675 | Protein Structure and Dynamics |
| BMEP | 6350 | Advanced Concepts in Molecular Biophysics |
| CORE | 6300 | Molecular Biophysics (required for Biomedical Engineering students) |
| CTSC | 5600 | Statistics in Clinical Research |
| CTSC | 5601 | Utilizing Statistics in Clinical Research |
| CTSC | 5610 | Introductory Statistical Methods II |
| CTSC | 5650 | Survival Analysis |
| CTSC | 5740 | Systematic Reviews and Meta-Analyses |
| MPET | 6813 | Tutorial in Systems Pharmacology |

Generally, you will take Core 6150 and Core 6100 (or Core 6300 in the Biomedical Engineering track) in MS1 and GS1, respectively, unless you have demonstrated mastery of the material by testing out of these courses. In addition, from the list presented above, we require that you take at least two courses. Students in the BMEP track take will take Core 6150 in MS1 but satisfy the other quantitative biology requirements through other track required courses.

Additional MD-PhD activities during the Research Phase (GS1-GS3 or GS4)

MD-PhD Conferences: You will attend Weekly MD-PhD Conferences at all stages of the Program. The MD-PhD Journal Club and MD-PhD Clinical Pathological Correlations that are part of these conferences are organized and presented by the students in the Research Phase of the Program.

Integration of Continuing Clinical Education with Research Training: In addition to involvement in the MD-PhD Clinical Pathological Correlations, you are encouraged to build and maintain your clinical skills and perspectives during the PhD research years in one of several ways. First, by working at the Good Samaritan Health Clinic, a free clinic resulting from a partnership between Salvation Army and the Mayo Clinic, or by identifying a physician or physician scientist in your specialty area of interest with whom to maintain clinical contact throughout your PhD training. The Director, Associate and Assistant Directors are happy to help identify appropriate mentors for this clinical work and MCSOM clinical credits are given for these activities. Second, members of the MD-PhD training faculty who have inpatient clinical responsibilities will provide you with the opportunity to participate in rounds when they are on service or assist in the operating room. Third, you have the option of taking a long-term outpatient clinical elective (e.g., 1-2 half days a month) in a general medicine clinic, which in aggregate will accrue clinical time to count as a clinical clerkship (e.g., in

Family Medicine) in the MCSOM. Fourth, in your final year of the PhD phase you will have a clinical rotation in the primary care internal medicine clinic, one half-day per month (Sept. to April), supervised by PCIM consultants, and will have clinical responsibilities similar to third year clerkship students.

Training in Translational Research: MD-PhD students may apply for appointment to the Mayo Clinic CCaTS (TL1 Pre-doctoral Translational Research Program) and are selected on the basis of their interest in, and aptitude for, translational research. Most MD-PhD students opt for more basic thesis projects. Nonetheless, students with strong interests in translational research will benefit from the course offerings provided by the CCaTS, including advanced courses in biostatistics, bioinformatics, epidemiology and clinical trial design.

Medical School re-entry counseling: Although clinical activities have been integrated into the research phase of your training, formal re-entry to full time medical school is a stressful time for many MD-PhD students. A strategy has been devised to help with this transition. The MD-PhD Executive Committee will assemble a “re-entry” study plan that involves both self-directed activities as well as MCSOM activities, including (i) a recommended weekly student-led USMLE review course that is offered January-April each year; (ii) a 6-week Preclinical Block offered May-June of each year (second year MD students take this course at the end of Year 2 of medical school, while MD-PhD students take this block after their thesis research but before re-entering MCSOM); and (iii) a mandatory Clinical Re-Entry Course. These activities will help you to perform at the same level as other third year medical students without significantly interfering with your ability to complete your PhD theses and related publications.

MD-PhD Clinical Re-entry Course: To ease the transition back to clerkships, MCSOM has developed a one-week MD-PhD Clinical Re-entry Course directed by Dr. Aimee Yu-Ballard, MD, PhD. In addition to didactic sessions, Dr. Yu-Ballard utilizes small group interactive learning sessions and hands-on patient care. Her main goals are to refresh your medical knowledge, build up your physical exam skills, and develop your patient-doctor communication. She has structured the course to meet with the students on several half-days. Overall, the re-entry course gives you a helpful refresher on common medical issues for both the inpatient and outpatient setting, and is very useful before you start your MS3 clinical rotations. Because most students re-enter MCSOM in the summer, the re-entry course is typically offered in June. However, Dr. Yu-Ballard is available to work individually with students who re-enter MCSOM outside of the regular schedule.

Clinical Phase (MS3-MS4)

You will return to MS3 after completing and successfully defending your PhD dissertation, typically in summer or early autumn. Required MS3 clerkships involve a combination of clinic- and hospital-based learning, including Internal Medicine, Surgery, Neurology, Psychiatry, Obstetrics and Gynecology, Pediatrics, and Family Medicine. You are also required to complete a 6-week acting-internship. Beyond that, you will be able to take additional elective rotations, particularly to explore your chosen subspecialties. Further clinical clerkships, and a set number of electives that are required of regular MD students, are not required for MD-PhD students.

Additional MD-PhD activities during the Clinical Phase (MS3 or MS3-MS4)

Counseling on Research Residency Positions: Counseling regarding physician scientist training programs (PSTPs) began during your first visit to Mayo Clinic as an interviewee. During your orientation to the Mayo Clinic MD-PhD Program, the Director and Associate Directors provided examples of career paths of former graduates, including graduates who entered PSTPs. Dissemination of information about PSTPs will continue with discussions on research residencies

led by Dr. Karl Nath, Director of the Mayo Clinician Investigator Training Program (Mayo Clinic's equivalent of a PSTP) or by recent alumni of the Mayo Clinic MD-PhD Program who are in training in PSTPs. These discussions will be held as one of the annual *Career Development Talks* that are part of the Weekly MD-PhD Conferences.

