THE 2016-2017 COLLABORATION SUMMARIES

MAYO CLINIC

EDUCATION, RESEARCH & INNOVATION PLATFORM
PARTNERSHIP BACKGROUND

COVER: An inhibitor of the Karonudib family, here shown as a surface rendering (purple) bound to the MTH1 protein, is a first-in-class anti-cancer treatment developed by the Mayo Clinic (MC) - Karolinska Institutet (KI) collaboration. Joint MC-KI efforts demonstrate treatment efficacy in advanced ovarian cancer, cholangiocarcinoma and acute myeloid leukemia. The collaboration has unearthed a novel synergy between Karonudib and taxanes and efforts are under way to jointly translate this concept into a first-in-man clinical trial at the MC. See collaboration summary on page 8. Image credit: Evert Homan. Collaborators T. Helleday, S. Kaufmann, R. Hurley, A. Wahner Hendrickson. KI Innovations collaborated in the early development of MTH1 inhibitor intellectual property.
Mayo Clinic (MC) and Karolinska Institutet (KI) are continuing their remarkable 24-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 collaboration steering committee was formed, and a 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, annual 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. A Master Research Collaboration Agreement was signed in early 2017 and will remain in effect for five years. Also in 2016 a comprehensive independent program evaluation was completed by experts from MC and KI. This evaluation report identified the MC-KI collaboration as a remarkably successful model of international synergy and productivity.
RECENT MILESTONES
2013
060 MC attendees at annual meeting in Stockholm
300 Total attendees
013 MC travelers at KI funded by travel awards
009 KI travelers at MC funded by travel awards

2014
059 KI attendees at annual meeting in Rochester
330 Total attendees
011 MC travelers at KI funded by project + travel awards
009 KI travelers at MC funded by project + travel awards

2015
140 MC attendees at annual meeting in Stockholm
400 Total attendees
025 MC travelers at KI funded by project + travel awards
021 KI travelers at MC funded by project + travel awards
016 Stockholm County Council leaders at MC on Stockholm Health Care Senior Executive Study Tour

2016
080 KI attendees at annual meeting in Rochester
350 Total attendees
015 MC travelers at KI funded by project + travel awards
018 KI travelers at MC funded by project + travel awards

2017
110 MC attendees anticipated at annual meeting in Stockholm
300 total attendees anticipated
021 MC travelers at KI funded by project + travel awards
013 KI travelers at MC funded by project + travel awards

NOTES:

2016-2017 RECENT MILESTONES
Structure-Function Analysis of the Measles Virus Fusion Apparatus

Chanakha Navaratnarajah and Roberto Cattaneo (MC), Mathilda Sjöberg and Gunilla Karlsson Hedestam (KI)

This collaboration seeks to understand how measles virus enters cells. The team collects high-resolution structural information on the hemagglutinin and the fusion proteins that constitute the viral membrane fusion apparatus. This fundamental knowledge illuminates the detailed mechanism of measles infection.

Targeting the Non-Oncogene Addiction Cancer Phenotype Utilizing MTH1 Inhibition in Biliary Tract Malignancies

John Bergquist, Matthew Hernandez, Gregory Gores, Mark Truty (MC), Thomas Helleday, Ulrika Warpman-Berglund (KI)

This project evaluated a novel chemotherapeutic agent in a rare disease by utilizing patient tumors grown in immunocompromised mice. This team’s work continues in a 2017 project grant.

Phenotypic Study of Plaque-Resident Smc in The Pathogenesis of Human Atherosclerosis: Characterization of IL-1 Signaling and Clinical Relevance in Human Atherosclerosis

Feilong Wang, Joerg Herrmann (MC), Xintong Jiang, Zhongqun Yan, Göran K. Hansson (KI)

This research initiative identified a new immune subtype of vessel wall smooth muscle cells and characterized their functional role in atherosclerosis, the arterial disease process leading to acute myocardial infarction and stroke. The team further investigated the role of a specific inflammatory molecule, IL-1, in atherosclerosis.

