Biomedical Sciences Research Facilities Funding Program

2024 Report to the Minnesota State Legislature
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UNIVERSITY OF MINNESOTA

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Report to the Minnesota Legislature:

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OVERVIEW

The University of Minnesota has set its sights on becoming one of the top public research institutions in the world. Achieving this goal requires state-of-the-art biomedical research facilities that can support leading edge research and attract and retain top-tier research faculty.

To catalyze this effort, the University asked the State of Minnesota to create the Biomedical Facilities Authority as the mechanism to provide a predictable funding source for planning and building research facilities that, in turn, would allow the University to attract and retain the nation's top biomedical research talent.

The State established the $292 million Minnesota Biomedical Research Facilities Funding Program in 2008. This dedicated funding program provided appropriations by the State to the University for up to 75% of the costs to design and construct four new and expanded research buildings on the University's Twin Cities Campus, in the area known as the Biomedical Discovery District (BDD). The State's portion of this funding program is $219 million; while the University's portion is $73 million.

PROGRESS TO DATE

Project #1 – Expansion of the Center for Magnetic Resonance Research – Completed July 2010
Project #2 & #3 – Cancer Cardiovascular Research Facility – Completed July 2013
Project #4 – Microbiology Research Facility – Completed October 2015

These four projects comprise 422,000 gross square feet of new research space housing 130 faculty and 739 research support staff.

The Cancer-Cardiovascular research facility also includes 35,000 square feet of shared research commons and support spaces. These areas house common instrumentation and research processing and support facilities, which are available to researchers throughout the district and broader University community, including:

- University Imaging Center
- University Genomics Center
- Mouse Genetics
- Flow Cytometry
- Chronic, long term testing laboratories

In addition, several of the planning principles for the Biomedical Discovery District provided for connectivity and the development of a cohesive research community. This interconnected, collaborative research environment is able to leverage common shared support spaces and resources while allowing for unique opportunities to collaborate across fields and disciplines of research.

The district has now been connected end-to-end by skyway to further enhance and support the principle of cohesiveness and opportunities for collaboration.

Current Occupancy

	Principal Investigators	Research Associates / Staff / Post Doc / Students	Minnesota Biomedical Research Program Total
Cancer & Cardiovascular Research Building	67	423	490
Center for Magnetic Resonance Research	40	150	190
Microbiology Research Facility	23	136	159
District Support Staff		30	30
TOTAL	130	739	869

Summary Research Programs

Project # 1 – Center for Magnetic Resonance Research (CMRR)

The CMRR is focused on advancing methodologies and instrumentation for biomedical imaging using ultrahigh field magnetic resonance imaging (MRI) and spectroscopy. As an integral part of its mission, the CMRR also provides access to its unique instrumentation, technical expertise, and infrastructure through collaborations and service functions to enable the faculty, trainees and staff at the University of Minnesota and in the larger biomedical research community, to carry out basic biomedical, translational and clinical research. Examples of the current large-scale research projects being conducted by CMRR includes a focus on technological developments to usher in the next generation of MR instrumentation, data acquisition and image reconstruction methods, the use of these advanced technologies in biomedical research and clinical practice, as well as development of new biomedical applications that range from basic neuroscience research to translational clinical studies in the brain (e.g., improvements in Deep Brain Stimulation (DBS), ataxias etc.), biomedical studies in the organ systems of the human torso, and clinical and research studies in the human musculoskeletal system. The CMRR provides essential resources and synergistic activities to other UMN centers, including the Institute of Engineering in Medicine, Masonic Cancer Center, and Masonic Institute of the Developing Brain, as well as several departments within the Medical School (e.g., Departments of Radiology, Neurology, Neurosurgery, Urology, Medicine, Medical Physics, Dentistry, Psychiatry and Neuroscience,) and outside the Medical School (e.g. Mathematics, Electrical and Computer Engineering, Biomedical Engineering, Mechanical Engineering, Chemistry, Physics, and Psychology). There are currently more than 300 collaborators throughout the University supported by CMRR. In each of the past five years the CMRR has experienced steady growth made possible by the investments in infrastructure and resources from the State of Minnesota.

