CMM News

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Newly identified group of immune cells that protect the aging brain

In a recent study published in *Nature Communications* **researchers from CMM discovered a unique subgroup of microglia cells enriched in the aging mouse brain. Augmenting the number of these cells in a mouse model of neuroinflammation resulted in reduced neurological disability. The results present a potential treatment target for age-associated neuroinflammatory diseases, such as progressive multiple sclerosis.**

Microglia are a type of cells found throughout the brain and spinal cord and they act as a first line of immune defense specific for the central nervous system.

"By characterizing cell populations in genetically modified mice under both healthy and neuroinflammatory conditions, we identified a previously undescribed subgroup of microglial cells that was more prominent in aging mice", says Rasmus Berglund, postdoc in Maja Jagodic's CMM Group, and first author of the study.

The researchers found that these cells are dependent on the signaling molecule interleukin-34 (IL-34) and on the cellular process known as autophagy, which is crucial for adapting to metabolic and immunological changes and signals. Further characterization of this microglia subpopulation revealed heightened levels of inflammation-associated markers which are common in various neurological diseases.

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"When we deleted Ulk1 in microglia, a gene that is crucial for the autophagy process, we could show a reduction of this specific cell population in the central nervous system of aged mice", Rasmus Berglund continues.

Interestingly, when the mice were exposed autoimmune neuroinflammation, the reduction in these microglia correlated with an increased mortality. Conversely, augmenting the number of these microglia by stimulating them with IL-34 mitigated the impact of neuroinflammation, reducing neurological disability in the mice. This implies a positive role for these inflammatory cells in promoting health.

> The findings present a promising treatment option through bolstering this microglia population in age-associated neuroinflammatory diseases.

These findings present a promising treatment option for bolstering the microglia population in age-associated neuroinflammatory diseases, such as progressive multiple sclerosis, which currently lack viable treatment alternatives.

To validate their research in connection with human disease, Rasmus Berglund and colleagues will study cytokine profiles in cerebrospinal fluids and analyze post-mortem brain tissue. They are also launching a project to create a drug screening pipeline using stem cell-derived microglia from both healthy donors and people with multiple sclerosis. Their aim is to identify compounds that improve the health-promoting capacity of microglia and find biomarkers linked to this improved state for better prognosis. By doing this, they hope to advance our understanding of multiple sclerosis as well as other age-associated neurological diseases.

Rasmus Berglund

Publication: Berglund R, Cheng Y, Piket E, Z Adzemovic M, Zeitelhofer M, Olsson T, Ortlieb Guerreiro-Cacais A, Jagodic M. The aging mouse CNS is protected by an autophagy-dependent microglia population promoted by IL-34. *Nat Commun*. 2024 Jan 9;15(1):383. doi: 10.1038/s41467-023-44556-6.

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Funding and Grants

Swedish Cancer Society Grants

Five researchers from CMM were awarded grants from the Swedish Cancer Society (Cancerfonden). The grants were published in November 2023.

Hanna Brauner: Cutaneous lymphoma – clinical and experimental studies on disease mechanisms, prognostic factors and effects of treatment, SEK 2 400 000.

Alexander Espinosa: A new IL8-humanized mouse model to dissect the role of IL8 in cancer. SEK 2 400 000.

Gunnar Nilsson: Studies of systemic mastocytosis – from cellular and molecular alterations to biomarkers for diagnosis, SEK 4 500 000.

Fredrik Wermeling: Molecular studies of cancer – understanding the evolution of drug resistance and identifying novel drug targets, SEK 3 000 000.