All Phases

Several ongoing activities bring MD-PhD students in all years of training together several times per month and increase their cohesiveness and camaraderie:

Weekly MD-PhD Conferences: The goal of the weekly conferences is to respond to the unique needs of MD-PhD students and to provide them with a greater sense of community. Students from all stages of the program are expected to attend, although MS3 and MS4 students are excused when clinical obligations intervene.

These conferences contain several components:

- *MD-PhD Journal Clubs*: The journal clubs bring the MD-PhD students together to discuss high impact publications chosen by the presenting students (the students in the PhD portion of the program). This journal club is unique in that students from seven different PhD tracks contribute their knowledge and perspective, which results in challenging questions and lively discussions, in addition to teaching the presenting student how to make a specialized topic clear and exciting to a scientifically broad audience. The papers, although usually chosen from *Science*, *Cell*, *Neuron*, *Nature*, *Nature Medicine*, *Nature Immunology*, *Nature Neuroscience*, *Cancer Cell* or *PNAS*, typically have a clinical/translational connection. Clinical experts in the area are often invited to attend to provide additional input and expertise. Sessions usually begin with a clinical vignette or brief continuing medical education review related to the topic of the paper.
- *Career Development Talks*: Examples of recurring talks include *How to Pick Your Research Problem*, *Transition to Graduate School* (student panel), *Transition to Medical School* (student-faculty panel discussion), *Residency/Match* (student-faculty panel discussion), *Physician-Scientist Training Programs* (panel discussion with Mayo Clinic's Clinician-Investigator Training Program Director and current trainees of this program), and *How to Balance Work and Personal Life* (group discussion).
- *MD-PhD Clinical Pathological Correlations*: This activity allows students in the research phase of the program to assess and present patients to other MD-PhD students. On a bi-monthly basis, our internal medicine faculty advisor Dr. Aimee Yu-Ballard, pairs two volunteering MD-PhD students with two internal medicine residents. The students each spend a half-day in the hospital with their resident, during which the student obtains a full history and performs a full physical exam on one patient. Subsequently, the student and resident discuss the patient's differential diagnosis, work-up, and care, before reviewing the patient's record and assembling a more comprehensive understanding of the patient and the course of the illness. Using various clinical resources (Harrison's online, UpToDate, Current Medical Diagnosis and Treatment, and Micromedex), each student then assembles a 20-minute presentation that focuses on clinical reasoning, the specific disease pathobiology, and relevant ongoing research in the area. The two participating students present their cases at one of the MD-PhD Conferences, allowing time for discussion and questions. Dr. Yu-Ballard, who typically attends the presentation, provides clinical insights and guidance to the discussion. This activity accomplishes four major aims for MD-PhD students immersed in Graduate School: (i) to maintain a clinical perspective, (ii) to refresh clinical skills, (iii) to review clinical knowledge, and iv) to encourage ongoing clinical exposure during the student's laboratory research training.

MD-PhD Retreat: The retreat is held each year during the last weekend in June and brings together the MD-PhD students, training faculty, and program alumni, as well as the deans of MCGSBS and MCSOM. In addition to a keynote address from an MD-PhD alum or prominent physician scientist on the training faculty who talks about his/her career path and research, the event includes poster sessions and scientific talks. MD-PhD students in GS1-GS3 are expected to present posters and those who are about to defend their theses present talks. A key component of this event is a student-led discussion of the *State of the Program* with the MCSOM and MCGSBS deans, the MD-PhD Executive Committee, and MD-PhD faculty. In this forum our students can speak as one voice with the opportunity to be heard at the highest level.

MD-PhD Day (Bench-to-Bedside Lecture): Each year, MD-PhD students in MS1 and MS2, in consultation with the Director, Associate and Assistant Directors, identify a world-class physician-scientist to visit Mayo Clinic to present a formal research seminar to the scientific community and to meet informally with MD-PhD students after the seminar and over dinner. At the dinner, the scholar typically describes his/her career course, including the reasoning behind career decisions and advice on how MD-PhD students might approach them. Although there are many formal research seminars at Mayo Clinic, this event provides the MD-PhD students with an opportunity to think about career development and to discuss career choices almost one-on-one with a prominent scientist who has faced the same career choices that they will be making over the next several years.

Meetings with the Director: You will meet formally at least annually with the Director to (i) review your progress, (ii) to discuss concerns unique to your stage in the program (e.g., upcoming choice of thesis advisor, transition back to MCSOM, application for residency), (iii) to evaluate long-term career goals, and (iv) to explore other issues of concern. You will also have opportunities to communicate with the Director, Associate, and Assistant Directors informally at MD-PhD Program activities, after sessions taught by the Directors in MCSOM and MCGSBS, and by e-mail. Drs. Lee and Kaufmann both maintain an “open door” policy and one or the other (or both) will meet with you whenever needed, typically within hours of an inquiry. Further, Dr. Lee has scheduled office hours for MD-PhD students every Friday at 1-2 pm.

Annual MD-PhD Program Progress Evaluation: Progress of all MD-PhD students will be monitored continuously through feed-back to members of the MD-PhD Executive Committee from MCSOM and MCGSBS. The progress of each student will be formally reviewed at least annually by the MD-PhD Executive Committee, which examines the following:

- Notes from the annual meeting of the Director with each student,
- Rotation evaluations and MCSOM transcripts for students in the Preclinical Phase of the Program,
- Minutes from the MCSOM Student Promotions Committee which tracks the progress of students through medical school,
- MCGSBS transcripts and bi-annual Thesis Advisory Committee Progress Meeting & Individual Development Progress (IDP) forms from each student/mentor pair, paying particular attention to updates of research description and discoveries as well as anticipated dates of re-entry to MS3,
- Self-reported publications and attendance at scientific meetings.