In 2022-2023, CMRR faculty and collaborators made major scientific advances related to MRI. Highlights include:

- Multiple CMRR faculty continue to make ground-breaking developments in neuroimaging, funded by numerous NIH grants, including a competitively renewed NIH's National Center for Biomedical Imaging and Bioengineering grant (P41), and 4 large grants funded under the national programmatic effort named the BRAIN (**B**rain **R**esearch through **A**dvancing **I**nnovative **N**eurotechnologies) Initiative (https://braininitiative.nih.gov). Developments accomplished in these large initiative alone include: 1) developing what is currently the highest magnetic field (10.5 Tesla) used for imaging humans; in the previous year, this effort accomplished new techniques and electronics for the 10.5 Tesla MRI system that will achieve the highest spatial resolution images ever of human brain connectivity and function; 2) award-winning technology called FREE that promises to reduce the expense, size, and infrastructure requirements of future clinical MRI scanners; and 3) novel physics-based AI algorithms that denoise and improve image resolution, while reducing the time needed to acquire the data.

- Conventional MRI scanners are seldom found away from urban hospitals due to their large size and extensive infrastructure requirements, including space to house a massive MRI magnet and its accessory hardware, and substantial electrical power and cooling sources. As such, access to this invaluable radiological imaging technique has remained mainly limited to metropolitan areas. The Garwood laboratory at the CMRR, together with collaborators from University of Sao Paulo (Brazil), Victoria University of Wellington (NZ), and Columbia and Yale Universities, have recently completed design and manufacture of a highly compact 0.7 Tesla MRI scanner for brain imaging via an NIH U01 grant. The 0.7 Tesla scanner's magnet is highly compact, excluding the patient's shoulders and allowing the patient to see through the side of the magnet. The very compact form of the magnet has been achieved by increasing the variation in magnetic field over the imaging volume from the few parts-per million (~100 Hz) usually found in clinical MRI scanners to several hundreds of ppm (~10,000 Hz). Necessarily, this scanner will only work with specialized MRI pulse sequences and reconstruction techniques compatible with a non-uniform magnetic field. To meet this challenge, the team developed broadband MRI techniques that create strong MRI signals despite a magnetic field with >10,000 Hz. The team is currently performing extensive tests of this radical new MRI scanner and hope to perform the first imaging of healthy participants in early 2024.

- In 2015, the Minnesota Legislature committed funding to the University of Minnesota Medical School to support the creation of Medical Discovery Teams (MDT) focused on tackling four major health concerns facing the state and nation. The teams were part of a recommendation by a commission appointed by Gov. Mark Dayton in 2014 to develop strategies for elevating the Medical School's national ranking. CMRR was awarded the MDT on Optical Imaging and Brain Science as a multi-disciplinary effort focused on mapping the detailed circuits that underlie sensation, perception and complex behaviors in the developing and mature brain. This 10-year, $30 million award focuses on a central vision within the BRAIN Initiative for the development of

new approaches (e.g., microscopes, lasers, scanning methodologies, new fluorescent probes etc.) to overcome the limitation of optical techniques and the development of new computational and theoretical methods to exploit such rich data. This combination of technologies would provide the ability to bridge the scales of organization going from individual neurons to the whole brain networks envisioned in the BRAIN Initiative. The combined neuroimaging would also provide a bridge to electrophysiological recordings carried out in clinical settings, such as in DBS (Deep Brain Stimulation) surgery and TMS (Transcranial Magnetic Stimulation).

- The MDT in Optical Imaging and Brain Science is located within CMRR and has added 2 new faculty members in the last 2 years (Drs. Madhuvanthi and Ganesh Vasan) bringing the total to 6 faculty members, 2 optical engineers, and 31 postdoctoral fellows, students, and lab staff. Construction of lab space in CMRR for the 2 new faculty members is on schedule to be completed by the end of 2023.

