THE CENTER FOR INFECTIOUS MEDICINE (CIM) was created in 2002 around a completely new constellation of young scientists operating in a new integrated geographically co-localized "under-the-same-roof"-environment sharing office space, laboratory space, facilities and equipment within the Department of Medicine, Karolinska Institutet at the Karolinska University Hospital at its Huddinge site. The Center has since its inauguration rapidly grown and gained national and international recognition. In 2003, the Swedish Foundation for Strategic Research recognized it as one of six “Strategic Research Centers” within life sciences in Sweden. In 2009, it was recognized as one of nine translational “Theme Research Centers” within Karolinska Institutet and the Stockholm County Council.

The Center for Infectious Medicine is organized around a large group of exceptionally talented young research group leaders, normally recruited to the Center from successful post-doctoral periods at leading international universities. Many of the leaders who were recruited during the first years of the establishment of the Center are still working at the Center, and have obtained faculty positions or other types of senior research positions in external competitions. Many of them have been honored with distinguished awards for their scientific achievements over the last years. Some group leaders have gone on in their careers and obtained leading positions elsewhere at other universities within our outside the country, in the health care sector, or at governmental organizations. This is a natural, very much desired, development.

THE GOAL of the Center for Infectious Medicine is to conduct research within immunology and infection-immunity in humans. Specific efforts are directed towards implementing discoveries made at the Center by taking assertive actions to acquire patents, perform proof-of-principle studies in animal models, guide compound production, and direct phase I/II clinical trials in humans. With these goals, we foresee a better understanding of immunity, and in specific situations loss of immunity, against human pathogens. We also foresee the development of new and better immunomodulatory strategies to prevent and treat infectious diseases of global importance. In addition, we foresee the continuous fostering of a new generation of scientists who will be of value not only for the Center in the near future but who will also benefit society at large as future leaders at universities, governmental institutions and/or industry.

THE VISION of the Center is to be one of the leading translational research centers within immunity and infectious diseases in Europe. Research conducted at the Center should be of the highest international standards and have prospects to improve human health in the long run.

Hans-Gustaf Ljunggren, Director
December 2012
BRIEF FACTS ABOUT CIM

- Built around 18 research groups
- Trains at the moment around 25 graduate students and 20 postdocs
- Has excellent clinical collaborations and international collaborations with more than 50 leading international universities as well as with research sites in several developing countries
- Research competence areas within the Center include
  - Viral immunology
  - Microbial immunology
  - Parasite immunology
  - Hematology/cancer
  - Diabetes/autoimmunity
  - Immunotherapy/vaccinology
  - Immunogenetics/genomics
  - Structural biology
- Organized around defined platforms including model systems for disease, diagnosis, pathogenesis, prevention, and therapy
- Leading the development in advanced flow cytometry
- Has strong platforms in atomic, cellular, tissue and intra vital whole body imaging techniques. Access to GMP-production unit for vaccines and cells for therapeutic use
- International advisors visit the Center at a regular basis to provide advice and feedback on the latest research developments
- Maintains close interactions with biotech and industry, and have been involved in the formation of several Biotech companies
- Since 2003 more than 500 research articles have been published from the Center. Of these more than 100 have been published in journals with an impact over 10

The vision is to be a leading translational research center within immunity and infectious diseases in Europe
Research conducted at the Center should be of the highest international standards and have prospects to improve human health in the long run.
ESTABLISHMENT OF THE CENTER

THE FIRST IDEA OF ESTABLISHING a new translational research center with a focus on immunology and infectious disease research came about in the year 2000.

The inspiration came from the identified need for more and better translational research environments in Sweden, highlighted in two reports from the Swedish Cancer Society and the Swedish Research Council. Simultaneously, several international evaluations also emphasized the need of promoting translational research as well as creating better platforms for interactions between basic and clinical scientists.

Basic research to clinical trials
In 2001, the creation of a new “Center for Infectious Medicine” at Karolinska Institutet was proposed by Hans-Gustaf Ljunggren and Jan Andersson. It was proposed that research at the Center should have a focus on basic and translational research within infection-immunity, with an intention of being able to bring results of basic research at the Center all the way to clinical trials. Furthermore, research at the Center should have important clinical questions as grounds for the formulation of research projects.

A physical plan for a tentative Center was conceived in 2001. Appropriate physical localities were provided by the Karolinska University Hospital at its Huddinge site, close to the clinical Infectious Disease Department. The hospital director at that time, Björn Rosén, was instrumental in this process. The Center for Infectious Medicine, CIM, was completed in 2002 and inaugurated in 2003.

It comprises 750 square metres of renovated and fully equipped laboratory facilities. CIM has since its inauguration been able to attract some of the most talented young Swedish scientists actively engaged in human immunology and infectious disease research.

The Center expanded
While the Center has its main activities in its premises at the Karolinska University Hospital at its Huddinge site, it has over time grown out of space. Hence, it currently has one group located to Department of Microbiology, Tumor and Cell Biology, one group at the Swedish Institute for Infectious Disease Control, one group at the Science for Life Laboratories, and finally currently one group located to the NIH, Bethesda, USA. The latter group, headed by Karin Loré, will relocate to the Center in the year 2014.

Currently (year 2012) CIM encompasses in total some 75 scientists, organized in 18 smaller research groups. Around 20 post docs and 25 doctoral students receive their training at the Center.
ORGANIZATION OF THE CENTER

THE CENTER IS LEAD by the Director Hans-Gustaf Ljunggren who has overall responsibility for the Center’s administration and scientific development.