Follow-up with MD-PhD students and/or mentors will be divided among members of the Executive Committee if any issues need further discussion.

National MD-PhD Student Conference and APSA National Conference: MD-PhD students are encouraged to participate in the annual National MD-PhD Student Conference, held in Colorado

and hosted by the University of Colorado MD-PhD students, as well as the APSA National Conference held in conjunction with the joint meeting of the American Society for Clinical Investigation and the American Association of Physicians (a Mayo Clinic APSA Chapter was recently established). These conferences provide a forum for interaction with MD-PhD students from throughout the country. To facilitate participation by our students, the Program will pay the entire cost for the student representatives on the MD-PhD Program Committee to attend the National MD-PhD Student Conference each year and the Program will pay the registration fees for other students who wish to attend either of these conferences.

FACILITIES AND OTHER RESOURCES AVAILABLE FOR RESEARCH

Mayo Clinic Resources Overview

Mayo Clinic is a nonprofit organization committed to comprehensive medical care, education and biomedical research. These three “shields” () serve not only as Mayo’s emblem but also as its ethical base and administrative foundation. Mayo Clinic is the first and largest integrated, not-for-profit group practice in the world. Doctors and researchers from every medical specialty work in collaborative teams to care for patients, joined by integrated support systems and a core philosophy that *the needs of the patient come first*. Over 4,500 physicians and scientists and 57,000 allied staff work at Mayo Clinic, with main campuses in Rochester, Minnesota; Jacksonville, Florida; and Scottsdale/Phoenix, Arizona.

Clinical Resources

Mayo Clinic’s mission is to provide the best care to every patient every day through integrated clinical practice, research, and education. With more than 32,000 staff, Mayo Clinic Rochester occupies approximately 15 million square feet of space. There are two hospitals – Saint Mary’s and Rochester Methodist. The remainder of the medical center space is utilized for (a) patient evaluation, radiological and laboratory diagnostic services;(b) biomedical research; (c) medical and research-based graduate education programs; and (d) administration. Clinical support at the Rochester site is provided by 2,000 full-time staff in medicine, surgery, and allied disciplines. Moreover, there are 2,700 residents, fellows, and students. Mayo Clinic Rochester treats over 340,000 patients each year, comprising 1.5 million patient visits.

Research Resources

Mayo Clinic stands among the world’s elite biomedical research institutions. Mayo Clinic’s commitment to patients includes maintaining comprehensive and robust research programs that lead to improvements in patient care. Mayo provides an ideal research environment, where multidisciplinary teams, reflecting Mayo’s broad expertise and unique approach to bench science and direct patient care, develop an infrastructure capable of conducting meaningful patient-oriented research. In addition to 332 research faculty, more than 750 physicians are directly engaged in research activities. In total, 3,120 personnel work full-time in research. This spectrum demonstrates the continuum at Mayo that links laboratory, clinical and translational research -integrated and aligned with Mayo Clinic strategic goals. In this spirit of collaboration, considerable effort and investment has been devoted to cultivating a diverse and dedicated group of investigators. Presently, there are approximately 200 established laboratory-based research programs, funded by more than 4,800 extramural grants and contracts. Across the three main campuses, the research physical infrastructure spans an immense 952,000 square feet.

At Mayo Clinic, support for research has grown consistently. Total research expenditures for 2016 stood at \$710M, a combination of Mayo reinvestment, extramural funding, and benefactor support. That included \$420M in extramural research funding, of which more than \$254 million was awarded by the National Institutes of Health (NIH), ranking Mayo in the top 25 for overall NIH research support. Internally, Mayo reinvested over \$290M of its own revenue in 2016 back into research. In 2016 Mayo's research programs generated 2,937 new protocols; over 11,000 active human research studies; and more than 7,600 research publications and review articles in peer-reviewed journals.

Mayo Clinic Hybrid Clinical Research Centers

Mayo Clinic is dedicated to numerous specialty research centers, laboratories and facilities. These centers provide opportunities for cross-disciplinary training and collaboration for both faculty and students. In all, Mayo supports more than 30 dedicated centers and programs. They include the Mayo Clinic Cancer Center, a National Cancer Institute-designated comprehensive cancer center since 1973, and Mayo's Center for Clinical Translational Science (CCaTS), one of the largest NIH-funded translational centers in the nation (National Center for Advancing Translational Sciences). Mayo Clinic is also advancing new, cutting-edge medical research through three recently established "transformative centers": the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (study of healthcare systems, patient-centered outcomes and population science); the Center for Individualized Medicine (genomic and molecular-based research); and the Center for Regenerative Medicine (dedicated to tissue and organ regeneration and transplant science). These five centers are described briefly below.

Mayo Clinic Cancer Center

The Mayo Clinic Cancer Center is an independent multidisciplinary program that governs cancer practice, cancer research, and cancer education across all three Mayo Clinic sites and the Mayo Clinic Health System. Mayo Clinic Cancer Center is dedicated to understanding the biology of cancer, to discovering new ways to predict, prevent, diagnose and treat cancer, and to transforming the quality of life for cancer patients today and in the future. More than 122,000 cancer patients from every U.S. state and from around the globe come to Mayo Clinic Cancer Center each year. More than 1,000 physicians, care providers and researchers at Mayo Clinic collaborate across cancer programs and specialties to help cancer patients, their families and caregivers find individualized solutions that address all aspects of their cancer journeys.

Mayo Clinic Cancer Center offers a wide range of cancer-related clinical education opportunities, including residency and fellowship programs, conferences, grand rounds, and Mayo Clinic School of Continuous Professional Development courses. Mayo Clinic Cancer Center's Cancer Education Program offers classes, sessions and support to cancer patients, their caregivers and the public at all three Mayo Clinic campuses.