Three-year total research expenditures for investigators in CMRR have been $55.3M.

<u>Projects #2 & 3 – Cancer and Cardiovascular Research Building (CCRB)</u>

- Integrative Biology and Physiology (IBP) moved up the NIH rankings to #28 – breaking into the 20s of the Blue Ridge Rankings for the first time. Put another way, this NIH ranking per research faculty member is considered top tier nationally in the field.

- A new recruit into the space two years ago, Eric Batchelor received a five-year grant from NIH/NIGMS (R01GM149666) to study the tumor suppressor p53 and proto-oncogene MYC, which are regulators of two of the most important pathways in preventing the development of human malignancies. This project will examine how dynamic expression of p53 and MYC controls cell fate responses to DNA damage. The results will provide novel insight into the basic functioning of one of the most important stress response pathways in human cells, and are likely to inform innovative therapeutic strategies based on improved timing of the delivery of therapies.

- The Masonic Cancer Center (MCC), University of Minnesota is the only National Cancer Institute-designated Comprehensive Cancer Center in the Twin Cities, and is now in its 25th year of continuous support. To maintain this national designation, appropriate laboratory space must be available to the center to enhance the conduct of federally funded research. At MCC, funded cancer research continues to increase, with over $88.1M in direct cost cancer related research funding in the past year. The CCRB is one of two MCC directed laboratory research facilities. This building was originally designed to house two types of investigators; those with research focused on chemical synthesis and analysis and those with fundamental work in cancer biology. This unique laboratory space has led to substantial progress in several fields with some examples noted below:

- Irina Stepanov, PhD, is creating a new Shared Resource that builds upon the existing tobacco research capacity and world-renowned expertise at MCC. The Exposures and Effects Resource will support translational research ranging from the chemical analysis of tobacco products and their emissions to studies in cells and laboratory animals, to human trials of product use and innovative biomarkers of exposure and health outcomes. Development of a new, state-of-the-art Tobacco Product Testing Laboratory (TPT) and updates to the Tobacco Research programs space will allow for testing tobacco products and conducting in vitro and in vivo studies using advanced, specialized smoking machines and exposure systems.

- A multi-Investigator grant (P01CA138338) led by Stephen Hecht, PhD, was recently renewed by the National Cancer Institute for a third funding period. This long running project aims to develop tools to identify former smokers with increased lung cancer risk to target for increased lung cancer screenings. The continued success of this grant is directly due to the analytical biochemistry capabilities housed within CCRB.

- The laboratory of Lisa Peterson, PhD has been awarded a grant (U2CES026533) to serve as a resource for all studies performed in the Human Health Exposure Analysis Resource (HHEAR). The Targeted Analysis Resource will predominantly use high-throughput mass spectrometric methods with well-established quality-control procedures to provide timely and reliable quantitative data relevant to 3 major areas of importance to human health: Exposure to tobacco-specific compounds; exposure to environmental, lifestyle, and nutritional toxicants and carcinogens; and variations in levels of endogenous electrophiles and dietary compounds. This award was built on the expertise in measuring toxicant and carcinogen exposure in human biospecimens. This strength is based on the longstanding history of transdisciplinary collaboration among MCC members as well as the state-of-the-art Mass Spectrometry Lab in CCRB.

- The impact of environmental pollution on hematological cancer risk in MN is the subject of a new UG3 cancer cohort grant called the 10,000 Families Cohort: a new study to understand the environmental causes of cancer (UG3CA265791). Researchers Jen Poynter, PhD, Heather Nelson, PhD and Lisa Peterson, PhD received over $14M in funding to measure environmental exposures with carcinogenic potential for those living in MN, including PFAS, glyphosate (RoundUp), and radon. The impact of these exposures may be especially relevant for populations that have been typically underrepresented in existing cohort studies, such as individuals living in rural areas, racial/ethnic minorities, and immigrants. This study is open for enrollment through the MCC MNCCTN network, funded by state MN DRIVE support. Again, the longstanding expertise in measuring exposures and core facilities housed in CCRB led to this award, as did the strong transdisciplinary collaboration between population (Poynter, Nelson) and laboratory (Peterson) scientists. Exposure measurements take place in the Mass Spectrometry Lab in CCRB.