SWECAP: Ultrasound Shear Wave Elastography for Characterization of Atherosclerotic Plaque Vulnerability

Matthew W. Urban, Carolina Amador, Ivan Z. Nenadic, Sara Aristizabal, Dan Dragomir Daescu, Kent Carlson (MC), Matilda Larsson, Erik Widman, Elira Maksuti, David Larsson (KI/KTH Royal Institute of Technology), Kenneth Caidahl (KI)

This project used ultrasound shear wave elastography to characterize atherosclerotic plaques through new numerical and experimental techniques and protocols. The successful ongoing collaboration has resulted in four peer-reviewed publications, three conference proceedings, and five meeting abstracts.

Epigenetic Glutamate Dysregulation in Rapid Cycling Bipolar Disorder: Development of Biomarkers

Marin Veldic, Mark Frye, Doo-Sup Choi, Sun Choi, Kathryn Wininger, Yun-Fang Jia (MC), Catharina Lavebratt, Martin Schalling, Vincent Millischer (KI)

This team’s research is aimed at the development of biomarkers for early diagnosis and individualized treatment of bipolar disorder with rapid cycling, characterized by increased rates of suicide and addiction.

Brain-Derived Neurotrophic Factor (BDNF) Promoters I and IX Methylation Patterns In Early Onset Bipolar Disorder Patients: Methylation Markers at Age of Onset and Interaction with Val66Met Variants

Malik Nassan, Mark Frye, Joanna Biernacka, Marin Veldic, Euijung Ryu (MC), Claudio D’Addario, Lars Terenius, Vladana Vukojevic, Vlad Radoi (KI)

This team studied the association between BDNF genes and early onset bipolar disorder at the genetic and epigenetic levels to understand the interaction between the Val66Met genetic variant and BDNF DNA methylation.

Electrophysiological Biomarkers of Epilepsy

Brian Lundstrom, Greg Worrell (MC), Gerald Cooray, Martin Ingvar, Daniel Lundqvist (KI)

One of the principal challenges in epilepsy surgery is precisely localizing epileptic tissue. The goal of this collaborative research was to develop non-invasive electrophysiological biomarkers for spatial localization of the epileptic cortex. Magnetoencephalography (MEG) offers an attractive modality due to its high spatial resolution and ability to obtain control data from healthy humans. This project combined expertise in MEG at KI with expertise in high frequency EEG biomarkers at MC.
Focal Inflammation and Dopamine Neurotransmission: Mechanisms and Markers of Deep Brain Stimulation Antidepressant Action

Susannah Tye, Mark Frye, Malik Nassan, Luis Lujan, James Trevathen (MC), Lilly Schwieler, Sophie Erhardt, Rajas Kale, Cecilia He (KI)

This project investigated the role of inflammation and dopamine neurotransmission in the antidepressant actions of deep brain stimulation (DBS). This work helped the team develop new insights into the acute early mechanisms of DBS action in psychiatric disease, including the potential for therapeutic neuromodulation approaches to be augmented by pharmacology. Using this information, the collaborators hope to optimize DBS treatment approaches for depression.

Expanding the Role of MTH1 Inhibition in the Treatment of Platinum-Resistant Ovarian Cancer

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

Ovarian cancer is the most lethal gynecologic malignancy, often undetected until the cancer has spread. These collaborators are studying new kinds of chemotherapeutic drugs of the Karonudib family, developed in the Helleday lab at KI. These drugs inhibit the MTH1 enzyme, responsible for removing 8-oxoguanine (an oxidative damage product) from the pool of DNA precursors. Oxidative damage is prevalent in tumor cells, making such cells more vulnerable to MTH1 inhibition. This work assesses biomarkers from ovarian cancer cell lines and animal models that will guide a phase I clinical trial of Karonudib. KI Innovations collaborated in the early development of MTH1 inhibitor intellectual property.