Following the most recent NCI competitive grant renewal, Mayo Clinic Cancer Center earned the NCI's highest ranking, "Exceptional", and received more than \$28M in funding over five years.

Center for Clinical Translational Science (CCaTS)

Mayo Clinic's Center for Clinical and Translational Science is a continuation of Mayo's nation-leading work in translational research which extends the prior Center for Translational Science Activities (CTSA) (first funded in 2006) and the initial Mayo Clinic General Clinical Research Center, a span of continuous NIH and internal funding that stretches back more than 40 years and one of the first such centers funded in the US. Mayo's CCaTS is a leader among the 60 such centers

across the US. The new CCaTS designation is in alignment with the NIH's National Center for Advancing Translational Science (NCATS), aiming to accelerate the pace of new treatments and cures. CCaTS works closely with Mayo Clinic's Cancer Center, Center for Individualized Medicine, Center for the Science of Health Care Delivery, Center for Regenerative Medicine, Children's Research Center, and the Robert and Arlene Kogod Center on Aging.

CCaTS provides four broad categories of support for clinical investigators:

- Educational resources
- Research infrastructure and facilitating late-stage translational research
- Community engagement
- Clinical trial services.

Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery

The science of health care delivery focuses on how patients actually receive care. From using engineering principles to determine the most efficient way to schedule patient appointments to research focusing on the most successful, cost-effective means for delivering treatment, this discipline's aim is to enhance the patient's experience with health care by improving quality, outcomes and cost. The Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery builds upon more than a century of health care delivery research at Mayo Clinic. The goal of the center is to focus and coordinate resources to analyze, evaluate and implement care delivery models that improve value for patients.

The center is highly focused on the "science" aspect of care delivery, not simply on anecdotal evidence that may suggest issues or solutions. Combining data analysis, engineering principles and health care delivery research, the center puts its theories, models and care delivery methods through the scientific rigor necessary to determine whether or not they improve patient care, outcomes and cost. Ideas developed and tested in the center can be seamlessly implemented into the Mayo Clinic practice. By developing best care practices at Mayo Clinic and with partners across the country, Mayo Clinic is working to alleviate the nation's health care problems and improve the standard of care nationwide.

Center for Individualized Medicine

The Mayo Clinic Center for Individualized Medicine seeks to help the Mayo Clinic emerge as the global leader in a new era of health care that focuses on the genomic, molecular and cellular interactions at the foundation of life and disease. Synthesizing a century of unrivaled clinical knowledge with the latest genomic sequencing and personalized medicine tools, the Center uncovers and applies new ways to predict, diagnose and treat disease. The Center works closely with physicians to identify specific clinical problems and then works backward to furnish providers with the tools to tailor treatments to each of their patients in ways never before possible.

The Center consists of five Translational Programs, which strive to ensure advances in individualized medicine find a place in clinical trials and studies:

- Pharmacogenomics: The right drug at the right dose at the right time based on the patient's genetic characteristics.
- Clinomics: A new class of bedside tools for the provider and patient with superior diagnostic, prognostic and decision-support capabilities.
- Epigenomics: The interaction among genes and their molecular and external environments. Tools to alter gene activity without modifying the underlying DNA sequence.

- Biomarker Discovery: Base-pair genetic mutations that allow for earlier and more accurate diagnosis, prognosis and drug therapy.
- Microbiome: Interaction of the viruses, bacteria, and fungi living in, on and around the human body (the microbiome) to either promote wellness or facilitate disease.

These translational efforts are supported by six Infrastructure Programs, which provide scientific and laboratory expertise to researchers across the Mayo Clinic enterprise:

- Bioinformatics. Deciphers and organizes research data and makes them relevant to patients, providers, and researchers.
- Biorepositories. Collects, processes, stores, distributes and manages Mayo Clinic biospecimens, including the Biobank.
- Bioethics. Informs all activities within CIM from an ethical and legal perspective.
- Medical Genome Facility. Generates and helps to interpret genomic and proteomic research data with an initial focus on whole genome sequencing.
- Information Technology. Accelerates translation and infrastructure through the development of new computational architectures.
- Administration. Provides operational structure and support, including facilitation of physician-administrative partnerships at all levels and across all shields.

Center for Regenerative Medicine

The Mayo Clinic Center for Regenerative Medicine aims to establish Mayo Clinic as a premier destination for regenerative medicine and surgery. Regenerative medicine is poised to transform healthcare by providing the prospect of definitive solutions that address the unmet needs of patients. The decisive goal of regenerative medicine is to advance care from palliation to on-demand repair, offering potentially curative therapies spanning disease, injury and congenital conditions.

A catalyst in advancing new knowledge on disease causes and cures into informed delivery of effective quality care, the Mayo Clinic Center for Regenerative Medicine aspires to:

- Discover, translate and apply regenerative medicine science into innovative clinical practice
- Develop regenerative medicine platforms and integrated disease-based programs
- Educate and train the regenerative medicine workforce encompassing scientists and providers
- Advance next-generation regenerative medicine products and service lines

Mayo Clinic Core Facilities and Shared Resources

Mayo Clinic offers an extensive technological and core facility infrastructure to support the state-of-the-art laboratories and clinical research efforts of the program's faculty members.

Mayo's state-of-the-art research cores and shared services are designed to support Mayo investigators for the express purpose of maintaining the quality and competitiveness of research at Mayo Clinic. The Mayo Clinic Research Committee has a long history of providing significant support for core facilities. The services within the Research Committee-sponsored Core Facilities are available to all Mayo investigators engaged in clinical or basic research with approved, peer-reviewed protocols or established research programs. There are over 30 cores and shared resources, offering a wide variety of technical services to Mayo researchers. Mayo Clinic Core

Facilities annually serve more than 900 Mayo investigators, greater than 80% of the researchers at the institution.