Anna Norrby-Teglund functions as Deputy Director of the Center and shares responsibility for administration and scientific development.

Jan Andersson also functions as Deputy Director of the Center and has overall responsibility for the Center’s clinical and industrial interactions.

The Center is organized around 18 independent research groups, including the Director’s group.

The research groups work in an integrated environment sharing office space, laboratory space, facilities and equipment. The groups normally consist of 3–6 members, including both graduate students and post docs. Almost all groups have clinical scientists affiliated with them. Many group leaders also share supervision of graduate students with clinical scientists.

CAREER OPPORTUNITIES

THE CENTER RECEIVES around 500 spontaneous applications every year for possible positions at all levels.

The Director is responsible for the recruitment of new group leaders, following advice from the CIM faculty group (which includes all group leaders and senior scientists at the Center) and from international scientific advisors.

The group leaders, in agreement with the Director, recruit postdoctoral fellows and graduate students to their individual research groups. Based on the spontaneous applications CIM receives, and applications in responses to specific calls, the Center and its group leaders select the most qualified applicants for any position that is available.

Key components in our ongoing recruitment processes are scientific excellence, qualifications for performing well, ability to interact in a geographically co-localized group of scientists, likelihood of contributing to the Center’s development and personal skills. Furthermore, the ability to bring in new technology, provide new methodological skills, add theoretical competence and contribute to the interdisciplinary environment is important.

The Center has, since its inauguration, actively striven towards having equal numbers of men and women at all levels including students, post docs, senior scientists and group leaders as well as technical and administrative personnel.
RESEARCH OBJECTIVES

1 To advance our understanding of the human immune system at a cellular and molecular level

Decades of intense cellular and molecular studies have resulted in the identification of components of the immune system. Studies of the mouse immune system, most particularly through the use of animals with targeted gene inactivation, have permitted linking these components to specific functions in immunity. In spite of this progress, the study of the human immune system has lagged behind that of the mouse. Improvements in technologies and reagents, however, now permit detailed analysis of the human immune system at cellular and molecular levels. Such analyses are crucial for furthering our understanding on how the human immune system combats infectious diseases.

2 To advance our understanding of immune reactions to pathogens in humans, and pathogen escape from immunity

With a clearer insight into functions of the human immune system gained through basic research as well as the development of new techniques, we can now address fundamental questions relating to host immune reactions to human pathogens and strategies employed by pathogens to evade immunity, at a level not previously conceivable. Improved understanding of host immunity to human infection set the stage for development of new intervention strategies such as, e.g., new vaccines.
3 To develop new immunomodulatory prevention and treatment strategies for human infectious diseases

Although many approaches to produce new vaccines have been initiated, systematic evaluation and optimization have proceeded slowly, in part because of factors such as the expense and complexities in advancing new candidate vaccines into phase I/II trials and scientific challenges.

Importantly, techniques for eliciting immunogenicity in new vaccines are lacking and sorely in need of complementary, safe adjuvants to help them reach full potential. Likewise, antigens must be optimized to yield the strongest possible immune responses. Vaccine-oriented projects focus particularly on optimizing strategies for HIV vaccination. However, several efforts presented here are equally applicable to vaccines against other major pathogens, e.g., HCV, influenza virus, and *M. tuberculosis*.

4 To test new immuno-modulatory prevention and treatment strategies in clinical phase I/II trials

The 21st century has witnessed a need to move research results more quickly to clinical settings. Clinical research helps to assure that new diagnostics, treatments and intervention strategies are safe and effective. Currently, this is a lengthy and sometimes (if not often) inefficient process. Meeting these demands requires new and more efficient processes from discovery to clinical validation of research results in humans.

Current clinical trials planned involves testing several new vaccine concepts. Studies are also ongoing aiming at testing new adoptive immunotherapy protocols with NK cells against specific hematologic malignancies.
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ADNANE ACHOUR GROUP

USING STRUCTURAL BIOLOGY TO EXPLORE IMMUNOLOGICAL QUESTIONS

Cellular communication is achieved through the interactions of specialized receptor molecules at the cell surface and their ligands. Our research group uses X-ray crystallography and Small Angle X-ray Scattering (SAXS) to study receptor-ligand interactions, such as e.g. between T or NK cell receptors and Major Histocompatibility Complex (MHC) molecules, as well as bacterial adhesins.

All of our studies are complemented by a wide array of immunological assays as well as an extensive amount of biochemical techniques, including surface plasmon resonance and circular dichroism. By understanding the structural details of proteins, we can probe their function and potentially design artificial ligands that could modulate their function and activity.

Selected publications


**JAN ANDERSSON GROUP**

**ELUCIDATING HUMAN TUBERCULOSIS PATHOGENESIS**

TB is caused by *Mycobacterium tuberculosis* (TB) and continues to be one of the world-leading killers among infectious diseases. The deadly synergy between TB and HIV infections is also a major key challenge to global health. TB is predominately a localized intracellular infection, which highlights the importance to study host-pathogen interactions in the infected tissue. Together with Susanna Brighenti we study the pathogenesis and immunoregulation of human tuberculosis (TB). A particular focus is devoted towards studies of how deficient immune responses in chronic TB contribute to disease severity in TB/HIV co-infected individuals.