Prime-Boost Strategies for Vaccines Against Viral Hepatitis to Prevent Development of Cancer

Michael Barry (MC), Matti Sällberg (KI)

The hepatitis B, C, and D viruses (HBV/HCV/HDV) are major global causes of chronic liver disease. Almost 2 billion people have been infected. HCV is the major cause for liver transplantation in the western world, and there is no effective therapy for HDV. For these three viruses there is a great need for vaccines. For HCV, new therapies have been introduced with a >90% cure rate, but currently cost almost

Novel Pharmacological Interventions for Critical Illness Myopathy

James Kirkland (MC), Lars Larsson (KI)

Critical illness myopathy (CIM) is a devastating, often fatal condition that occurs after a period of immobility, such as experienced during intensive care unit (ICU) admissions. CIM is a cause for increased length of stay and health costs at both MC and KI. Older age and muscle wasting are the two factors that most strongly predict mortality and morbidity in the ICU. At KI, an innovative rat model recapitulating ICU-related CIM has been developed. The goal of this pilot grant was to test the therapeutic potential of senolytic drugs in CIM.

Our collaborators were exceptional. They had a wide range of skills and were exceedingly generous with their time, expertise and resources. It was eye-opening to learn about how a different country and a different healthcare system approach the problems we all share.
I really appreciate this program! It has led to increased collaboration between administrators and a better understanding of our separate processes and demands – all setting the foundation for great service to great research.

The Collaborative Awards program allowed us to compare resident training at MC and KI. This experience will help us develop efficient training for the next generation of residents, to compensate for repetitions lost due to reduced work hours. This will be done by more structured training at simulation centers and access to online education and testing.
The direct and indirect costs of schizophrenia in terms of yearly healthcare and production losses are estimated to be 94 billion euros in Europe and $70 billion in the US. Understanding the neurobiological causes of schizophrenia is critical for development of improved therapeutics. Towards this goal, a collaborative effort was initiated at the 2015 annual MC-KI conference, leading to a 2016 collaborative travel award funded by the MC-KI partnership steering committee to support work by Drs. Doo-Sup Choi (MC) and Sophie Erhardt (KI). Through the work of Mayo Graduate School PhD student Alfredo Oliveros at both campuses, the team investigated the role played by glutamate signaling in the observed cognitive deficits associated with schizophrenia. The current understanding of this disease suggests neuroinflammation as a potential causative factor. Through implementation of neuroinflammatory models, the collaborative team furthered the understanding of the neurobiology underlying psychosis (1) and cognitive deficits (2). Importantly, these exciting findings have spurred a translational whole genome sequencing approach (3) to identify and confirm novel protein biomarkers from peripheral blood mononuclear cells in cerebrospinal fluid of patients with first episode psychosis. These Swedish patients were recruited by the KI Schizophrenia Project. By building on the existing MC-KI collaboration, the overarching collaborative goal is to establish functional genome-to-proteome molecular profiles that will enhance diagnostic clarity in order to provide meaningful individualized treatment.

REFERENCES


2016 TRAVEL AWARD SUMMARIES
**ADAPT (ADHD Medication and Predictors of Treatment Outcome)**

Jyoti Bhagia (MC), Linda Halldner Henriksson (KI)

These researchers aimed to identify which children have benefited from attention deficit hyperactivity disorder (ADHD) medicines. The team mapped symptoms, side-effects and predictors of treatment outcome in patients in the clinical setting. The travel award enabled reciprocal visits at the study sites to identify similarities and differences in the clinical/institutional setting that served as facilitators and/or obstacles to conduct the replicative ADAPT study.

**Learning From Each Other: Reviewing Quality of In-Hospital Deaths as an Indicator of End-Of-Life (EOL) Care - A Comparison Between MC Hospitals and Karolinska University Hospital**

Maria I. Lapid, Elise C. Carey, (MC) Carol Tishelman, Caroline Westerlund (KI)

Both the U.S. and Sweden have similar in-hospital death rates but different strategies for reducing in-hospital deaths and improving EOL care. The team learned about quality of care for hospitalized dying patients in each country, and identified opportunities to improve EOL care.