Numerous cores and shared resources are supported jointly by partnering leadership, departments and centers. These key supporters include the Mayo Clinic Cancer Center, the Center for Clinical and Translational Sciences, and the Center for Individualized Medicine, to name a few.

The Core Facilities provide the following resources to support research and trainees:

- Centralized use of shared instrumentation, which is expensive and requires dedicated technical expertise for optimal function;
- Theoretical and technical expertise within the Core, which provides both technical and collaborative support for the investigator;
- Training for graduate students or other personnel who wish to learn techniques in detail;
- Facilitation of collaboration between investigators who may use similar techniques.

Specific Descriptions of core and shared facilities are included below:

Antibody Hybridoma Core

Kay Medina, PhD, Director

The Antibody Core Facility generates monoclonal antibodies for clinical diagnostic assays and therapeutics. Services include custom hybridoma monoclonal antibody production for immunization, tissue culture, and purification of antibodies. The Antibody Hybridoma Core immunizes mice for immunization and antiserum collection. When immunized, boosted, and bled by core staff members, these mice are housed in a pathogen-free colony. To support fusion, the Core fuses spleen or lymph node cells with a myeloma fusion partner cell line. The Antibody Hybridoma Core utilizes the fusion partner cell line FOX-NY, a nonimmunoglobulin-secreting myeloma cell line that is hypoxanthine-aminopterin-thymidine (HAT) sensitive.

The Antibody Hybridoma Core offers hybridoma, clone and subclone supernate screening by enzyme-linked immunosorbent assay (ELISA), Western blot assay and fluorescence-activated cell sorting (FACS). For each positive hybrid that is producing the specific antibody of interest, the Core will clone and subclone to maintain the stability and monoclonal character of the hybridoma. As subclones test positive for relevant antibodies, one subclone is selected, saved, and is now called a monoclonal antibody. Each monoclonal antibody supernate is isotyped for immunoglobulin subtype, which is needed to determine the type of purification technique to perform and how it will be used in assays. Monoclonal antibody cell lines are then cryopreserved in liquid nitrogen for future use. Monoclonal antibodies are obtained from culture supernate or ascites fluid, while polyclonal antibodies are obtained from mouse antiserum. Purification of antibody from these sources may be performed using ammonium sulfate or protein A or G affinity columns.

Biobank

James R Cerhan, MD, PhD, Director

The Mayo Clinic Biobank is an institutional resource for biological specimens, patient provided risk factor data and clinical data on patients recruited to the Biobank. The Biobank was funded by a Mayo Clinic initiative for Individualized Medicine to assist investigators throughout the institution in obtaining 'normal' samples to serve as controls for their patient populations. The consultative aspects of the resource aid investigators in determining whether these samples would serve as a methodologically sound source of controls for their studies, and assisting with various logistical aspects.

Bioinformatics Core

Jean-Pierre A Kocher, PhD, Director

The Bioinformatics Core (BIC) at Mayo Clinic supports investigators in leveraging genomics, proteomics and metabolomics data to diagnose or improve the treatment of patients. The

Bioinformatics Core is part of the Bioinformatics Program within the Center for Individualized Medicine and has its academic home in the Division of Biomedical Statistics and Informatics Statistics (providing statistical design, analysis, and data management for the clinical and basic science research staff of the Mayo Clinic since its initiation in 1932). The Bioinformatics Core includes more than 20 informatics specialists with MS and PhD degrees in bioinformatics. The core provides bioinformatics service lines to investigators engaged in translational research and personalized medicine, delivering cutting-edge bioinformatics analytical and interpretative support to investigators. Bioinformaticians in the Core pre-process genomics, proteomics and metabolomics data and report results to investigators. They also implement and maintain the bioinformatics infrastructure needed to execute analytical work flows and manage large "omics" data sets. Services include Single nucleotide polymorphism (SNP) selection for custom genotyping panels; Array-based differential gene expression; Illumina next-generation sequencing data pre-processing; Pacific Biosciences next-generation sequencing data pre-processing; Proteomics data pre-processing; Data annotation and pathways analysis; Assessment of internal and external genomics data sets; Access to genotype, gene expression and methylation data from the Gene Expression Omnibus and The Cancer Genome Atlas.

Biomedical Imaging Resource

David R. Holmes, III, PhD, Director

The Mayo Biomedical Imaging Resource (BIR) is dedicated to the advancement of research in the biomedical imaging and visualization sciences. The BIR provides expertise, advanced technology and comprehensive software related to biomedical imaging and scientific research visualization, including image management, processing, display and analysis; volume visualization; image databases; virtual reality; virtual environments; computer graphics; video animation; computer workstations; networks and computer programming. The BIR lab is actively engaged in several areas of translational research with emphasis on scientific analysis and visualization of multi-modal images and on image-guided, computer-assisted, minimally invasive clinical procedures. The principal asset in the BIR is the imaging software package called Analyze, completely developed and supported by the BIR. Analyze is installed on 250 workstations at Mayo, and used in over 300 institutions around the world. Analyze consists of over a million lines of source code, and provides facile multidimensional image access, analysis, visualization, and measurement. Analyze is layered into algorithmic oriented libraries and task oriented user interface modules. The AVW imaging software library is a comprehensive set of imaging functions that facilitates the development of applications for the full exploration and analysis of multidimensional, multimodality biomedical image data sets. The modular AVW function set includes the following areas: image transformation (resampling, slice extraction, registration/fusion); image processing (histogram manipulations, spatial filtering, FFTs, deconvolution); image segmentation (automated boundary detection, region growing, watershed segmentation, morphological processing, multispectral classification); volume visualization (volume rendering, surface rendering, parametric mapping); structure modeling (surface extraction); quantitative analysis (distance, angles, density, 2D/3D regions of interest (ROIs), shape, stereology, fractal signature); and image input/output (standardized DICOM support, volume construction). The C-based AVW software toolkit contains over 600 optional image-processing functions. AVW is accessed through a simple, consistent Applications Programmer Interface (API) that allows easy integration of the functionality into any software development environment.