Ning Xu Landén: Erasure radiation memory of skin cells to treat adverse skin reactions of radiotherapy, SEK 1 600 000.
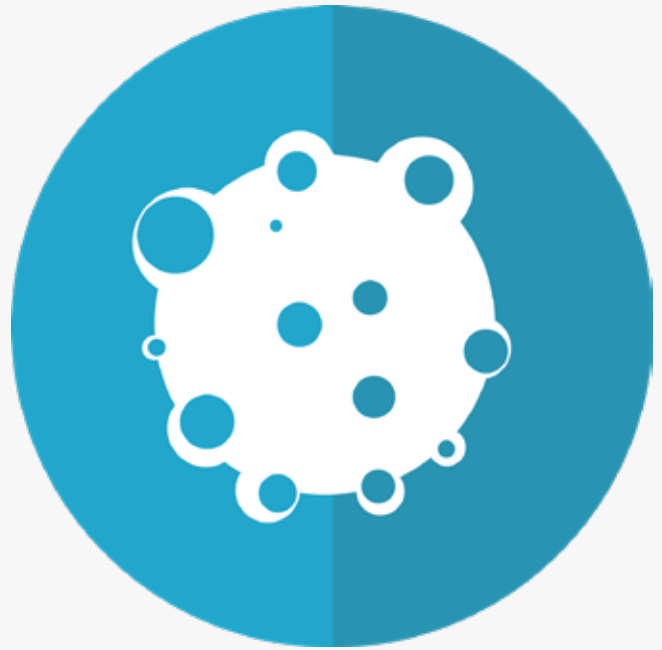
Swedish Research Council international postdoc
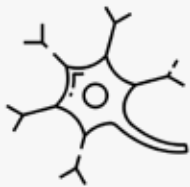
Ana Coehlo in Stephen Malin's lab received an international postdoc grant from the Swedish Research Council (VR). Based in Stephen's lab, she will do her postdoc in at Icahn School of Medicine, NYU, NYC with Fil Swirski on the neuro-immune basis of stress responses in rheumatic diseases.

Funding for studies of T cells in rheumatic diseases

Ravi Kumar received 500 000 SEK from Åke Wibergs Stiftelse and 75 000 SEK from Tore Nilsons Stiftelse för Medicinsk Forskning for the project titled 'Signatures of autoreactive T cells in autoimmune rheumatic diseases: towards patient directed therapies'.

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The Leo Hanke Team

NEW CMM TEAM

The Hanke Team is broadly interested in viral infections and develops innovative strategies for prevention and treatment. The team is part of the Division of Infectious Diseases, headed by Anna Färnert, who is also a CMM group leader.

The interdisciplinary research in the Hanke Team spans virology, immunobiology, structural biology, computational methods, and protein biochemistry. We prioritize emerging and re-emerging RNA viruses that present significant outbreak and pandemic risks, such as Hendra, Nipah, and Lassa virus. Our approach involves the use of alpaca-derived single-domain antibody fragments (also called nanobodies) and computational 'de novo' designed protein binders to inhibit or force virus-host interactions. By elucidating the mechanistic and structural basis of these interactions, we aim to rationally design better antiviral strategies. This includes the targeting of cryptic epitopes or the recruitment of specific immune effectors. Besides advancing antiviral therapies, our work has implications for vaccine antigen design and stabilization.

You can find us on the 7th floor (J7:20) of the BioClinicum building. Please come visit if you want to learn more about the techniques we use. We are especially interested in expanding our approach also to other fields, such as cancer, in the coming years.

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Leo Hanke

Leo performed his PhD work in Hidde Ploegh's lab at the Whitehead Institute for Biomedical Research/MIT in Cambridge, MA, where he used alpaca-derived single-domain antibody fragments (nanobodies) to inhibit and study RNA viruses. In 2017, Leo joined Karolinska Institutet and established a nanobody discovery platform. In 2020 he published one of the first SARS-CoV-2 neutralizing nanobodies and later one of the most comprehensive SARS-CoV-2-specific nanobody collections. He was involved in many early SARS-CoV-2 vaccine and antibody studies. He was appointed Assistant Professor and joined CMM in 2022 and became a CMM Team Leader in 2023.

Mirte Pascha

Mirte is a molecular virologist who defended her PhD at Utrecht University in February 2024. In her thesis work, Mirte focused on inhibitors of influenza A virus entry and influenza neuraminidase vaccines. She is an expert in cell-based reporter assays that help elucidate the mechanism of action of novel antivirals. In her postdoc, Mirte will exploit rarely targeted epitopes for antiviral intervention and therapy, with a focus on Lassa virus.

Carl Johan Hagströmer
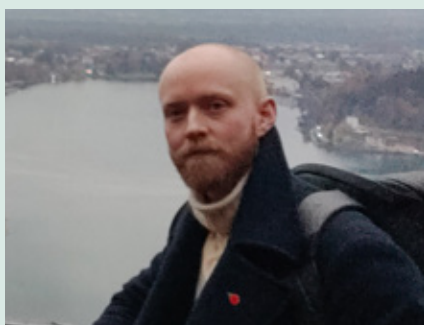
Carl Johan is a postdoc and structural biologist. He received his PhD from Lund University in 2023, focusing on the structural and functional aspects of aquaporins. In the Hanke lab, he continues his interest in dynamic membrane proteins with a focus on the structure and function of viral glycoproteins using cryoEM. His current favorite proteins are the attachment and fusion proteins of Hendra and Nipah viruses, of course in complex with nanobodies.

