CELEBRATING 20 YEARS OF COLLABORATION

MAYO CLINIC

EDUCATION, RESEARCH & INNOVATION PLATFORM
The relationship between Mayo Clinic and Sweden began in 1914, when Dr. William Mayo first visited Scandinavia. He and his brother, Dr. Charles Mayo, frequently hosted Swedish physicians in Rochester over the ensuing years. 

To honor Dr. William Mayo’s service to Sweden, he was named Commander of the Royal Order of the Northern Star by His Majesty the King of Sweden in 1937. In 1950, the Nobel Assembly at Karolinska Institutet selected Mayo staff member Dr. Philip S. Hench, Dr. Edward C. Kendall along with Swiss chemist Dr. Tadeus Reichstein to receive the Nobel Prize in Physiology or Medicine for the isolation of cortisone.

An annual research symposium began in 1994 between diabetes and metabolism investigators from the Mayo Clinic and the Karolinska Institutet. In 2011, Mayo Clinic and Karolinska Institutet signed an agreement that formalized and encouraged partnerships between the two institutions toward goals in research, education and innovation.

By 2014, this annual meeting has grown to include sessions in the areas of cancer, neurodegeneration, psychology and psychiatry, education, regenerative medicine, innovation, cardiovascular diseases, administration, autoimmune disorders, the science of health care delivery, diabetes and metabolism, and infectious disease.

Today, the Mayo Clinic - Karolinska Institutet relationship includes competitive opportunities for financial support, with funding provided by both institutions. Collaborative Travel Awards support individuals from Mayo Clinic who travel to Stockholm, Sweden, to work with collaborative partners. In turn, Mayo Clinic welcomes Karolinska Institutet travelers to Mayo Clinic’s three locations. Collaborative Project Awards provide competitive funds to Mayo Clinic-Karolinska Institutet collaborations to conduct joint research projects for up to one year, with the goal to be competitive in applying for future national or international research grants.

Grants and awards reflect proposals made jointly by teams representing each institution. Descriptions of current funded projects are found on the following pages.
**Polypolyscope: A novel pro-inflammatory and pro-coagulant biomarker**

Dr. Jeffrey Meuesuin, Linda Laiibertor, Dr. James S. Hernandez, Dr. Christine Snozek, Dr. Thomas Renni, Dr. Paolo Parni

Polypolyscope is a novel pro-coagulant platelet-derived mediator. This collaboration aims to establish polypolyscope as a prognostic cardiovascular biomarker. With mutual site visits to Mayo Clinic and Karolinska Institutet, the project established a new diagnostic assay for polypolyscope, analyzed polypolyscope as a predictive cardiovascular risk factor, and established the technology to analyze polypolyscope in patients, among other achievements.

The recipients write: “This program is an excellent approach to combine basic experimental science primarily located at Karolinska Institutet, and applied patient related science primarily at Mayo Clinic. It is the chance for researchers from both sides to learn from other experts, experience the atmosphere of another campus and to exchange knowledge.”

**Single-cell pharmacogenomics of metformin effects on cancer metabolism**

Dr. Quin Wilt, Dr. Mattias Rantalainen, Dr. Liewei Wang, Dr. Richard Weinshilboum

This study focuses on metformin, an anti-diabetic drug known for reducing cancer risk. Through sequencing hundreds of breast cancer cells and high throughput genome editing, the project aims to include metformin in therapy mechanisms and predict “driver” genes.

The recipients write: “This funding has acted as a nidus for collaboration and has spurred two further collaborations between Mayo Clinic, Karolinska Institutet and Oxford University...helping us make the best use of complementary strengths in domain knowledge, available technologies and modeling.”

**Preclinical evaluation of a synergistic nanomedicine combination treatment**

Dr. Debabrata Mukhopadhyay, Dr. Andreas Nyström

This project aims to develop therapeutic strategies that overcome drug delivery challenges facing pancreatic cancer treatment. The collaboration strives to bring therapeutic strategies to clinical practice.

The recipients write: “This is one of the few small seed funding opportunities available for Swedish and US collaborative efforts. As a result of this grant, we have secured national funding from STINT that can be used on both sides of the Atlantic, for research, travel and higher education.”

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**COLLABORATIVE PROJECT AWARD SUMMARIES**

**Human cell transplantation and genetically engineered pigs**

Dr. Scott Nyborg, Dr. Steven Strom, Dr. Eva Ellis

Epithelial-mesenchymal transition (EMT) is a trans-differentiation process that stimulates breast cancer progression and metastasis. This project aims to discover the role of Forkhead transcription factors in EMT. The collaboration produced data proving FoxP4 to be a regulator of EMT in breast cancer.

The recipients write: “The Collaborative Award program has driven our research project in directions that would not have been possible without its support. It has created personal interactions between Investigators at Karolinska Institutet and Mayo Clinic that will likely lead to other research projects.”