The Mayo Clinic BIR has undertaken development of a new software system, which is physician friendly and clinical task focused. This new software system, called AnalyzeMD, has been designed and implemented as a case-based, procedure-driven, clinical workflow architecture in which specific applications for clinical imaging tasks are easily integrated and used in a plug-and-play manner. The infrastructure development is complete and features reusable power "widgets" for advanced multi-

dimensional, multi-modality image visualization, segmentation, classification, registration, measurement and database management. Several clinical applications have already been developed and successfully tested. The AnalyzeMD system also provides comprehensive patient and application specific output report generation for all workflow modules added to the system. The BIR has a computer-multimedia equipped conference room that seats 25 people for presentations, teaching and use as a library with journals and books in biomedical imaging and engineering.

Biostatistics Core

Jay Mandrekar, PhD, Director

The Biostatistics Core, part of the Division of Biomedical Statistics and Informatics, provides comprehensive biostatistics consulting and analysis services to Mayo Clinic investigators at all stages of the research process — serving more than 2,000 ongoing investigations. Core key services include genetic analyses, clinical trials, outcomes research and clinical studies with individual Mayo Clinic departments. Core members include PhD statisticians, bioinformatics specialists and programmers. Personnel also include more than 60 master's-level statisticians and more than 90 statistical programmer analysts who support data management and analysis. More than half of the doctoral staff are extramurally supported.

Cytogenetics Core (Cancer Center Supported)

Patricia T. Greipp, DO, Director

The Cytogenetics Core, supported by Mayo Clinic Cancer Center, provides cytogenetic and molecular cytogenetic analysis of human and animal model research samples.

Core specialized services include:

Cell culture: Services include setup, culturing, harvesting, slide preparation and slow freezing. These services are available to assist investigators with any culture project or goal. The core can culture a variety of tissue types and animal models using numerous culture systems.

Fluorescence in situ hybridization (FISH): The Core provides services for a variety of specimen types, including non-paraffin, paraffin, and paraffin tissue microarray. FISH can be performed to enumerate the copy number of cancer-related genes and patterns of gene-related gains and losses; map the location of DNA sequences, genes or transgene insertions; and determine the presence or absence of interspecies cells in xenograft or chimeric animal models.

Probe Development and Labeling: The Cytogenetics Core can develop and produce DNA, RNA, and cDNA FISH probes from various species. Probe size can be a limiting factor in detecting genetic abnormalities. As a result, a variety of fluorophores, labeling methods and amplification techniques are available.

Routine cytogenetic analysis: Typically, 20 to 30 metaphases are analyzed, with GTL banding (G banding) primarily used unless other staining methods are required. Other staining methods available are: QFQ banding (Q banding), Distamycin-A/DAPI staining, CBL banding (C banding, AgNOR staining for satellite regions, Non-banding.

Spectral karyotyping (SKY): Spectral karyotyping is used to identify marker and ring chromosomes; detect and analyze complex chromosome translocations and insertions; identify cryptic translocations; and karyotype human, mouse and rat chromosomes. Each chromosome is specifically labeled with a unique combination of fluorochromes, with analysis based on the spectral properties of the fluorochrome(s) present at each pixel. Wavelengths are measured at each pixel, and the computer assigns a classification color for the wavelength corresponding to the respective chromosome.

Genomic Analysis Shared Resource

Eric D Wieben, PhD, Director

The Gene Analysis Shared Resource is comprised of four related cores: Gene Expression Core, Genotyping Core, Molecular Biology Core, and RNA Interference Core

Gene Expression Core

Jin Jen, MD, PhD, Director

The Gene Expression Core supports researchers in the Mayo Clinic Cancer Center by providing comprehensive services and technical support for the measurement of gene expression. The GEC facility works closely with the Mayo DNA Sequencing Core to provide a variety of gene expression analysis services including the massively parallel Next Generation sequencing (NGS) methods for both mRNA and miRNA. In addition, the GEC provides high throughput gene expression measurements by microarray and quantitative real time PCR. On an annual basis, the GEC provides services to approximately 100 different principal investigators, supporting nearly 300 different grants and activity funds.

Genotyping Core

Julie M Cunningham, PhD, Director

The Genotyping Core, part of the Medical Genome Facility, an infrastructure program of the Center for Individualized Medicine (CIM), which brings together seven different genomics-oriented shared resources to facilitate interactions with the Mayo research staff and to increase the coordination and efficiency of laboratory services. With support and cooperation between CIM, Research Administration, and the Mayo Clinic Cancer Center, the MGF laboratories provide professional, efficient, and low-cost access to the latest genomics technologies to all Mayo investigators, as well as researchers around the world.

RNA Interference Core

E Aubrey Thompson, PhD, Director

The RNA Interference Shared Resource at Mayo Clinic offers the complete Sigma-Aldrich Mission RNA interference (RNAi) line of lentiviral vectors, with a large in-house library that continues to grow. A number of companies offer lentiviral and other shRNA expression vectors, and some of these vectors appear to have features that make them attractive for specialized purposes. The RNA Interference Shared Resource offers one of these libraries, the GIPZ library from Open Biosystems.