Avadhoot Jadhav

Avadhoot is a first-year PhD student with a master's degree from the Indian Institute for Science Education and Research (IISER) in Pune. Avadhoot is interested in using a synthetic approach to recruit immune effector function to virus-infected cells. He uses deep-learning based protein design to create novel protein fusions and study the activation of immunoglobulin effector functions. With his work, he aims to provide a new perspective on immune effector functions that will guide the development of future immunotherapies, not only against pathogens.

William Purba and Julius Lingnau

William Purba

Julius Lingnau

William and Julius are master student's from Radboud University, The Netherlands, and the University of Bonn, Germany, respectively. Williams is working on computationally *de novo* designed replication inhibitors of the influenza A virus to identify new possible targets for effective inhibition. Julius combines computational structure prediction and biochemical assays to map epitopes of nanobodies targeting Hendra and Nipah viruses.

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New CMMers

MARIE WAHREN-HERLENIUS´ GROUP

Dr Grégoire Martin de Frémont is a freshly registered PhD student in Marie Wahren-Herlenius´group. After an initial MD training in Lille (France) and international experiences in London and Boston, he specialized as a MD in Immuno-Rheumatology in Paris in 2017. On top of his Immunology-centered clinical training, he completed the Pasteur Institute's Advanced Immunology MSc in 2021. His two main fields of interest are immune mediated inflammatory diseases especially in the setting of pregnancy as illustrated by his research on pregnancies in women with Sjögren's disease (Lancet Rheumatology 2023), and immuno-hematology, as shown by his training and previous publications. His PhD research focuses on the pathogenesis and epidemiology of congenital atrioventricular blocks in newborns from mothers with anti-SSA antibodies. During this project supervised by Prof Wahren-Herlenius, the group will collaborate with Prof. Gaetane Nocturne (co-supervisor - Prof Xavier Mariette´s group, Immuno-Rheumatology, APHP, France).

HANNA BRAUNER'S GROUP
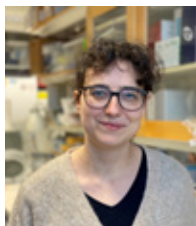
Berenice Fischer is a new postdoc in the team of Hanna Brauner. Berenice did her PhD on lymphomagenesis at the Institute for Research in Biomedicine, Bellinzona, Switzerland. She will focus on experimental studies of the immune pathogenesis of cutaneous lymphoma.

Despoina Tsakona is a new master student in the team of Hanna Brauner. Despoina will perform a master project during spring 2024, and will investigate how SAMHD1 impacts the interactions between cutaneous lymphoma and NK cells.

CAROLINA HAGBERG'S GROUP
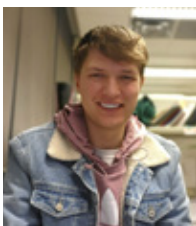
PhD Filip Vlavcheski is a new postdoc in Carolina Hagberg's group at the Division of Cardiovascular Medicine at BioClinicum. He defended his PhD thesis in 2023, in Canada (Ontario), within the field of Medical Sciences (Health Biosciences) specializing in fat induced insulin resistance and adipocyte biology. Filip will be exploring the connections between adipocyte enlargement and functionality by targeting metabolic pathways that could improve adipocyte function thus preventing obesity and metabolic diseases.

Thadoe Thukha is a final year MSc student in Cardiovascular Sciences at the University of Göttingen, Germany, who is carrying out a lab rotation in Carolina Hagberg's group at the Division of Cardiovascular Medicine at BioClinicum as an 12-week academic exchange. He will be studying cholesterol transport in adipocytes using the "Human Unilocular Vascularized Adipocyte Spheroid (HUVAS)" model. In parallel, he is conducting a Bioinformatics project to investigate the expression of genes associated with insulin resistance in lean and obese adipocytes from publicly available RNA sequencing data.
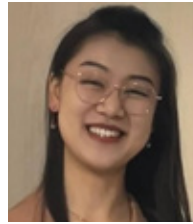
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New CMMers

EDUARDO VILLABLANCA'S GROUP

Vlad Farcas, student from the Master's Programme of Toxicology at Karolinska Institutet, joined Eduardo Villablanca's group to conduct his master thesis titled "Screening for environmental modulators of the activity of IBD-risk non-coding elements in vivo" under the supervision of Rodrigo Morales.