The overall purpose is to discover specific cellular and molecular targets relevant for diagnosis of TB disease and for immune reconstitution in vivo. A specific aim is devoted towards studies of specific immune responses including the induction and regulation of antimicrobial effector functions in macrophages and T cells, particularly at the local site of *M. tuberculosis* infection. Integration of patient materials with well-defined cell and tissue models in vitro are also used to explore pathogenic mechanisms of human TB and TB/HIV. An increased understanding about the establishment and progression of active TB disease will facilitate the discovery of novel biomarkers for diagnosis or disease treatment.

**Selected publications**


Our group is interested in questions relating to the activation of early “innate” immune responses. Our overall goal is to use molecular tools to design more effective vaccines. We are also interested in probing the molecular mechanisms of host-pathogen interactions and subsequent pathology.

Ongoing research is using a DNA-encoded flagellin protein to activate innate immune receptors to boost humoral and cellular immunity to DNA-encoded antigens. We have demonstrated proof-of-principal in vaccine models, and have studies going on showing that adjuvant effects work when vaccines are delivered by systemic, dermal, or mucosal routes. Current pre-clinical studies involve the HIV-1 antigens gp160, Gag, as well as Influenza A HA, NP, and Norovirus antigens.

Using similar molecular tools, we also study inflammasome activation using DNA-encoded flagellin tails in macrophages to study the downstream inflammatory outcomes of activated cell death (pyroptosis). These projects are revealing novel insight into inflammatory cell death, which occurs during bacterial sepsis as well as hypoxia reperfusion injury with whole-organ transplantation.

**Selected publications**


Our current research on parasitic infections integrates immunology with molecular parasitology to understand how obligate intracellular parasites evade and direct host immune systems to their own advantage. The research aims to define the pathogenic mechanisms utilized by the opportunistic human pathogen *Toxoplasma gondii* and related apicomplexan parasites (malaria, cryptosporidium) to promote colonization and transmission of infection.

The precise mechanisms leading to systemic dissemination of parasites (acute infection) and life-long persistence (chronic infection) in the human host remain poorly understood. We have recently discovered that intracellular *T. gondii* hijack dendritic cells by inducing a hyper-migratory phenotype that potentiates dissemination while avoiding clearance. Findings on the migratory pathways of *Toxoplasma* contributed to the identification of a novel family of parasite-derived serine-threonine kinases with a strong association to virulence.

The processes of systemic dissemination and persistence are studied using various imaging modalities, including in vivo biophotonic imaging in animal models. Understanding the immune evasion strategies utilized by *Toxoplasma* may provide key elements of pathogenesis and on the rationale for designing future treatments and vaccines.

**Selected publications**


Our research is focused to study the pathogenesis and immunoregulation involved in the development of human tuberculosis (TB) and how deficient immune responses in chronic TB contribute to disease severity in TB/HIV co-infection. The overall purpose is to discover specific cellular and molecular targets relevant for diagnosis of TB disease and for immune reconstitution in vivo.

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We aim to study specific immune responses including the induction and regulation of antimicrobial effector functions in macrophages and T cells, particularly at the local site of *M. tuberculosis* infection. Integration of patient materials with well-defined cell and tissue models in vitro are also used to explore pathogenic mechanisms of human TB and TB/HIV. An increased understanding about the establishment and progression of active TB disease will facilitate the discovery of novel biomarkers for diagnosis or disease treatment.

**Selected publications**


Subsets of lymphocytes, such as cytotoxic T cells and natural killer (NK) cells, can kill infected or neoplastic cells. Individuals carrying mutations in specific genes required for such lymphocyte cytotoxicity may develop life-threatening disorders. In the most severe cases, these are often triggered by viral infections and elicit uncontrolled immune cell proliferation and hyperinflammatory immune pathology. Otherwise, such mutations may predispose to malignancies.

We have developed methods for quantification of human cytotoxic lymphocyte responses. Our research strives to understand the complex regulation of cytotoxic lymphocyte function in health, infection, and disease in the setting of human genetic variability and environmental factors. Moreover, we aim to develop refined techniques for determining human immune status. We hope that outcomes of this work will include fundamentally new conceptualizations of immunological disorders, basic immunological and genetic insights, and potent, specific immunomodulatory interventions for treatment of disease.

Our laboratory is based at the Center for Infectious Medicine and employs a wide range of techniques including multiparameter flow cytometry, confocal microscopy, live-cell imaging, next-generation sequencing, and biochemical techniques. To gain clinical and scientific insights into human diseases, we collaborate closely with clinicians at Karolinska Institutet, across Scandinavia and the rest of the world.

Selected publications


The main focus of our research is to investigate the role of natural killer (NK) cells in the development of adaptive immune responses. The research focuses along two lines. (1) The interaction between dendritic cells (DC) and NK cells. (2) How NK cells can affect T and B cell mediated responses by direct physical interaction.

In particular, we are looking at the role of TRAIL in the elimination of DC in vivo and the role of 2B4 (CD244) on NK cells in the stimulation of T cells. How NK cells interact with DC or cells of the adaptive immune system has implications for the generation of a successful immune response aimed at eradication of infections or tumors. The studies also have relevance for the uncontrolled immune reactions occurring during autoimmune reactions and during allergic responses.