Immunochemical Core Laboratory

Ravinder J. Singh, Ph.D., Director

The Immunochemical Core Laboratory (ICL) provides laboratory testing at minimal cost to Mayo researchers as a component of the Mayo Clinic CCaTS program. When capacity is available, testing is also provided for investigators outside Mayo on a collaborative basis. The ICL staff is actively involved in new assay development and improvement of current assay methodology.

Materials and Structural Testing Resource

Kenton R. Kaufman, PhD, Director

The Material and Structural Testing Core is a full-service core facility. It offers experimental design, prototype fabrication, testing, and analysis to all investigators within Mayo. The facility also provides a resource to investigators from outside the institution. The experimental analyses are performed on universal and custom-made equipment with the purpose of examining the mechanical characteristics of various materials and structures. The facility has also developed an additional form of experimental analysis using an optical tweezer/interferometer system to analyze materials at the cellular and molecular levels. Theoretical analyses are performed using finite element analysis. This resource is also capable of designing and fabricating custom testing equipment, instrumentation, and software. This laboratory occupies 7,500 square feet on the first floor of the Guggenheim Building. It is comprised of a: 1) material testing facility for in vitro analysis of bone and connective tissue mechanical properties, including nanoindentation; 2) kinematic testing facility for in vitro assessment of normal and pathological motion; 3) computational stress analysis facility; 4) specimen preparation room; 5) experimental machine shop for machining or modifying joint implant

prototypes, experimental prostheses, internal fixation devices, and testing apparatuses; 6) tissue culture room; and 7) tissue analysis laboratory for basic immunohistochemistry.

Microscopy and Cell Analysis Core

Jeffery L Salisbury, PhD, Director

The Microscopy and Cell Analysis Core (MCAC) is a Cancer Center supported research resource facility that provides specimen preparation, transmission and scanning electron microscopy, X-ray probe microanalysis, immunogold labeling procedures, and imaging services to investigators from both clinical and basic science laboratories within the Mayo campuses. The facility features three transmission electron microscopes and one scanning electron microscope. In addition, this resource provides two similar, but complimentary technologies to researchers. While the type of data obtained and the specimen preparation can be quite different for flow cytometry and optical morphology evaluation, both technologies give information on the properties and characteristics of cells or particles through the use of fluorescent probes, lasers, advanced electronics, high quality optics, and specialized software. Through the combination of these technologies, the Flow Cytometry/Optical Morphology Resource is able to provide investigators with both high-speed population based analysis and morphological information.

Nuclear Magnetic Resonance Core

James R. Thompson, PhD, Director

The Nuclear Magnetic Resonance Core (NMR) Facility exists to assist Mayo investigators with applications of high-field NMR to biochemical and biological systems, in particular, structure-function studies of biomacromolecules. The NMR Facility at Mayo currently supports three main fields of NMR biomedical application: Study of the structure of biomacromolecules in solution by high field, high resolution NMR spectroscopy; NMR spectroscopy of small laboratory animals; and NMR imaging of small laboratory animals. At present, NMR spectroscopy is the only technique that can provide detailed solution structure of small proteins and polynucleotides. The facility contains high-field state-of-the-art NMR spectrometers for data acquisition, computers for processing and analyzing NMR data, and a fully equipped wet laboratory for sample preparation.

Proteomics Core (Cancer Center Supported)

Daniel J. McCormick, Ph.D., Director

The goals of this facility are to provide skills, tools, and methods to foster a complete understanding of the human proteome and apply this knowledge to predict, prevent, and cure human disease. The Proteomics Core (formerly Protein Chemistry and Proteomics Shared Resource) has been a part of Mayo Clinic Cancer Center since 1992. The Proteomics Core is designed to provide investigators throughout Mayo Clinic with the tools needed for proteomic analyses. The members of the Core carry out research and provide services in the areas of differential and global cell protein expression, protein quantitation, protein sequencing, protein-protein interactions and protein structure and function. The Proteomics Core focuses on providing state-of-the-art instrumentation and methods for the separation, characterization, identification, quantification of proteins, protein complexes and other biomolecules. Other services include: i) solid phase peptide synthesis; ii) protein identification; iii) de novo Edman N-terminal chemical sequencing; iv) mass spectrometry analysis of biomolecules; v) one- or two- dimensional polyacrylamide gel electrophoresis and differential analysis; vi) fractionation of proteins from complex mixtures by two-dimensional liquid chromatography (2D-LC) for both proteomics and biomarker discovery applications; vii) fractionation of samples for protein isolation in solution by both FPLC, RP-HPLC and off-gel isoelectric focusing; and, viii) in silico modeling and design of synthetic peptides for protein structure analysis and development of protein specific bioassays. Larger projects (biomarker discovery) include differential protein expression methodologies by mass spectrometry and traditional two-dimensional electrophoresis (2D-PAGE).

Transgenic and Knockout Core Facility

Jan van Deursen, PhD, Director

The Mayo Clinic Cancer Center Supported Transgenic and Knockout Core generates transgenic and gene-targeted mice for researchers at Mayo Clinic's campuses in Arizona, Florida, and Minnesota. Mouse models are important tools for studying the underlying causes of many diseases, including cancer. The Transgenic and Knockout Core can assist investigators with the design of transgenic DNA constructs.

Transgenic and gene-targeted mice generated by the core enable researchers to observe how genes, or mutant variations of genes, are expressed. In the Core, transgenic mice are generated by pronuclear microinjection of foreign DNA fragments into one-cell-stage mouse embryos. On average, it takes about three to four months to generate a transgenic mouse strain. The service lines provided include: cryopreservation, gene targeting vector construction, production of gene targeted mice, and production of transgenic mice.