Yuqing Zhou, student from the Master's Programme of Toxicology at Karolinska Institutet, joined Eduardo Villablanca's group to conduct her master thesis titled "Assessing in vivo the toxicological impact of PPAR signaling activity in the intestine" under the supervision of Rodrigo Morales.

Lara Thielcke, a Bachelor's student in the Biomedicine program at Karolinska Institutet, is joining Eduardo Villablanca's Lab for her thesis project. Together with Bianca Kern she aims to explore the role of LXR in regulating B cell homeostasis.

ROBERT HARRIS' GROUP

Ana Bekavac is a PhD student from the University of Zagreb. The main focus of her PhD research is understanding the development of cerebral cortex and neurodegeneration in Down syndrome by using cerebral organoids. She has received a grant from the Croatian Science Foundation to do a three-month research exchange in the Robert Harris' group, as part of Sebastian Lewandowski's team. Ana's research at Karolinska Institutet will be based on digital image analysis of immunohistochemical images of ALS patients, as well as the automatization of the analysis process.

Appointments

Nicolas Ruffin has been appointed as Pedagogical Ambassador for doctoral education with four other researchers from Karolinska Institutet.

Pedagogical ambassadors in doctoral education started as a project to develop and promote an educational culture in close partnership with doctoral programmes and research schools at Karolinska Institutet.

Each pedagogical ambassador designed a development project in doctoral education at Karolinska Institutet. Nicolas' project is entitled "Supporting the Enhancement of Active Learning (SEAL) and formative assessment in doctoral programme in Neuroscience"
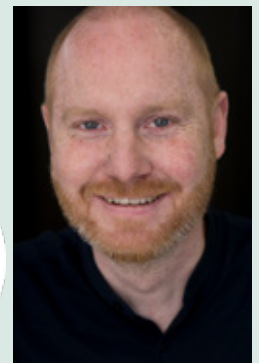
Logo for the SEAL project designed by Nicolas Ruffin.

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Publications

Berglund R, Cheng Y, Piket E, Z Adzemovic M, Zeitelhofer M, Olsson T, Ortlieb Guerreiro-Cacais A, Jagodic M. The aging mouse CNS is protected by an autophagy-dependent microglia population promoted by IL-34. *Nat Commun*. 2024 Jan 9;15(1):383. doi: 10.1038/s41467-023-44556-6.

Edsfeldt A, Singh P, Matthes F, Tengryd C, Cavalera M, Bengtsson E, Dunér P, Volkov P, **Karadimou G, Gisterå A**, Orho-Melander M, Nilsson J, Sun J, Gonçalves I. Transforming growth factor-β2 is associated with atherosclerotic plaque stability and lower risk for cardiovascular events. *Cardiovasc Res.* 2023 Sep 5;119(11):2061-2073. doi: 10.1093/cvr/cvad079.

González-López P, **Yu Y, Lin S,** Escribano Ó, Gómez-Hernández A, **Gisterå A**. Dysregulation of micro-RNA 143-3p as a Biomarker of Carotid Atherosclerosis and the Associated Immune Reactions During Disease Progression. *J Cardiovasc Transl Res.* 2024 Jan 25. doi: 10.1007/s12265-024-10482-1

Hagberg CE, Spalding KL. White adipocyte dysfunction and obesity-associated pathologies in humans. *Nat Rev Mol Cell Biol* 2023. doi: 10.1038/s41580-023-00680-1

Maestri A, Garagnani P, Pedrelli M, **Hagberg CE,** Parini P, **Ehrenborg E.** Lipid droplets, autophagy, and ageing: a cell-specific tale. *Ageing Res Rev* 2024. 94:102194.

Pennacchietti F, Alvelid J, **Morales RA,** Damenti M, Ollech D, Oliinyk O, Shcherbakova DM, **Villablanca EJ**, Verkhusha VV, Testa I. (2023). Bue-shift photoconversion of near-infrared fluorescent proteins for labeling and tracking in living cells and organisms. *Nat Commun* 2023. 14:8402.

Raposo B, Grönwall C. The diversity of anti-citrulline reactivity and ACPA-associated phenotypes. *Joint Bone Spine* 2023 Dec; 90(6):105617. doi: 10.1016/j.jbspin.2023.105617.