**Selected publications**


Dissecting the Possibility of an Infectious Etiology of Type 1 Diabetes

Type 1 diabetes results from the destruction of the insulin-producing pancreatic beta cell, but the mechanism(s) behind beta cell destruction remains to be established.

Infections with common viruses (e.g., Coxsackieviruses) have been linked to type 1 diabetes development in humans. Our present research seeks to define the role of the virus in the disease process. We are studying how the virus affects the infected host and the cross-talk between the virus, the immune system and the pancreatic beta cells. We expect that our studies will generate valuable information for the design of preventative treatments against type 1 diabetes.

Selected publications


The research in our group lies within the area of immunology, with the main focus on viruses and their interactions with the immune system.

Viral infections can cause a number of different acute and chronic conditions. The approaches to treat these conditions are limited, and for many viral infections, there are no alternatives at all. Our research focuses on advancing the knowledge in the basic principles of the immune response in natural infection in humans for viral infections, such as flavivirus (e.g., tick borne encephalitis virus) and herpes virus.

We also strive to identify factors important for severe infection in certain individuals. We combine basic biochemistry with cellular immunology methods and apply these techniques on patient material.

Our long-term goal is, aside from gaining knowledge in the function of the human immune system, to contribute to the development of new approaches for diagnosis, treatment, and vaccination strategies for viral infections.

Selected publications


HANS-GUSTAF LJUNGGREN GROUP
HUMAN NK CELLS IN HEALTH AND DISEASE

Natural killer (NK) cells are lymphocytes of the innate immune system. Our group has a long-term interest in exploring the molecular specificity and function of human NK cells in health and in different disease settings. Much of our work is carried out in collaboration with other scientists at the Center. Focus is aimed at characterizing NK cells in peripheral blood and different tissues in healthy humans.

Another focus is aimed at characterizing NK cells in peripheral blood and different tissues during viral infections and cancer. We are also exploring human primary immunodeficiency syndromes in which NK cells are not functioning properly, in particular with respect to their cytotoxic function. Finally, we are also interested in using NK cells in settings of adoptive immunotherapy, with a primary focus on hematological malignancies.

Selected publications


Our group has an ultimate goal to expand the on-going efforts to develop a preventative HIV-1 vaccine. However, we have over the past few years formulated a line of research focusing on general central questions in vaccine development related to identification of mechanisms for successful delivery of vaccine antigens, viral vaccine vectors plus adjuvants to dendritic cells (DCs), in order to optimize elicitation of both cellular and humoral immune responses.

We have developed physiologically relevant experimental systems using human primary blood and skin DCs. We characterize these DC subsets for their interactions with vaccine components including Toll-like receptor ligands, Adenovirus vectors and protein-based vaccine antigens such as HIV-1 Envelope glycoprotein and Influenza Hemagglutinin. The functions of distinct DC subsets and the importance of providing one or all of them with vaccine antigen and activation signals to optimize immunity is necessary for rational approaches to vaccine design. Our strategy is to operate at a powerful infrastructure and leverage our current expertise towards a more translational research profile aided by our network of strong collaborators and availability to novel reagents.

**Selected publications**


The group studies the molecular and cellular basis for NK cell differentiation and repertoire formation in health and disease. A key focus is to gain insights into how killer cell immunoglobulin-like receptors (KIR) influence the function of human NK cells.

KIR are HLA class I binding receptors with important functions in reproduction, immunity to infections, and in allogeneic hematopoietic stem cell transplantation (HSCT) for malignant disorders. We examine the intrinsic and extrinsic factors that shape human KIR repertoires during allogeneic SCT and the consequences for control of viral reactivation and leukemia relapse. In more translational efforts we have established a platform for NK cell-based immunotherapy for patients with refractory or relapsing hematological malignancies.

**Selected publications**


The main focus of our research is to investigate the differentiation, function and regulation of human Natural Killer (NK) cells during fetal development and in healthy adults, as well during viral infections.

Understanding how these cells develop and function during different stages of life, and during different conditions is important to achieve the long-term goal of our research, which is to aid in the development of new therapies in infectious diseases, cancer and transplantation. We continuously develop new techniques for advanced analysis of NK cells, and strive to be leading in flow cytometry analysis of human NK cells (currently 16-colour flow cytometry).

Selected publications


The battle between the human immune system and many viruses resembles a sophisticated version of hide-and-seek. The immune system is equipped with tools to restrict virus infection, and to sense and eliminate virus-infected cells. Viruses on the other hand have evolved mechanisms to evade restriction, recognition and eradication by the immune system.

A major focus in the group is to investigate functional, molecular and evolutionary aspects of immune evasion strategies evolved by human viruses. The aim of this work is to gain insight into both the significance of innate immune mechanisms in successful anti-viral immunity, and the relevance of viral immune evasion for establishment of infection and pathogenesis.

Our projects involve a number of viruses with a clear focus on two major human pathogens: human immunodeficiency virus-1 (HIV-1) and hepatitis C virus (HCV). Our work is based on a broad spectrum of methods including advanced cell isolation and culture techniques, confocal microscopy and flow cytometry.

Selected publications


Our overall goal is to decipher mechanisms contributing to severe manifestations of acute bacterial infections and thereby identify targets for therapeutic intervention. The research is translational in nature and is based largely on clinical isolates, patient materials and human cell and tissue model systems that mimic the clinical setting.