- The laboratory of Beau Webber, PhD moved to CCRB in 2023. His lab is focused on synergizing genome engineering, stem cell biology, and adoptive cellular therapy to develop novel treatments for genetic disease and cancer. His lab is well funded with research projects focusing on two pediatric bone cancers, Ewing sarcoma and Osteosarcoma. In collaboration with Branden Moriarity, PhD, he is currently testing an innovative approach to treating osteosarcoma using genetically engineered gamma delta T-cells, funded by a two-year grant from CURE Childhood Cancer. Dr. Webber was also recently awarded a five-year grant from the National Cancer Institute (R37CA276345) to study the molecular underpinnings of Ewing sarcoma, the second most common bone tumor in children and adolescents.

- The MCC's Genome Engineering Shared Resource (GESR) relocated into CCRB to be closer to the research community it primarily serves. This core facility provides state-of-the-art services in precision genome engineering of mammalian cell lines. The GESR can engineer human cell lines that allow MCC researchers to design mechanistic and therapeutic studies related to specific cancers. Access to these human cell lines and associated CRISPR/Cas9 technologies is critical for understanding the mechanisms of cancer and potentially for designing targeted therapies. The demand for genetically modified human cell lines is high, but genome engineering is technically challenging, time consuming, and demands a level of expertise not found in most clinical laboratories.

Lillehei Heart Institute (LHI)

The LHI was established in 1999 through philanthropic support from Kaye Lillehei, wife of the late Dr. C. Walton Lillehei ("Father of Open Heart Surgery"). The mission of the LHI is to discover novel strategies to improve cardiovascular health and reduce suffering from cardiovascular (CV) disease. To accomplish this mission, the LHI actively engages the entire University of Minnesota (UMN) community and fosters interdisciplinary collaborations to compete successfully for large grants, such as large multiple PI R01 grants, P or U series grants.

In the last 5 years, the LHI has witnessed a robust growth in membership and grant funding. Currently, the LHI has 131 members, spanning 10 Medical School Departments and 9 Colleges/Schools. In FY 2022, LHI faculty members held 125 grant awards, including 59 NIH and 5 DOD awards. These awards amounted to a total of >$48.8M (>$39.7M in direct costs and >$9.1M in indirect costs). Overall, the research portfolio of LHI faculty encompasses the entire spectrum of CV research domains: basic, clinical and translational, and population science. The LHI educational programs, including the LHI Summer Research Scholars program, ensure a pipeline of future physician-scientists and scientists to continue the tradition of excellence and innovation in CV research. On June 1, 2022, a new team assumed LHI leadership with the goal of steering the LHI to greater heights in fulfilling its potential of being an inclusive and integrated Medical School Center, Institute, or Program (CIP).

The LHI's new mission is active engagement of the UMN community to promote interdisciplinary collaborations that transcend traditional Departmental boundaries, as underscored by the following new priorities: (1) Broaden membership to include faculty from all Medical School Departments and other Colleges/Schools; (2) New organizational structure to effectively execute strategic plans; (3) Emphasize diversity, equity, and inclusion in all LHI activities; (4) Implement strategies to promote greater interdisciplinary collaborations among CIPs; (5) Emphasize interdisciplinary participation in educational activities (e.g., LHI lecture series); (6) Reorganize infrastructure cores to increase efficiency and utilization while fulfilling the needs of the Medical School community.