Steinmetz-Späh J, Jakobsson PJ. The anti-inflammatory and vasoprotective properties of mPGES-1 inhibition offer promising therapeutic potential. *Expert Opin Ther Targets*. 2023 Jul-Dec;27(11):1115-1123. doi: 10.1080/14728222.2023.2285785.

Ymeri G, Salvi D, Olsson CM, Wassenburg MV, Tsanas A, **Svenningsson P.** Quantifying Parkinson's disease severity using mobile wearable devices and machine learning: the ParkApp pilot study protocol. *BMJ Open*. 2023 Dec 28;13(12):e077766. doi: 10.1136/bmjopen-2023-077766.

Mini abstract:
The blood−DRG barrier is composed of endothelial cells with high permeability and is monitored by a subset of CD163+ perivascular macrophages, a process that is arteriovenously zonated. Vascular monitoring is abrogated by interfering with caveolar transcytosis in endothelial cells or by depleting CD163+ macrophages.

Lund H, Hunt MA, Kurtović Z, Sandor K, Kägy PB, Fereydouni N, Julien A, Göritz C, Vazquez-Liebanas E, Mäe MA, **Jurczak A, Han J, Zhu K, Harris RA, Lampa J**, Graversen JH, Etzerodt A, Haglund L, Yaksh TL, **Svensson CI**. CD163+ macrophages monitor enhanced permeability at the blood−dorsal root ganglion barrier. *J Exp Med* 2023. 221:e20230675. doi:10.1084/jem.20230675.

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CMM Events and Outreach

We organized a two-day long "R workshop for Cytometry Data Analysis" which was held at CMM between the 24th and 25th of January. It was supported by the AII doctoral education program. Dr Yann Abraham from Janssen Pharma, was our guide during this workshop. PhD students and postdocs joined the workshop during which we analyzed multi-color flow cytometry data using machine learning approaches. This workshop was organized by researchers from CMM: Begum Horuluoglu, Christina Gerstner and Ana Cristina Gonzalez Sanchez. We are looking forward to repeating this workshop in the future.

Begum Horuluoglu, Christina Gerstner and Ana Cristina Gonzalez Sanchez

Upcoming events

CMM Seminar Series 2024: The call for speaker nominations is still open

We would like to receive your nominations of excellent Swedish and/or international scientists that could be of broader scientific interest to the CMM community.

The nominations should include a brief description of the speaker's scientific profile and relevance to the CMM scientific community (not to exceed more than one page).

Please send your nominations to CMM Communication communication@cmm.se (no specific deadline). Selection of speakers will be made by the CMM Stering Group.

CMM will (together with the nominator) arrange a scientific programme for the invited speaker, hosting the seminar as well as providing the opportunity for networking reception after the talk, with some drinks and light bites. For a selected number of guests/speakers CMM can also contribute towards travel and accommodation costs if required.
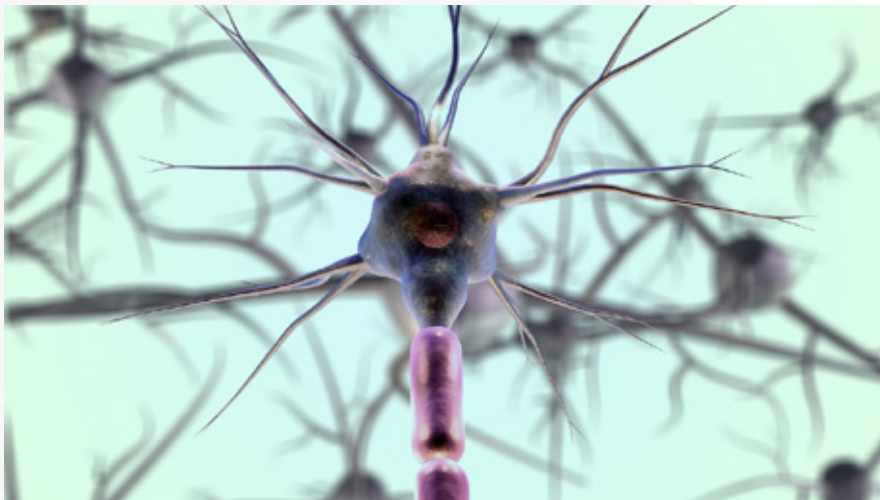
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Upcoming events

15 March, 9:00
Dissertation of Lovisa Brodin:
Parkinson's disease and Gaucher disease-focus on the GBA1 link

C1:87, Karolinska University Hospital, Huddinge.