Our research aims to:
- Link clinical presentation of severe sepsis/septic shock to microbiological aetiology and associated pathogen-specific disease mechanisms.
- Identify central mediators in severe sepsis/septic shock and deduce their mechanistic action and potential value as prognostic risk markers.

Of particular interest are the two Gram-positive bacteria *Streptococcus pyogenes* and *Staphylococcus aureus*, both of which may cause highly aggressive invasive infections such as toxic shock, necrotizing pneumonia and necrotizing fasciitis that are associated with substantial morbidity and mortality. The research strives to decipher bacterial properties contributing to disease outcome and events underlying tissue injury. A specific theme is to evaluate immunotherapeutic strategies in these diseases.

**Selected publications**


Cellular immune responses play an important role in protection from viral infections. These responses can also, however, contribute to the immunopathogenesis of chronic viral infections such as human immunodeficiency virus (HIV)-1 and hepatitis C virus (HCV) infections.

Another aspect of the complex relationship between host and pathogen is that most viruses have developed immune evasive mechanisms to avoid detection and elimination by the host cellular immune responses. Our research aims at understanding the nature and balance between protection, pathology and immune evasion during acute and chronic stages of viral infections.

We are particularly interested in HIV-1 infection, but we also study aspects of other chronic viral infections such as HCV and herpes simplex virus (HSV) where immune evasion mechanisms are significant. Another layer of complexity is added by vaccines, antiviral and immunomodulatory treatments used today and in development. These we bring in to our studies to learn lessons about the treatments as such, as well as about the basic immunology that we can learn from how the immune system responds to such treatments.

Selected publications


Anna-Lena Spetz Group

HIV-1 IMMUNOGEN DISCOVERY AND IMMUNOMODULATION OF DENDRITIC CELLS

The research group led by Anna-Lena Spetz is working towards the goal to discover new immunogens and immunization regimens that induces potent HIV-1 specific immune responses.

A long-standing goal for a HIV-1 vaccine is to induce both T-cell responses and broadly reactive antibodies that are able to neutralize the virus. The immune responses following stimulation with Toll Like Receptor (TLR) ligands and apoptotic cells are also investigated.

The aim with these projects is to enhance the understanding of early innate mechanisms during infections or tissue damage with the dendritic cell in focus. This knowledge will contribute to novel approaches of immune modeling during immune pathogenesis and the development of vaccine adjuvant, where the activation of dendritic cells has emerged as a key event in shaping the following adaptive immune responses.

Selected publications


Our group is interested in exploring functional properties of human immune cells, including dendritic cells (DC) and monocytes in specific tissues. We wish to increase the understanding of immune responses to pathogens locally and how “pathological” tissue affect immune cell function and contribute to disease manifestations. This information can be translated into the design of immunotherapies that can be used to regulate immune responses locally.

However, studying functional properties of human immune cells in tissue is difficult. Our approach of developing and using three-dimensional (3D) tissue models, so called organotypic models that mimic mucosal tissues, provides unique tools to study human immune cell functions that are present in live tissue and often missed in monolayer-based cell cultures.

Utilizing our unique human in vitro models together with relevant clinical samples, we aim at defining important aspects of DC and monocyte functions in different human settings, involving inflammatory diseases in mucosal tissues. In addition, our models provide unique tools for the identification and evaluation of the effect of small molecule inhibitors and pharmacological compounds.

Selected publications


ROBERT WALLIN GROUP
IMMEDIATE RESPONSES OF INNATE IMMUNE CELLS TO MICROBES

The group studies host-pathogen interaction. Our focus is the consequences of early responses triggered by TLR on innate immune cells, when recognizing microbes. The events we are investigating precede gene-transcriptional changes and thus involve direct effects of TLR signaling on already existing cellular machineries. We have described how TLR signaling regulate antigen uptake. Currently we are studying how TLR signals affect phagocytosis. The signaling requirements for the effects of TLR signaling on macropinocytosis, phagocytosis, podosome dynamics and adhesion is also being investigated, e.g., by screening a large numbers of inhibitors to establish signaling networks involved. All these effects seem highly dependent on MAPkinase activity, however downstream effectors have yet not been identified. Dendritic cells and monocytes are mostly studied, but the group also studies effects of TLR signaling on other immune cells such as neutrophils.

Selected publications
RESEARCH ACHIEVED

SCIENTISTS at the Center for Infectious Medicine have, since its inauguration in 2003, published more than 500 original research articles in international journals of high standard including more than 100 research articles in journals of highest international standards including Cell, Nature, Science, Nature Medicine, Nature Immunology, Nature Biotechnology, Immunity, Proc Natl Acad Sci (USA), J Exp Med, J Clin Invest, PLoS Medicine, PLoS Pathogens, PLoS Biology. More than 200 articles have been published in the period covering the present scientific report (2009–2012). Scientists at the Center have also written a large number of editorials, commentaries, and perspectives articles as well as meeting reports in leading international journals.

A compiled list of 100 selected publications, published between 2009 and 2012, is presented below. For a complete list of CIM publications for the period 2009 to 2012, see http://ki.se/cim under the heading “Publications”.

100 SELECTED PUBLICATIONS

2009


2010


2011


2012


Larsson PG, Lakshmikanth T, Svedin E, King C, Flodström-Tullberg M. Previous maternal infection protects offspring from enterovirus infection and prevents experimental diabetes development. Diabetologia. In press.