- Dr. Lin Yee Chen was appointed as the new Director of the LHI on June 1, 2022. Dr. Chen is a Professor of Medicine with tenure and holds the Fred C. and Katherine B. Andersen Foundation Chair in Adult Clinical Cardiology. Dr. Chen is a physician-scientist whose research has been continuously funded by the NIH or AHA since 2010. He is currently Principal Investigator of five active R01/RF1 grants and a K24 grant from the NIH. Two of his grants, RF1NS127266 and RF1NS135615, had a total grant award of $4.13 M and $4.39 M, respectively. He is an internationally recognized researcher in the areas of atrial fibrillation and atrial myopathy, and his work has been published in JAMA, Annals of Internal Medicine, JAMA Internal Medicine, Nature Genetics, Circulation, and other top-tier journals. He was elected to the American Society for Clinical Investigation in 2024. Since assuming the directorship of the LHI, Dr. Chen has implemented numerous new initiatives and programs to promote greater interdisciplinary collaborations such as pilot grant programs and joint scientific symposium between the LHI and other CIPs. He has also supported grant applications to facilitate the acquisition of state-of-the-art equipment that benefit investigators in the LHI and other CIPs. Dr. Chen works closely with the Vice Dean for Research to advance the mission of the LHI, which is to discover novel strategies to promote greater cardiovascular health and reduce suffering from cardiovascular disease.

- Dr. Sasha Prisco was recruited to the Cardiovascular Division and the LHI in 2023. Dr. Prisco is a cardiovascular physician-scientist who specializes in treating pulmonary hypertension. Her laboratory investigates mechanisms of right ventricular dysfunction in pulmonary hypertension. She received her M.D. and Ph.D. at the Medical College of Wisconsin and she completed her training in internal medicine and cardiovascular disease at the University of Minnesota through the Physician-Scientist Training Pathway. As a cardiology fellow, she secured a National Institutes of Health postdoctoral grant (NIH F32) and won early career investigator awards from the American Heart Association (AHA), American College of Cardiology, and Northwestern Cardiovascular Young Investigators' Forum. She recently received an AHA Career Development Award and a K23 grant from the National Heart, Lung and Blood Institute.

- Dr. Daniel Garry was awarded a Leducq International Network Center of Excellence Grant for his proposal, Exogenic and xenogenic pig organs for transplantation into humans. This is a prestigious $8M five-year award and is the first to be awarded to any program at the UMN. It started on January 1, 2024. This Network will be funded by the Leducq Foundation (for institutions based outside the U.S.) and the Leducq Foundation for Cardiovascular Research (for institutions based in the U.S.). The endorsement of this application by the Scientific Advisory

Committee is a statement of the committee's belief that Dr. Garry's proposed Network will make an important impact on the area of cardiovascular research through innovation in science, meaningful collaboration at the international level, and the active involvement of early career investigators in the research program. In addition to this award, Dr. Garry has a total of $5.98M in research expenditures over the past 3 fiscal years.

- Dr. Rita Perlingeiro is one of the most productive LHI principal investigators with research focused on the generation of skeletal myogenic progenitors from pluripotent stem (PS) cells and their application in regenerative medicine and *in vitro* disease modeling. By conditional expression of Pax3 or Pax7 in early unpatterned mesoderm, Dr. Perlingeiro's laboratory was the first to demonstrate functional improvement after transplantation of PS cell-derived myogenic progenitors in dystrophin-deficient mice (Nature Medicine, 2008). They have shown that this strategy also enables the generation of functional skeletal myogenic progenitors from human ES and induced PS (iPS) cells (Cell Stem Cell, 2012), and demonstrated proof-of-principle for combining patient-specific iPS cells with gene editing strategies (Molecular Therapy, 2019 and Cell Reports, 2021). Driven by an interest in developing strategies for the treatment of muscular dystrophies, they began addressing issues associated with scalability, purification (Cell Reports, 2017), and safety. Dr. Perlingeiro's lab recently submitted an IND application to the FDA requesting approval for a First-in-Human Phase 1 Safety/Dose Escalation Trial of iPS cell-derived skeletal myogenic progenitors for Duchenne Muscular Dystrophy (DMD) patients using intra-muscular injection. Between 2022 and 2023 Dr. Perlingeiro received 4 NIH grants to further advance the translation efforts, and has a total of $3.67M in research expenditures over the past 3 fiscal years.

