THE 2015-2016 COLLABORATION SUMMARIES

MAYO CLINIC

EDUCATION, RESEARCH & INNOVATION PLATFORM
Mayo Clinic + Karolinska Institutet

Mayo Clinic (MC) and Karolinska Institutet (KI) have enjoyed a remarkable 22-year collaboration that began with a small annual scientific meeting focused on diabetes and metabolism. A formal agreement was celebrated in 2011, and the collaboration has expanded to include many areas of shared scientific, academic, and clinical interest. In 2012, a joint competitive annual travel award program was initiated to promote short-term travel between institutions by faculty, staff, postdoctoral fellows and students to plan or conduct collaborative interactions during 2013. The following year, competitive project grants were added as a mechanism to build collaborative strength toward national or international project funding. In 2015, the awards program expanded to include funds for administrative projects. An annual joint conference alternates between Stockholm and Rochester. An updated agreement will be signed in 2016.
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<th>Year</th>
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<td>2013</td>
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Matti Sallberg (KI)
Michael A. Barry (MC)
Prime-boost strategies for vaccine against viral hepatitis to prevent development of cancer

In this project we are engineering adenoviral vaccines developed by Dr. Barry’s lab to carry hepatitis antigens engineered by Dr. Sallberg’s lab. It is through the KI visit in 2014 that we were able to begin our collaboration. This award generated an entirely new collaboration that weds a robust vaccine platform to a targeted application of vaccines clinically for hepatitis. This project allowed construction of three novel adenovirus vaccines against hepatitis C, a major contribution to achieving our project goals.

Anna Norrby-Teglund (KI)
Govindarajan Rajagopalan (MC)
Immunopathogenesis of community acquired methicillin resistant S. aureus (MRSA)

Methicillin-resistant Staphylococcus aureus causes more deaths in the U.S. than any other infectious disease, including HIV/AIDS. The ability of S. aureus to cause serious infections is due to the many toxins produced by these bacteria. At MC, we used animal models to understand the mechanisms by which these toxins cause disease. During the MC-KI meetings held at KI and then
at MC, our collaborators were able to meet and begin working together. In the short term, using the mouse model at MC, we were able to identify pathogenic strains of *S. aureus* that produce exotoxins. In the long term, we could use our mouse models to identify various pathogenic strains isolated in the clinic, understand their immunopathogenesis, and identify new therapeutic options or even vaccines. Thus, we were able to convincingly establish the robustness of our mouse models in understanding of the pathogenesis of diseases caused by *S. aureus*.

**Magnus Bäck, Tomas Jernberg, Lars Maegdefessel (KI)**

**Maurice Enriquez-Sarano, Jordan Miller (MC)**

The role of microRNA in valvular calcification and aortic stenosis

This collaboration aims to provide a platform of patient samples to optimize the outcomes of our studies of cardiovascular disease. In this project, we specifically study the role of non-coding RNA species as biomarkers and effectors in aortic valve calcification. The establishment of complementary cohorts using a variety of imaging techniques (CT, echocardiography) as well as complementary experimental methods (human valve samples and animal models) will allow common studies of specific targets, replication studies, and increased sample size for outcome studies. During this collaboration, we made the discovery of candidate microRNAs as biomarkers of aortic valve calcification, to be studied in large cohorts for their predictive and prognostic value. Presently, we plan a common study on other biomarkers of aortic valve disease. The MC-KI collaborative awards program has thus given us the opportunity to initiate a collaboration in the field of valvular heart disease. We envision that our common interests and complementary expertise will greatly enhance the possibilities for future discoveries in terms of both clinical and experimental research.

**Jens Frauenfeld, Pär Nordlund (KI)**

**Inna Ovsyannikova, Gregory Poland (MC)**

Application of nanotechnology for developing the next generation of influenza A/H5N1 peptide-based vaccine

The development of vaccines against pandemic influenza has become crucial to protecting the public health. The main objective of this study was to facilitate the delivery of the poorly soluble immunogenic influenza A/H5N1-derived peptides and to expand the understanding of immune responses of the peptides incorporated into the novel Saposin-lipoprotein (Salipro) nanoparticle system. The solubility and delivery aspects of the influenza A/H5N1 peptides, which can be used as a peptide-based vaccine, were the focus of the funded MC-KI collaboration. We have demonstrated that the solubility and delivery aspects of the influenza A/H5N1 peptides are important for the field of nanoparticle vaccines ("nanovaccinology"). This collaborative project would not have been possible without the MC-KI collaborative grant program. Thanks to this award, both institutions had the opportunity to evaluate the effectiveness of their inventions in helping people live healthier lives.
Ulrika Bergman, Thomas Hellday *(KI)*
John Bergquist, Gregory Gores, Mark Truty *(MC)*