DOCTORAL THESES

2009
Veronica D. Gonzalez. Innate and adaptive cellular immunity in chronic HCV and HIV-1 infection.

Henrik Lambert. Immune evasion and dissemination of Toxoplasma gondii.

Catrine M. Persson. NK cell and dendritic cell interactions in innate immune responses.

2010

Michael Hühn. Host-microbe interactions in coxsackievirus infection: Focus on innate immunity.

Stella Jacobson. Type 1 diabetes: The autoimmune process and islet transplantation.

Ulrika Johansson. Dendritic cell responses to apoptotic cells: Is there life after death?

Carlotta Kuylenstierna. Modulation of invariant NKT cell activity by cytokines and receptors in human disease.

2011
William C Adams. Regulation of human dendritic cells and T cells by adenovirus vectors types 5 and 35: Implications for vaccine design.

Niklas Björkström. Human natural killer cell activation and differentiation in health and viral infection.

Michael Alan Eller. Role of cellular immune functions through the course of HIV-1 natural infection in Ugandans.

Cornelia Gujer. Regulation of B cell function by plasmacytoid dendritic cells.

Oscar Hammarfjord. Toll-like receptor activation induced changes in dendritic cells.

Erika Hertzén. Streptococcus pyogenes: life within the macrophage.

2012
Venkatramanan Mohanram. On HIV-1 restriction in human dendritic cells and peripheral blood mononuclear cells.

Sandra Andersson. Formation of the inhibitory KIR repertoire in human natural killer cells.

Anette Sköld. Strategies for modulation of dendritic cell responses.

Adil Doganay Duru. MHC-class I restricted peptide based immunomodulation of CD8+ T and NK cells.

Hannes Uchtenagen. Elicitation and enhancement of T and B cell responses.

Emily Bond. Studies of human dendritic cells in the skin after antigen exposure.
TECHNOLOGICAL COMPETENCE AND MODEL SYSTEMS

The Center has invested a significant amount of economic resources to amass cutting edge technology and scientific expertise.

- **Imaging at the atomic level**
  Atomic visualization of the three-dimensional structures of proteins is essential for a complete understanding of the molecular basis underlying immune cell functions and development of infectious diseases. For this purpose, the Center has all required expertise in structural biology (X-ray crystallography) and biochemistry (production and isolation of soluble proteins) as well as several important techniques including circular dichroism and surface plasmon resonance.

  Besides the state of the art crystallography facilities within the Center, we also have full access to X-ray robotic facilities in the Structural Genomic Consortium (SGC) at Karolinska Institutet. Sampling of diffraction data from protein crystals at the highest achievable resolution is performed on a routine basis in several European synchrotrons.

  The ambition is to further develop the technical capacities of the Center in structural biology and biochemistry through the acquisition of additional state-of-the-art equipment, including novel Äkta Purifier with a specific refrigerator as well as temperature-controlled bacteria shaker, that allows for high performance purification, isolation and characterization of proteins.

  We are planning to purchase additional instruments for dynamic light scattering, circular dichroism spectroscopy as well as a Surface Plasmon Resonance Biacore 3000 system that will allow for analyzes of protein binding affinity and thermodynamics.

- **Imaging at the cellular and tissue level**
  To perform complete studies of immunological and pathogenic mechanisms, it is essential to have advanced equipment for visualization and quantification of immune cell functions.

  At the Center, researchers have established an advanced visualization facility that provides researchers with front-line imaging technology, technical support and imaging-related expert advice to researchers. Specific acquired computerized image analyses programs for quantification of biological and immunological mediators have been developed in the research environment.

  The Center also holds advanced equipment for fluorescence microscopy analyses, including a Nikon A1R confocal microscope, which is an excellent tool for studies of immune cell functions, viral and bacterial entry into host cells, as well as intracellular vesicular transport and diffusion mechanisms. It allows studies of single molecule dynamics, surface structures, exocytic and endocytic trafficking, receptor/ligand and cell-cell interactions in living and fixed specimens. The Nikon A1R is equipped with the total internal reflection fluorescence (TIRF) application, which is an ideal tool for live imaging investigating both the mechanisms and dynamics of protein interactions at the cell membrane surface.

  As a joint effort with S. Strömblad and R. Toftgård at the Novum Research Center in Huddinge, the Center has established a state-of-the-art imaging facility. The new facility offers a wide range of microscopes for advanced fluorescence microscopy and
includes a multiphoton confocal microscope Zeiss 710, which allows extended time lapse experiments on live cells. This includes four-dimensional (4D, i.e. 3D over time) imaging of dynamic cellular events and quantitative modeling of molecular mechanisms regulating immune cell behavior in more complex settings such as, e.g., organotypic cultures, tissue explants, and whole body organs. This microscope allows simultaneous analyses of a range of fluorophores and also provides a cutting edge technology for imaging of live human immune cells and host pathogen interactions under more physiological conditions.

- **Tissue model systems**

  At the Center, researchers have access to unique biopsies from patient cohorts.

  Analyses of sections or isolated cells from biopsies at the cellular or molecular level provide information of high clinical relevance that are further strengthened by detailed analyses in appropriate human cell and tissue model systems.

  The 3D tissue models can be frozen and sectioned for histological analysis. Hematoxylin and Eosin staining of the lung model epithelium is shown.

  From simple co-culture models of human tissue cells and, ultimately, to the generation of whole organs or representations of whole organs in the laboratory, scientists in the research environment develop human tissue model systems in vitro that can complement essential work currently achievable only in vivo.