,*Genetic risk factors in the type I interferon signaling pathway in rheumatic muscle inflammation, myositis*

Dr. Ingrid E. Lundberg, Dr. Ann Reed, Dr. Leonid Padyukov, Dr. Miranda Houtman, Dr. Lina-Marcela Diaz

The hypothesis of this study is that large scale production of human hepatocytes is possible in models possessing a deficiency in the liver enzyme fumarylacetoacetate hydrolase (FAH-KO Pig). FAH deficiency provides a selective advantage to transplanted normal human cells under condition of fetal tolerance. The one-year project involved transplantation of human hepatocytes into two litters of FAH-KO pigs and assessment of donor cell engraftment and expansion in recipient pigs.

The recipients write: “Our experience with the Mayo Clinic-Karolinska Institutet Collaborative Award has been outstanding. This source of funding allowed us to do important studies toward our eventual goal of large-scale production of human hepatocytes in genetically engineered pigs.”

**Role of novel Forkhead transcription factors in coordinating the induction of EMT in breast cancer cells**

Dr. Jonas Rude, Dr. Derek Radisky, Dr. Joel Johansson, Dr. Laura Lambutt, Dr. Magdalena Cichon

The recipients write: “The Collaborative Award program has driven our research project in directions that would not have been possible without its support. It has created personal interactions between Investigators at Karolinska Institutet and Mayo Clinic that will likely lead to other research projects.”

**Structural and functional studies of the DNA damage response using new chemical probes**

Dr. Georges Mer, Dr. Nico Dantuma, Dr. Haico van Attikum, Dr. Stephen Frye

The recipients write: “We have been very pleased with this funding opportunity. It has helped us establish a new collaboration that will have value in a shared publication and constitutes a solid base for a long-term collaboration between Karolinska Institutet and Mayo.”

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**PROJECT AWARD SUMMARIES**
C9ORF72 is a common mutation carried by frontotemporal dementia patients. This project studies the pathology and genetics of the disorder and works to identify genetic modifiers of different pathologic proteins. Because this group created antibodies to proteins that are specific to C9ORF72, they are able to use pathology to discover a genetic mutation. This is remarkable in the study of neurodegenerative diseases.

The recipients write: “We are all very pleased with the Collaborative Award program. It has fostered collaboration not just between two principal investigators, but between students, technicians, post-doctoral fellows, and clinicians as well as geneticists and neuropathologists.”

The primary objective is to form an ongoing collaboration to study the DUB enzyme and its inhibitors in Waldenström's macroglobulinemia and other cancers.

This project studies hereditary tyrosinemia type I (HT 1) and fumarylacetoacetate hydrolase (FAH), which can cause severe problems in infants. The study models the metabolic liver disorder through PCR genotyping, FAH protein assays, histopathological analysis, blood analysis, and NTBC kinetics.

This project deciphers regenerative differences between undifferentiated and cardiopoietic human mesenchymal stem cells (hMSCs) in acute and chronic infarction models by comparing their metabolic activity, in vivo survival and regenerative capacity. The collaboration works to evaluate if implantation of cardiopoietic hMSCs into the left ventricle in patients with advanced heart failure treated with left ventricular assist devices (LVAD) is safe, improves myocardial function and functional capacity of patients.

The recipients write: “Broad background and expertise in the study of MSCs regenerative properties and regulation of cellular energy metabolism at the Center for Regenerative Medicine at Mayo Clinic, unique cell material and novel culturing protocols from the Karolinska Institutet lab, along with participants’ great motivation lead to enthusiastic teamwork.”

Investigation of b-AP15 (and its derivative VLX 1500) in preclinical models of Waldenström’s macroglobulinemia

Dr. Asher Chanan-Khan, Dr. Stig Linder

Fumarylacetoacetate hydrolase deficient pigs are a novel large animal model of metabolic liver disease

Dr. Raymond Hickey, Dr. Shennen Mao, Dr. Jamie Glorioso, Dr. Joseph Lillegard, Dr. James Fisher, Dr. Bruce Amiot, Dr. Per Olofsson, Dr. Cary Harding, Dr. Ronald Marler, Dr. Milton Finegold, Dr. Markus Grompe, Dr. Scott Nyberg

Cardiopoietic human mesenchymal stem cells (hMSC) for the treatment of heart failure

Dr. André Terzic, Dr. Clifford Folmes, Dr. Karl-Henrik Grinnemo, Dr. Ivana Bulatovic
This project was motivated by a previous Mayo Clinic/Karolinska Institutet project that focused on C9ORF72. The scientists at Karolinska Institutet are characterizing neuropathology with antibodies that are specific to a genetically linked neurodegenerative disease. The collaboration will continue and both institutional respective bio banks will be useful.

The recipient writes: “As a PhD student from Mayo Graduate School, being able to work with other researchers and immerse myself in another lab is a great experience. This grant was beneficial in fostering further exchange between brain banks at the two institutions.”

In attempts to individualize treatment for Bipolar disorder, the collaborative travel led to studies of pharmacological response and biological predictors of the disease.

The recipients write: “As experienced clinicians and researchers at Karolinska Institutet, it is great to collaborate with Mayo Clinic, a medical institution that has succeeded in integrating research with clinical practice. We found this collaboration and site visits to be stimulating and exciting.”