**Development of “teaching, assessing and remediating” for residents at Karolinska University Hospital and KI in collaboration with the FIRST team at MC**

David Farley, Daniel Price, James Colletti, Kharmene Sunga (MC), Pia Nerfeldt, Karin Moks, Viktorija Matulevičienė Anāņiņa, Björn Eriksson (KI)

This project sought to improve surgical and theoretical skills for residents in surgical specialties by extending and validating didactic principles developed by the FIRST team at MC. A training program inspired by the FIRST team began for ear, nose and throat residents at KI in the spring of 2017.

**The Role of the Gut Microbiome in the Progression of Liver Cirrhosis: A Research and Educational Collaborative Project**

Lewis Roberts (MC), Amelie Plymouth (KI)

This team jointly studied molecular mechanisms causing liver cancer, the sixth most common cancer worldwide and the second most common cause of death from cancer. The travel grant enabled a strong collaborative link that will facilitate future educational and research exchanges.

**Investigating the Combinatorial Effect of the p53 Stabilizer, Apr-264, with the Cell Cycle Regulator, Seliciclib, as a Novel Treatment Option for Melanoma**

Antoneicka Harris (MC), Rainer Tuominen, Johan Hansson (MC)

MC PhD student Antoneicka Harris visited Sweden to collaborate on determining which single-agent drug concentrations would be optimal. This work will facilitate future combinatorial drug therapy in KI experimental models.

**Strategy benchmark exercise: KI Innovation Office and MC Office of Translation to Practice and Drug Discovery**

Richard Cowburn (KI), Andrew D. Badley, Clark C. Otley (MC)

The purpose of this travel award was to learn and share best practices related to the ways that KI, MC Ventures, and the Office of Translation to Practice execute drug and product development activities in partnership with pharmaceutical and biobusiness companies. The team also studied and compared technology transfer and innovation support at the two institutions.

**Preconditioning Strategies in Hepatocyte Transplantation**

Bruce Amiot, Scott Nyberg (MC), Ahmad Karadagi, Ewa Ellis (KI)

The goal of this research was to initiate a broader collaboration concerning large-scale isolation of hepatocytes with oxygenation, and large-scale production of cell spheroids for potential transplantation. The team initiated a long-term collaboration involving large-animal studies and translation toward clinical use.

**Vaginal Bromocriptine for Medical Management of Uterine Adenomyosis**

Johanna Andersson (KI), Elisabeth Stewart (MC)

Adenomyosis is a disease that causes heavy menstrual bleedings and pain. This team enrolled patients from both MC and KI, treated them with vaginal medication for six months, and monitored symptom reduction.

Members of my host lab cared about my well-being and looked after me when needed. My visit to KI corresponded to a lovely season rich in Swedish academic culture and traditions. I was able to participate!
Legal, Contractual and Compliance Issues Related to Joint Projects Between KI and MC

Virginia “Nickie” Bruce And Legal Contract Administration colleagues (MC), Cecilia Martinsson Björkdahl (KI)

This project enabled the awardees to meet and discuss how their respective administrative processes and procedures could be improved and streamlined to facilitate research collaborations between MC and KI, in particular, the five-year Master Agreement.

Enhancing KI - MC Research Interaction with Harmonized Biobank Lims Systems

Corey Carlson, Jodie Ice, Stephen Thibodeau, Joshua Spencer, Mine Cicek (MC), Rafat Samara, Mark Divers, James Thompson, (KI)

A key observation from this project involved semi-automated sample intake and accessioning processes at KI. If implemented at MC, such improvements could bring key benefits.

Interprofessional Education: Faculty Development and Clinical Training

Heather A. Billings, Suzanne M. Norby (MC), Eva Broberger, Ewa Ehrenborg, Margaretha Forsberg-Larm, Tanja Tomson (KI)

To advance interprofessional education (IPE) programming at MC, an IPE faculty development workshop was facilitated and assessment tools were created to provide foundational context and opportunities for IPE across the institution. Evaluation of this program has led to the development of multiple pilot projects modeled after successful KI initiatives.