*Targeting the non-oncogene addiction cancer phenotype utilizing MTH-1 inhibition in biliary tract malignancies*

Our project seeks to evaluate a novel chemotherapeutic agent in a rare disease utilizing patient tumors that are incubated in immunocompromised mice. Collaborators met at the 2014 MC-KI symposium in Rochester after Dr. Hellday’s keynote talk. Short-term outcomes include characterization of biliary tract patient-derived xenografts (PDX) from the Truty laboratory for MTH-1 expression using western blotting and immunohistochemistry. We have identified a cadre of PDX with varying levels of MTH-1 expression and are working to assess the effectiveness of MTH1 inhibition in these PDX. This has been an outstanding collaborative program that provided needed support to the early stages of our joint project.

Anders Arner *(KI)*
Frank Brozovich *(MC)*

*Vascular mechanisms in pulmonary arterial hypertension*

Pulmonary arterial hypertension (PAH) is a rare but incurable disease. Patients with PAH complain of shortness of breath, which is progressive and severely limits their activities. The cause of PAH is unknown, and this study proposed to develop techniques that would determine the defects in smooth muscle that result in this disease. We hope to create novel tools to investigate the mechanism for PAH. We have developed an adeno-associated virus and demonstrated that, after tail vein injection in the rat, the virus infects the small pulmonary arteries. This result is a proof of concept that gene therapy might be used to modulate protein expression in the lung vasculature. This will enable novel studies to determine the etiology of PAH, as well as novel therapies. This is an outstanding program to begin collaborative work.
Glutamate-NMDA receptor signaling in schizophrenia disorders

The molecular basis of schizophrenia (SCZ) is unknown. As observed in SCZ patients, we have first shown that exposure to the bacterial endotoxin lipopolysaccharide (LPS) increases kynurenic acid and cognitive deficits. Secondly, neuroproteomics of prefrontal cortex in G-protein coupled receptor kinase 3 null mice (Grk3-/-) identified key proteins associated with SCZ, which may lead to novel therapeutics. We are truly appreciative for this legacy collaboration. This research award furthers our understanding of SCZ as a debilitating disease, strengthened the scientific training of our students, and enhanced the research acumen of both institutions. We feel that the collaborative research award promotes collaboration toward our common mission of effectively helping our patients.

Channelopathies in irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common gut disorder, and 2-3% of patients appear to have mutations in the channel gene SCN5A. Ion channels are directly involved in the mechanisms of gut motility and also visceral pain, hence this project aimed at testing the potential role of channel genes in IBS predisposition. The channel gene TRPM8 (which encodes a nociceptor expressed in visceral afferent sensory neurons) showed significant GWAS association with IBS, and replication in independent cohorts with similar genetic risk effects. A trend for lower capsaicin pain response was observed in carriers of TRPM8 risk alleles. Results have been included in a manuscript.

Long-term collaboration plans include work on SCN5A and the (epi)genetic control of its expression by miRNA, and large-scale GWAS studies of IBS susceptibility where Mayo Genome Consortia data will be included. A broader project will involve data from Mayo Clinic and the Mayo Genome Consortia (using International Classification of Disease codes) shared with the KI team as part of a large-scale multi-center study on IBS predisposition (the bellygenes initiative) studying IBS genetic and phenotypic data in several hundred thousand Europeans.
Sophie Erhardt, Carl Sellgren, Lilly Schwieler (KI)
J. Blair Price, Shari Sutor, Mark Frye, Susannah Tye (MC)

*Ketamine reduces prefrontal kynurenine levels and increases mTOR signaling in an animal model of treatment resistant depression*

We developed a novel rodent model for treatment resistant depression combining stress hormone and inflammatory challenges. We then tested the efficacy of low dose ketamine (a rapid acting antidepressant) and quantified specific biomarkers (metabolic and inflammatory) associated with treatment response. Samples have been collected from patients in our clinical trial also to validate the translational utility of these biomarkers. We gained new information on the metabolic and inflammatory mechanisms through which ketamine elicits its rapid antidepressant actions. This is helping us to understand the optimal physiological state for ketamine efficacy. As we validate this work clinically, we hope to be able to more accurately predict and optimize treatment response in patients. As we move towards establishment of a ketamine clinic, we plan to utilize the data obtained in the current study to inform personalized approaches to patient care. We will extend this work to other emerging rapid acting antidepressant medications. These outcomes are particularly important for MC and KI as a high proportion of severely treatment resistant patients are served. The grant improved collaborations between our laboratories through student and faculty training, as well as accumulation of valuable data. Skills have been shared between lab personnel. This has helped to standardize our research approaches as we apply for joint funding. The collaboration involves training of two PhD students and one MD research student.