  Our commitment to this development is essential. It includes specialized cultures of tissue cells as well as ex vivo explant models. Several approaches have been adapted to study immune cell interactions with tissue specific cells in monolayer-based cultures. Although these culture systems have provided important information with respect to tissue-specific influences on immune cell function, moving from cell monolayers to three-dimensional (3D) cultures is motivated by the need to work with cellular models that mimic the functions of living tissues.

  Scientists in the research environment engineer 3D tissue models, so-called organotypic cultures that also contain immune cells. Our approach of developing and using 3D tissue models that mimic real tissues provides unique tools to study human immune cell functions that are present in live tissue and often missed in monolayer-based cell cultures.

  In 3D cultures, tissue specific cells acquire a polarized phenotype and a large number of cell-cell contacts occur, which are likely to affect immune cell function and responses to external stimuli, such as pathogens. In addition, the 3D tissue model allows performance of live imaging of immune cells within tissue using 4D, i.e. 3D over time fluorescence imaging techniques. For this purpose we generate tissue models with fluorescent cells, e.g. epithelial cells, fibroblasts, dendritic cells and monocytes. Thus, creating tissue models with immune cells provide us with a technological platform to increase our understanding of human immune cell responses, migration and positioning in tissue, in addition to interactions with pathogens in more physiological models.
**In vivo imaging**

To increase our understanding of infectious diseases it is crucial to have sophisticated models for studying immune responses and disease progressions in vivo.

Non-invasive in vivo biophotonic imaging is a new technology that allows the detection of light-producing biological reactions in living animals in real time. Recently, a system has been acquired allowing combined bioluminescence and fluorescence imaging, as well as 3D reconstruction of signal localization in organs. This new system allows the assessment of up to 12 parameters simultaneously.

Ongoing and projected areas of application include assessment of disease progression in infection models with luciferase or fluorophore-tagged parasitic, bacterial and viral pathogens. Also, by adoptive transfer of luciferase-expressing or fluorophore-tagged immune cells, the involvement of these cells in various infection models can be monitored in vivo in settings of acute and chronic infection.

**Advanced flow cytometry**

Researchers at the Center have been at the leading edge since 2003 in the field of flow cytometry technology.

The advanced flow cytometry lab at the Center is equipped with two BD LSR Fortessa instruments with four lasers that allows assessment of up to 18 fluorescence parameters simultaneously. This technology allows characterization of immune cell subsets at high resolution in exquisite detail, and the value of rare patient samples can be maximized. The instruments are currently used by many groups in the environment in research related to human immune cell function and infectious diseases.

**Large-scale isolations of human cells**

To study functional aspects of human immune cells it is crucial to have efficient methods of obtaining primary human cells.

Researchers at the Center have developed several sophisticated methods for isolating large numbers of specific primary cells. As an example, our researchers now isolate human hematopoietic progenitor cells (HPC) from bone marrow and cord blood.

A number of other cell isolation systems have been established within the Center for isolation of large numbers of differentiated cells. For example, researchers have developed unique sorting procedures for isolation of distinct dendritic cell (DC) populations directly from blood. DC isolation is managed in collaboration with the Department of Transfusion Medicine at the Karolinska University Hospital. In a similar way, sorting procedures for isolation of NK cells directly from blood has been established. In addition, a protocol for isolation of DC directly from healthy skin (i.e., Langerhans cell DC and dermal DC) has been established. Other
important sources of human immune cells are lymphoid tissues, e.g., tonsils, lymph nodes and gut-associated lymphoid tissue.

Many studies also involve isolation of parenchymal cells, including, e.g., hepatocytes and pancreatic islet cells. A method for isolating lymphocytes from the human liver has recently been developed in the research environment in collaboration with the Department of Transplantation Surgery.

Human pancreatic islet cells are obtained from the Nordic Network for Clinical Islet Transplantation.

**In vivo models**

Experimental models constitute an important complement to in vitro experiments and studies on patient material. Researchers at the Center use experimental models with an aim to gain increased understanding for complex host-microbe interactions, disease mechanisms and for testing new vaccine- and drug candidates. The Center is also actively involved in the generation of needs-driven, novel in vivo models for studies within these and related research areas.

**Large scale GMP-production unit**

Tailored cell therapies may become the treatment of choice in some infectious and tumor diseases as well as transplantation medicine.

Several phase I/II clinical trials are currently planned or ongoing at the Center. To minimize the risk during the cell processing procedures and storage of cells intended for treatment, the EU and EMEA have developed guidelines for handling of cells.

At the Karolinska University Hospital, the Vecura unit is a GMP contract manufacturer of gene and cell therapy products. Researchers at the Center have a close collaboration with Vecura, where cells are now produced in large scale for cell-based immunotherapies. This includes isolation of NK cells for adoptive transfer to patients with hematological malignancies.
SCIENTISTS AT THE CENTER have extensive collaborations with clinical scientists at the Karolinska University Hospital. Such clinical collaborations have developed significantly over the last years. Presently, clinical scientists from more than 20 different clinical departments at the Karolinska University Hospital are involved in collaborative projects with scientists at the Center. Through these interactions, the Center has catalyzed a number of translational and clinical research projects within the Karolinska University Hospital. A large number of scientific collaborations also exist with other scientists at different departments of Karolinska Institutet.