Opponent:
David Bäckström, MD, PhD, Department of Clinical Science, Umeå University.

Principal supervisor:
Professor Per Svenningsson, Department of Clinical Neuroscience, Karolinska Institutet.

Co-supervisors:
Docent Andrea Carmine Belin, Department of Neuroscience, Karolinska Institutet.

Docent Ioanna Markaki, Department of Clinical Neuroscience, Karolinska Institutet.

Professor Maciej Machaczka, Department of Hematology, Karolinska University Hospital.

Ellen Hertz, MD, PhD, Karolinska Institutet.

Examination Board:
Docent Shala Ghaderi Berntsson, Department of Medical Sciences, Uppsala University.

Professor Ingrid Skelton Kockum, Department of Clinical Neuroscience, Karolinska Institutet.

Professor Johan Lökk, Division of Clinical Geriatrics, Karolinska Institutet.

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Upcoming events

22 March, 9:00
Dissertation of Miranda Stiernborg:
Exploring the gut microbiome in ADHD and schizophrenia spectrum disorder

CMM Lecture Hall, Visionsgatan 18, L8:00, Karolinska University Hospital, Solna.

Opponent:
Luisa Warchavchik Hugerth, Department of Medical Biochemistry and Microbiology, Uppsala University.

Principal supervisor:
Catharina Lavebratt, Department of Molecular Medicine and Surgery, Karolinska Institutet.

Co-supervisors:
Yvonne Forsell, Department of Global Public Health, Karolinska Institutet.

Philippe Melas, Department of Clinical Neuroscience, Karolinska Institutet.

Vincent Millischer, Department of Molecular Medicine and Surgery, Karolinska Institutet.

Examination Board:
Rochellys Diaz Heijtz, Department of Neuroscience, Karolinska Institutet.

Frida Hållenius, Department of Process and Life Science Engineering, Lund University.

Shafqat Ahmad, Department of Medical Sceinces, Uppsala University.

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Upcoming events

Upcoming events

Oral-Gut Conference 2

Dear colleagues,

It is with great enthusiasm that I extend to you an invitation to attend at the upcoming "Oral-Gut Conference 2: Expanding the Horizons of GI tract Immunology and Microbiology". Building on the success of our 2020 symposium in Santiago, Chile, we are excited to present a second, more expansive edition at the Karolinska Institute in Stockholm, Sweden, slated for June 11th-12th, 2024.

This conference, co-organized with Juliana Barreto de Albuquerque (Harvard Medical School), Claudia Rivera (NIH), and Eduardo Villablanca (Karolinska Institute), is sponsored by the Karolinska Institute and the Society for Mucosal Immunology (SMI). Our vision is to foster a comprehensive dialogue spanning the broad spectrum of immunology and microbiology research within the mucosal surfaces of the gastrointestinal tract and its related organs. The conference's main topics include intestinal and oral mucosal immunity, the interplay between oral and intestinal health, and the systemic implications of intestinal perturbations. We anticipate that the gathering will not only disseminate cutting-edge knowledge but also foster sustained collaboration among attendees.

We are privileged to confirm as Keynote Speakers: Dr. Yamine Belkaid (NIH/NIAID – President of the Institut Pasteur), Dr. Oliver Pabst (RWTH Aachen – Chair of Molecular Medicine), and Dr. Niki Moutsopoulos (NIH/NIDCR).

We welcome your abstracts for submission. The deadline for submission is March 15th, 2024. For further details on the conference and the submission process, please visit *www.oralgut.com.*

We look forward to your participation and contribution to a fruitful and enlightening conference.

With warm regards,

Gustavo Monasterio
Cancerfonden Postdoctoral Fellow, Department of Medicine, Solna, Karolinska Institute.

Claudia Rivera
Damon Runyon Postdoctoral Fellow, NIAID, National Institutes of Health.

Juliana Barreto de Albuquerque
Postdoctoral Research Fellow, Massachusetts General Hospital/Harvard Medical School.

Eduardo Villablanca
Associate Professor, Department of Medicine, Solna, Karolinska Institute.

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Next deadline for sending in contributions to CMM News:

14th of March 2024

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