Ulrika Warpman Berglund, Thomas Helleday (KI)
Andrea Wahner Hendrickson, Rachel Hurley, Scott Kaufmann, S. John Weroha (MC)

*Evaluation of MTH1 inhibition in ovarian cancer*

Ovarian cancer is the most lethal of all gynecologic malignancies. MTH1 has been identified as a new anticancer target by the Helleday laboratory at KI. Using patient derived ovarian cancer xenografts, we assessed the efficacy of two MTH1 inhibitors in an effort to develop preclinical data that will support further study of this class of drugs in ovarian cancer. The MC-KI Collaborative Awards program allowed an MD-PhD student at MC to form a collaboration with an internationally recognized group at KI involved in DNA repair and targeted cancer therapies. This collaboration has allowed study of a novel cancer therapy in ovarian cancer with the goal of initiating clinical trials at MC.
Mayo Clinic-Karolinska Institutet

Steering Committee:

Pernilla Witte, Dr Jim Maher, Dr. Ulrika Widegren, Dr. Jan Andersson, Josh Derr, Dr. Anders Gustafsson, Dr. Martin Schalling, Dr. Eric Wieben, Dr. Sree Nair, Jacquelyn Gosse, and Julie Henry.
Susanna Lundström, Roman Zubarev (KI)  
David Barnidge, David Murray (MC)  

*Using high resolution mass spectrometry to isotype monoclonal immunoglobulins*

Our groups are developing and publishing better ways to diagnose patients with cancer and autoimmune diseases by measuring antibodies using mass spectrometry. We are developing an efficient way to combine the KI expertise in bottom-up immunoglobulin sequencing with MC expertise in top-down immunoglobulin analysis to create a new diagnostic approach to monitor cancer and autoimmune diseases. We initiated the next phase of the project using the methods we developed in our first collaboration to identify patients with high molecular mass lambda light chains. We are defining a new class of immunoglobulin kappa light chains that have not been described previously by gene sequencing techniques. The collaboration has been outstanding. We published the findings that resulted from our first travel grant and are continuing to interact to publish additional information stemming from our second travel grant. We are appreciative for this wonderful opportunity.
Ulrika Bergstrom, Ida Nilsson (KI)
Mark Frye, Leslie Sim (MC)

Novel mechanisms behind severe failure to thrive/avoidant restrictive food intake-mitochondrial dysfunction

Animal models of failure to thrive show reduced mitochondrial function. We now investigate mitochondrial function in children with failure to thrive. We have been able to structure and define which patients and controls are needed, which biospecimens will be used, and analysis methods. We had the opportunity to present KI knowledge and ideas at with MC colleagues, and vice versa, thus setting the stage for future collaborative work. Our scientific networks have greatly expanded. We obtained valuable input on new methods to identify mitochondrial dysfunction and identified crucial steps in the handling of biospecimens for our tests. The visit to MC was a very intensive, friendly and fruitful exchange.

Pontus Aspenström (KI)
Nisha Durand, Peter Storz (MC)

Elucidating the effects of PKD1-mediated phosphorylation of PIP5K1γ on focal adhesion dynamics and cell migration

Post-translational modifications are critical mechanisms by which cells regulate diverse biological processes from proliferation to migration. We studied how phosphorylation of the lipid kinase PIP5K1γ by PKD1 affects the turnover of focal adhesions and cell migration processes. During a 3-week initial visit, live cell imaging at KI was used to determine the migration trajectories of individual cells expressing PIP5K1γ.WT, PIP5K1γ.S448A or PIP5K1γ.S448D mutants. Preliminary data obtained from these initial experiments suggest that phosphorylation of PIP5K1γ by PKD1 is a likely mechanism by which the path and velocity of cell migration can be regulated. The project allowed Ms. Durand, a MC PhD student, to gain novel insights and findings at KI for her thesis project, and has greatly contributed to her development and training as a graduate student.
Jill Blomstrand, Åsa Garmager, Eva Gipperth, Riitta Ljungström (KI)

David M. Moertel (MC)