Zebrafish Core

Steve Ekker, Ph.D., Director

The Mayo Zebrafish Core Facility plays a significant role in multiple research laboratories, serving as a critical hub for new scientists as they learn to tap into the potential of this model system. The Facility serves as an important focal point for the education of other laboratories, students and visiting scientists. To date, faculty from seven different departments/divisions are members of the current user pool. New areas are under development to directly impact patient care, notably in the area of nicotine addiction treatment. The scientific and technical expertise represented by the zebrafish faculty at Mayo represents an internationally recognized resource, with Stephen Ekker, Ph.D., serving as the Editor-in-Chief for the main journal in the field, *Zebrafish*. While maintaining a global reach, the Zebrafish Core Facility is the main local scientific resource for zebrafish expertise whose vision is fully aligned to the broader vision of delivering the world's best health care at Mayo Clinic.

Other Shared Resources

Animal Facilities

Thomas R Meier, DVM, MBA, Department Chair

The Department of Comparative Medicine/Laboratory oversees the animal care and use program and facilities at the Rochester campus of Mayo Clinic. The facilities meet all federal regulations and guidelines. Mayo Foundation is registered with the United States Department of Agriculture (41-R-0006) as an animal research facility and maintains a National Institutes of Health animal assurance statement (A3291-01) with the Office of Laboratory Animal Welfare. Mayo Clinic's campus in Rochester, Minnesota animal care and use programs have been reviewed and are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) #000717.

The Rochester campus houses four animal facilities in close proximity to its labs. There are three facilities in the downtown campus: Guggenheim Building (42,781 sq. ft.), Medical Sciences Building (13,713 sq. ft.), and the Stabile Building (13,232 sq. ft.). There is an animal facility in the Alfred Building (7,394 sq. ft.), which is within the Saint Mary's Hospital Complex one half mile from the downtown campus. There are also four animal support buildings at the Institute Hills property (34,181 sq. ft.).

The entire 20th floor of the Guggenheim Research Building at Mayo Clinic is devoted to the housing and health of mouse colonies. Four animals are housed per cage, with adequate food and

water provided by veterinary assistants under the direction of a full time veterinarian. Surgical suites are available adjacent to the animal quarters.

Most of Mayo's animal facilities are conventional; however, there are three rodent barriers and a biohazard suite in the Guggenheim Building. All facilities include cage washing facilities, procedural areas, necropsy rooms, and fully equipped survival surgery suites. Animals in all locations are observed on a daily basis. Five board-certified laboratory animal veterinarians (Diplomats of the American College of Laboratory Animal Medicine) oversee the animal care and use program. Veterinary care, including postoperative care, is provided by the veterinarians with the assistance of six full-time veterinary technologists. Animal husbandry is accomplished by 39 animal care technicians, who report to the facility supervisor.

Training:

In compliance with Federal regulations and accreditation standards, principal investigators, supervisors or allied health staff members who are listed on an animal protocol are required to:

1. Remain current with IACUC introductory training and Occupational Health and Safety training provided by Mayo Clinic's internal online learning system
2. Complete new species-specific training module(s) in the AALAS Learning Library by July 15, 2017

Investigators or any staff listed on a protocol, and new hires must complete all training requirement before protocol submission.

Mayo Clinic Libraries

Mayo Clinic is served by an integrated system of libraries, knowledge centers, and archives including extensive online resources and efficient delivery systems. The system includes the Mayo Digital Library of electronic resources accessible 24/7 at all institutional sites, and physical locations on the Florida, Rochester, and Arizona group practice campuses, and selected regional practices of the Mayo Clinic Health System.

Special collections include hospital-based patient libraries supporting the needs of hospitalized patients and their families; special knowledge centers serving the needs of students and faculty of Mayo Medical School and Mayo School of Health Sciences; and, archival collections illustrating and documenting the history of Mayo Clinic. Rare medical works (books from 1479; journals from 1665) of scholarly significance, first descriptions, and classic accounts as well as works which help explain the development of medicine are housed in the Mayo History of Medicine Library. The "Find a Library" tab on the website provides access to more details about Mayo libraries and knowledge centers including hours and distinguishing features.

Resources available to employees and students include a rich collection of digital and traditional resources networked throughout all Mayo sites. The collections cover the entirety of clinical medicine, nursing, biomedical research, medical humanities, and related fields including administration and management of healthcare. The Mayo library system contains an extensive collection of traditional journals and books totaling around 400,000 archival volumes. Mayo employees and students have access to approximately 4,490 electronic journals and over 2,020 electronic textbooks and finding tools. Desktop access on a 24/7 basis to the Mayo Digital Library is available at over 50,000 institutional workstations at all Mayo sites. The breadth and depth of these resources and their integration using common online management systems and a knowledge portal makes the Mayo Clinic Libraries among the most comprehensive in North America.

Mayo Clinic libraries are fully automated utilizing a variety of proprietary and in-house systems including database discovery tools, library and archives management systems, data driven web portal, faculty publication database (Mayo Authors Database), electronic document delivery system

(Celsus), automated current awareness system, subject guide system, and digital link resolver system. A conceptual diagram of library systems is available.

Services include traditional library services such as circulation, electronic document delivery, and interlibrary loan. A full range of training and staff-mediated services is also available: online database training, evidence-based medicine training, expert literature research for staff and students, consultation on online retrieval strategy, in-depth reference and consultation services, current literature alerting, and scanning services. Mayo libraries participate in regional and national interlibrary loan networks including the National Network of Libraries of Medicine and can obtain material not owned or licensed by a Mayo library from a variety of library collaborators and commercial sources.

The Mayo Clinic Library employs nearly 50 FTEs and has an annual budget approaching \$7 million. It holds over 337,000 volumes and a current collection of over 4,300 medical and scientific journals, in addition processing over 32,000 interlibrary loans each year. An on-line bibliographic search system, Mayo Search, is easily accessible and includes the complete MEDLINE database (from 1966), PubMed. In addition, the library provides over 2,500 E-Journals.