Three-year total research expenditures for investigators in CCRB have been $168.5M, including $21.6M for the LHI.

<u>Project # 4 - Microbiology Research Facility (MRF)</u>

The Department of Microbiology and Immunology moved in January of 2016 from the Mayo Memorial Building into the 80,000 sq. ft. **Microbiology Research Facility (MRF)**, the fourth building in the Biomedical Discovery District (BDD), and the first building on campus to be designed and built using new "Smart Lab" technology to reduce energy costs.

The faculty in MRF share with other investigators in the BDD the objective to "pursue discoveries by bringing together talented investigators and encouraging them to work on the new cures and therapies for our most challenging and important health conditions." Department of Microbiology and Immunology faculty are the anchor tenants in MRF, but MRF, since its inception, has been home as well for the **Infectious Disease Corridor of Discovery (IDC)** whose mission is to understand the microbes and the diseases they cause as the foundations for discovering better ways to prevent, treat and cure infectious diseases with special emphasis on the great killers-HIV/AIDS/TB/influenza/ and other deadly bacterial, fungal and viral infections. That mission and vision is now at the center of the University of

Minnesota Institute on Infectious Diseases (UMIID) whose goal is to *create innovative solutions to emerging infections of epidemic or pandemic potential by bringing together UMN expertise across 20 departments and 8 colleges to discover better responses to pandemics, life-threatening infections, and antimicrobial resistance through basic, clinical, and translational research.*

MRF highlighted accomplishments over the past two years are the continued contributions, advances and commitments of the Department of Microbiology and Immunology and UMIID's shared goal of becoming a center renowned worldwide for its research on pandemics and life-threatening infections:

MRF IN THE TIME OF THE COVID-19 PANDEMIC AND BEYOND

During the peak of the COVID-19 pandemic and beyond, MRF, and MRF investigators, contributed substantially to the UMN response to the pandemic:

- Space in MRF was converted to process COVID-19 clinical samples for testing of a million diagnostic tests run on behalf of Minnesotans.
- MRF was used to create a COVID-19 biobank to support clinical and basic science research on COVID-19.
- Haase/Schacker Lab research identified causes and rationale treatment strategies for COVID-19 pneumonia.
- Langlois lab heads the Virology Core for the NIHs Midwest Antiviral Drug Discovery Center, funded by a $66M award from the National Institute of Allergies and Infectious Diseases (NAID) to identify and develop new drugs to target current and future pandemics.
- Langlois lab developed a new model to study how viruses cross species barriers which could help to inform how new viruses enter the human population.

CURING HIV/AIDS

Haase Lab

- Identified the first cell HIV infects and its role in HIV persistence during ART and viral rebound when treatment is interrupted

Schacker Lab

- Advanced HIV cure agenda by first ever studies of cell-based therapies to eradicate viral reservoirs
- Identified mechanisms of inflammatory tissue damage and immune dysregulation in treated HIV infection associated with depletion of CD4+ T helper cells
- Continued work on the role systemic inflammation plays in reducing efficacy of many vaccines

Skinner Lab

- Continued work on immune cell elimination of HIV from lymphoid tissue sanctuaries

Herschhorn Lab

- Continued work on optimizing HIV-antibody therapy for HIV infections

ANTIMICROBIAL RESISTANCE AND DRUG DISCOVERY

TB & MULTIDRUG RESISTANT BACTERIA

Baughn/Aldrich Labs

- Continued development of improved drugs to treat TB, including multidrug resistant TB

Willett Lab

- Continued discovery of new drug targets for multidrug resistant *Enterococcus and related bacteria*

DEADLY FUNGAL INFECTIONS

Nielsen/Boulware Labs

- Continued discovery of mechanisms of resistance and new drug targets in *Cryptococcal* meningitis

Selmecki Lab

- Conducted groundbreaking genetic studies of drug resistance in *Candida albicans* and *auris* with a long-range plan to prepare for and develop treatments

Three-year total research expenditures for investigators in MRF have been $120.1M.