KI administrative leadership visit to MC

The purpose of the visit was to learn about MC organization of effective administrative support relevant for the new Biomedicum Research Building at KI. We sought to develop together a network for continuous exchange of experience between our respective institutional and departmental administrative organizations. The visit gave KI participants insight into the organization of the research activities at MC, including electronic systems supporting administration. A strong MC work environment and sustainability focus was found to permeate all activities. There was discussion on accounting for the entire life-cycle of a product when making purchases. As KI plans administrative services in Biomedicum, valuable input was obtained from MC. The concept of a Research Service Center with contact persons for different departments was attractive. Organizing research service into pre-award and post-award components was seen as logical. The teams will focus on finding the best processes and supporting them with templates and standard operating procedures. The goal of an electronic system with all the applications registered, the conditions registered for all financing bodies, and control mechanisms will be an outcome of the visit.

Volkan Özenci (KI)

Ritu Banerjee, Robin Patel (MC)

Rapid antimicrobial susceptibility testing of Gram-negative bacilli recovered from blood culture bottles

This program involved the clinical microbiology groups at MC and KI to promote educational exchange in clinical microbiology/infectious diseases and to develop a collaborative research proposal for submission for extramural funding. The experience from the visits resulted in planning to implement rapid clinical diagnostic methods. Medical education strategies were exchanged to assist KI in implementing new pedagogical strategies for the teaching of clinical microbiology at KI. The program was successful in meeting all preliminary collaborative goals.
Karin Moks, Pia Nerfeldt, Par Stjarne (KI)
EeeLN Buckarma, David Farley, Becca Gas, Nimesh Naik, T.K. Pandian (MC)

Novel surgical education and assessment methods for millennials

This was an interactive overview of surgical education and assessment at MC and KI. After developing better understanding of surgical education at KI, educators provided an overview of the teaching and assessing of MC residents. This led to wonderful interaction with Swedish educators and trainees, helping MC educators identify weaknesses from the external perspective. Collaborators at KI then better understood that a formal education curriculum could be enacted with minimal cost. We are hopeful that components of such a curriculum might slowly be introduced to trainees at KI. In addition, we believe new educational ideas can be shared between the organizations and future educational research can be collaborative. We are grateful for the wonderful opportunity the MC-KI travel award program provided us.

Ebba Carbonnier, Britta Steneberg, Kerstin Tham, Annika Östman Wernerson (KI)
Katrin Frimannsdottir, Mark Warner (MC)

Quality management exchange

Our collaboration seeks to develop a coherent Quality Management System, integrated with university healthcare, in order to realize KI’s Strategy 2018. The KI visitors sought to collaborate with and benchmark the MC integrated Quality Management System. KI perceives that MC sets a good example in integration of healthcare, research and education. The visit provided an opportunity to learn more about the MC Quality Management System. The award was a great opportunity to identify common areas where KI and MC can develop further. Our organizations are at different stages of development in the planning, steering and follow-up of research, education and healthcare. The teams noted that MC and KI have advanced and developed different areas, which creates opportunities. We are thankful for this award and look forward to the annual meeting in September in order to intensify our collaboration.
All photographs courtesy of Ulf Sirborn Photography, Stockholm, Sweden
Facilitating research collaboration between MC and KI – a biobank perspective

This project facilitates collaborations that leverage KI and MC biobanks and related infrastructure by addressing critical barriers to sample and data sharing and enhancing general communication and visibility of these biobanks among researchers. Short-term outcomes include increased visibility and understanding of our respective biobanks and the services they provide, recognition of how the biobanks can work in concert to support KI/MC research, and cross-referencing each other’s biobanking. We plan to continue collaboration while also disseminating learned information on resources and direct “match making” of researchers. Site visits between the two major biobank operations (MC-Rochester in April 2015, and KI in September 2015) revealed striking operational and conceptual similarities that make knowledge sharing easy. Each center has made significant advances in different areas, so that it became clear that continued interaction will benefit both infrastructures. This project was great way to facilitate collaboration between the two organizations. It provided the chance to initiate a valuable and rewarding collaboration. The project exceeded our expectations.
We are developing a collaborative platform to support joint grant applications and administration at the pre- and post-award stages. We are sharing knowledge and expertise in the support of joint grant applications to increase collaborative efforts. Our goal is to facilitate increased funding for researchers at both institutes by combining knowledge of international funding mechanisms through the NIH and the EU Horizon 2020 program. Much has been learned from this collaboration. We have developed long-term relationships and reference points for the future.