This collaboration studies the risk of impaired sleep in individuals with celiac disease. Collaborators examined cases before and after celiac disease diagnosis and are working to finalize the study. This research project has inspired future collaborations between Mayo and Karolinska Institutet within sleep medicine, pediatric gastroenterology, perinatal/life-course research and epigenetics.

The recipients write: “This award helped to orchestrate a research visit that was professional, inspiring and productive. We are confident that this visit will facilitate future research collaborations.”
With the opportunity to create an anatomy teaching space in the new Karolinska University Hospital, Dr. Jorgen Nordenstrom, head of the Clinical Anatomy Centre Project Team at Karolinska Institutet, traveled to Mayo Clinic to observe the Procedural Skills Laboratory functions, operations and innovations.

The recipients write: “The collaborative travel grant concept is a well-designed and well-executed program. With the exchange of ideas and best practices, visits were productive for both sides.”

This project is identifying small folded RNA inhibitors for each of hundreds of human transcription factor proteins. In order to perform simultaneously hundreds of in vitro selections at once, this collaboration adapted an RNA selection protocol of the Maher Lab to the high-throughput methodology of the Taipale Lab.

The recipient writes: “As a Mayo Graduate School PhD student, there are truly no words to describe the impact and importance of this travel experience and collaboration on my scientific development. Thanks to this opportunity, we were able to create a large library of RNA decoys, crucial to testing my PhD thesis hypothesis. The experience also fueled in me an unprecedented passion for science, fomented by my day-to-day interactions with my new colleagues.”

The project combines two powerful technologies, the Mayo wireless instantaneous neurochemical concentration sensing system (WINCS), Mayo Investigational Neuromodulation Control System (MINCS), and Karolinska Institutet’s organic electronic ion pump (OEIP), to generate a novel device to study the epidemiology and molecular epidemiologic investigation of gliomas: A Mayo Clinic – Karolinska Institutet collaboration.

The recipients write: “Travel Awards are essential for the development of meaningful collaborations between Mayo Clinic and Karolinska Institutet. The process worked particularly well for us because of our prior scientific connections.”

Surgeons often suffer from repetitive motion musculoskeletal conditions, such as shoulder disorders, that limit their ability to perform surgery. This study observes posture measurements to confirm instruments that could be used to help surgeons in the operating room.

The project aims to overcome drug delivery challenges in patients with advanced pancreatic cancer by creating a 3D in vitro drug screening system. The collaboration works on treating pancreatic cancer by using nano-medicine to develop the drug delivery system.

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With the use of an open label design with measurements of biomarkers, the collaboration works on identifying remedial actions of ketamine on depression and suicide.

The recipients write: “The collaboration has set up a clear division of tasks between the two sites. Site visits and meetings give the collaboration confidence.”

By combining Mayo Clinic and Karolinska Institutet technologies, the group is working to create a wireless controllable closed-loop system that delivers and detects neurotransmitters in the brain.

The recipients write: “The overall experience has been hugely successful and everything went smoothly from the beginning. It is exciting to see ideas that were formed during the visits at the partner institution take off into actual projects. There is really nothing more we could wish to gain from a travel grant.”

This collaboration focused initially on Cerebrovascular Disease. Mayo Clinic is working to join the Karolinska-led SITS stroke network and strives to take the role of SITS coordinator for the United States. The collaboration aims to make Sweden a participant in the CREST-2 carotid disease primary prevention trial.

The recipients write: “Prior to the interactions supported by the Mayo Clinic-Karolinska Institutet Collaborative Travel Award program, our capability to collaborate was limited in scope and our efforts were fragmented. The visit catalyzed concrete actions and will serve as an excellent foundation for short- and long-term accomplishments.”

Dr. Brigitte Twelkmeyer visited the Mayo Clinic Metabolomics Core to analyze ceramide content in plasma and muscle biopsies from samples from Copenhagen and Karolinska Institutet. The main goal when analyzing ceramide samples is to predict responders and non-responders to exercise.

The recipient writes: “I consider my stay very rewarding and I am thankful for the chance to visit Mayo Clinic. I had the opportunity to learn through troubleshooting with an experienced and creative specialist. Along with a jump in knowledge, this grant helped me to strengthen my professional relationships.”

This group develops individualized approaches to treat and evaluate alcoholism through collaborative research utilizing the expertise of each site. Lab experiments and clinical trials at Karolinska Institutet combined with genetic and pharmacogenetic research at Mayo Clinic help future projects study addiction phenomenology.

The recipients write: “This award allowed us to combine talents and expertise from each partner site. Bringing together the lab experiments and clinical trials at Karolinska Institutet and the genetic and pharmacogenetic research at Mayo Clinic is a unique and promising opportunity that will benefit the world of medicine.”
“This project would never have been attempted without the award funding our Mayo Clinic - Karolinska Institutet collaboration.”

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“The complementarity between Karolinska Institutet and Mayo Clinic is remarkable - Karolinska Institutet is a premier medical university and Mayo Clinic is a premier medical center.”

“This project grant was very stimulating and will serve as a starting point for broader collaboration...”