SCIENTISTS AT THE CENTER have numerous national and in particular international collaborations. At any given time, several of the scientists belonging to the Center work abroad in collaborative projects with other groups. Similarly, the Center hosts many international visitors working at the Center for short periods in collaborative projects. Presently, scientists from 18 different countries work at the Center. More than 65% of the publications from Center involves collaborations with co-authors outside the Sweden. In total, such collaborations involves more than 50 international departments and/or universities.

SCIENTISTS AT THE CENTER have given interactions with developing countries high priority. Scientists at the Center have long-standing scientific collaborations with e.g. the ICDDR.B, Dhaka (HIV and tuberculosis); Indian Institute of Science, Bangalore, India (S. aureus); Black Lion University Hospital, AHRI, Addis Ababa (HIV and tuberculosis); Medical University of Post Graduate Studies, St. Petersburg (HIV and tuberculosis); Kaunas Medical University, Kaunas, Lithuania (tuberculosis); and Vilnius University, Lithuania (tuberculosis and HCV). These collaborations offer unique possibilities for mutual exchanges of knowledge and access to clinical material for research not available in Sweden.

SCIENTISTS AT THE CENTER have given interactions with biotech and industry high priority. Scientists in the research environment have, as outlined above, been involved in founding several biotech companies. Many scientists in the research environment have also had extensive collaborations with other small biotech companies as well as with industry. Interactions with these companies involve development of new technologies, diagnostic tools, treatment strategies and clinical protocols etc.
The Center for Infectious Medicine shall be neutral regarding gender in all decisions and actions. Help and support to scientists and other personnel at the Center shall be provided to the same extent regardless of gender. The Center’s premise is that the capacity for research and/or other tasks of expertise is independent of gender. The Center recognizes that development advances best in an environment where men and women equally contribute with their competence and expertise. The Center has defined concrete goals (see below) to ensure equal opportunities and will reevaluate its goals on a regular basis. Deviations from those goals will be remedied with high priority.

**EQUAL OPPORTUNITY**

**THE CENTER** for Infectious Medicine shall be neutral regarding gender in all decisions and actions. Help and support to scientists and other personnel at the Center shall be provided to the same extent regardless of gender. The Center’s premise is that the capacity for research and/or other tasks of expertise is independent of gender. The Center recognizes that development advances best in an environment where men and women equally contribute with their competence and expertise. The Center has defined concrete goals (see below) to ensure equal opportunities and will reevaluate its goals on a regular basis. Deviations from those goals will be remedied with high priority.

**Scientists and other personnel at the Center 2012***

<table>
<thead>
<tr>
<th>Position</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group leaders</td>
<td>11 (57%)</td>
<td>8 (43%)</td>
<td>19</td>
</tr>
<tr>
<td>Post docs</td>
<td>10 (48%)</td>
<td>11 (52%)</td>
<td>21</td>
</tr>
<tr>
<td>Graduate students</td>
<td>13 (41%)</td>
<td>19 (59%)</td>
<td>32</td>
</tr>
<tr>
<td>Technical personnel</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td>3</td>
</tr>
<tr>
<td>Administrative personnel</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>35 (46%)</td>
<td>41 (54%)</td>
<td>76</td>
</tr>
</tbody>
</table>

*In addition to scientists and personnel listed above, several visiting scientists, rotation students, and other scientists work at the Center for shorter periods of time (normally a couple of weeks to several months).
FINANCIAL SUPPORT

THE CENTER WAS IN 2003, in national competition, awarded a start-up grant of 52 million SEK for a period of six years (2003–2008) from the Swedish Foundation for Strategic Research. Following a half-time evaluation in 2005, it was awarded an additional seven million SEK for the remaining time period, 2006–2008. This grant financed the initial planning and organization of the Center. Funds were used for the recruitment of several young group leaders to the Center.

For its continuation, the Center was in 2009 awarded a "Translational Theme Grant” of 52.5 million SEK for a period of six years (2009–2015) from Karolinska Institutet and the Stockholm City Council. This grant finances the Center’s further strategic development including providing funds for new technology and methodology, as well as salaries to selected senior scientists, core personnel and infrastructure.

All specific research projects and other salaries to scientists in the research environment are funded by external grants obtained in competition such as national grants as well as international grants obtained from the EU, NIH and other international funding agencies. In 2011 only, scientists at the Center obtained more than 40 million SEK in funding for specific research projects and salaries.
**Major contributors 2009–2012**

Clas Groschinsky Foundation  
European Foundation for the Study of Diabetes  
European Union (EU)  
Histiocytosis Association of America  
Ingabritt and Arne Lundberg Research Foundation  
Jeansson Foundation  
Juvenile Diabetes Research Foundation (JDRF)  
Karolinska Institutet (KI)  
Knut and Alice Wallenberg Foundation  
National Institutes of Health (NIH)  
Royal Swedish Academy of Science (KVA)  
Stockholm County Council (SSL)  
Swedish Cancer Society (CF)  
Swedish Childhood Cancer Foundation (BCF)  
Swedish Foundation for Strategic Research (SSF)  
Swedish Heart and Lung Foundation (HLF)  
Swedish International Development Agency (SIDA)  
Swedish Research Council (VR)  
Swedish Society of Medicine (SLS)  
Tobias Foundation  
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Wennergren Foundations  
Åke Olsson Foundation  
Åke Wiberg Foundation