MIMS
Molecular Infection Medicine Sweden
Nordic EMBL Partnership for Molecular Medicine
Clinical Research Fellows
Visit and Mini-symposium
27–28 May 2013, Umeå
The MIMS Clinical Research (CRF) Programme

In order to strengthen clinical research and more closely incorporate preclinical and clinical research, MIMS decided in 2009 to initiate a programme for Clinical Fellows. The intention is to connect existing, mostly preclinical research projects closer to the clinic and to offer resources corresponding to half-time research positions for two years for young clinicians. Thereby MIMS will strengthen clinical research in infectious diseases and contribute to a fruitful translational interaction between clinicians and MIMS research programs.

In the first phase of the program four medical doctors with clinical appointments at Umeå University Hospital have been recruited to the programme and are connected since 2010 to MIMS groups.

In order to expand the programme to a national level a National Advisory Committee consisting of Kristian Riesbeck, Lund, Birgitta Henriques-Normark, Stockholm, Ann-Marie Svennerholm, Göteborg, Björn Olsén, Uppsala, Lennart Svensson, Linköping, has been recruited.

From 2013 six CRFs have been appointed and during 27–28 May they were invited to Umeå to meet the MIMS group leaders and to visit some research infrastructures. In a mini-symposium the CRFs and the new MIMS group leaders Maria Fällman and Sun Nyunt Wai present their research in connection with the visit by also the Executive Board which held its meeting in Umeå.

The whole Laboratory for Molecular Infection Medicine Sweden warmly welcomes Peter Bergman, Arvid Edén, Josef Järhult, Fredrik Kahn, and Sofia Nyström to Umeå!

Bernt Eric Uhlin  
Professor  
Department of Molecular Biology  
Director of MIMS

Anders Sjöstedt  
Professor  
Department of Clinical Microbiology  
Deputy Director of MIMS and responsible for the Clinical Research Fellows Programme
The MIMS Clinical Research Fellows recruitment 2010/2011

Malaria and bacterial concomitant infection
Concomitant infections occur at high frequencies in sub-Saharan Africa. Bacteraemic co-infection together with malaria aggravates disease and significantly raises both mortality and morbidity. Our previous work suggest that bacterial infection together with malaria unbalances the sensitive chain of events that takes place in the immune system during these infections. We have established a case-control study of co-infected patients on the major categories of severe malaria, severe anemia, cerebral malaria and respiratory distress. This study is currently carried out in three district hospitals, namely Ngarama, Nyagatare and Kanombe in Rwanda.

Rapid diagnosis of community acquired pneumonia
Community acquired pneumonia is a major cause of morbidity and mortality. Empiric antibiotic treatment is given based on clinical symptoms, x-ray and laboratory findings. Clinical scoring systems, like PSI and CRB-65, aid the physician in decisions regarding treatment in hospital or outpatient treatment, level of hospital supervision and treatment. My aim is to develop more sensitive, specific and rapid diagnostic tools to be useful in the clinical setting (quantitative PCR, microsphere-based multiplexed assays, metabolomics).

Molecular epidemiology and infection metabolomics
Our research explores two interconnected topics: 1. Infectious disease diagnostics using metabolomics for rapid identification of causative bacteria and antibiotic resistance traits. 2. Infectious disease epidemiology using microbial genotyping and spatial models. We have recently commenced metabolomic studies of specimens from humans with severe sepsis and from laboratory mice with experimental infection aiming at early specific detection of bacterial infections and identification of biomarkers for disease severity. High-resolution genotyping is used in our research for studying transmission routes of bacteria and their acquisition of various resistance genes in hospitals, the society, and reservoirs in nature. We are using clinical specimens for doing molecular epidemiology and population genetic studies of infections caused by *Escherichia coli*, *Staphylococcus epidermidis*, and *Francisella tularensis*.

Åsa Gylfe, see below!
Mini-symposium 28 May, Lecture hall Betula, bldg 6M

8:30  New Senior Group Leaders at MIMS
(chair: Bernt Eric Uhlin)

Maria Fällman, professor, Department of Molecular Biology
**Bacteria-Host interplay in gastrointestinal infections**

Sun Nyunt Wai, professor, Department of Molecular Biology
**Secretion of proteins via the type zero and type six routes of Vibrio cholerae**

9:15  Research Projects of the MIMS Clinical Research Fellows
(chair: Anders Sjöstedt)

10 min talk + 5 min questions each

Peter Bergman, Clinical Microbiology, Karolinska University Hospital, Stockholm
**Vitamin D and human immunity - experimental and clinical studies**

Arvid Edén, Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg
**Central nervous system viral “escape” and neuronal damage in HIV-1 infection**

9:45  Coffee break and picture taking of all MIMS members, of the Executive Board, all CRF, and the management
Mini-symposium 28 May, Lecture hall Betula, bldg 6M

10:15 Research Projects of the MIMS Clinical Research Fellows

Åsa Gylfe, Department of Clinical Microbiology and Norrlands University Hospital, Umeå
Strategies against antibiotic resistant bacterial infections: novel antibacterial compounds and rapid diagnosis with infection specific metabolites

Anders Johansson, Department of Clinical Microbiology and Norrlands University Hospital, Umeå
Molecular epidemiology and infection metabolomics

Josef Järhult, Department of Medical Sciences/ Infectious Diseases Uppsala University/Uppsala University Hospital
Antimicrobial resistance in a One Health perspectives

Fredrik Kahn, Department of Clinical Sciences, Infection Medicine, Lund University
Bacterial manipulation of host defence systems in sepsis

Sofia Nyström, Molecular Virology, Department of Clinical and Experimental Medicine, Linköping University Hospital
Immunomodulatory effects exerted by HIV-1 on dendritic cells and the induction of regulatory suppressor T cells

11:30 Lunch

13:00 The Clinical Research Fellows have the possibility to visit the scientific infrastructures at Chemical Biological Centre KBC

14:30 Conclusions of the visit, old library, Department of Molecular Biology
Vitamin D and human immunity - experimental and clinical studies

Vitamin D regulates calcium balance and bone health. In addition, it has a key role in adaptive and innate immunity. Low serum levels of vitamin D is associated with an increased risk of respiratory tract infections. We hypothesized that vitamin D supplementation could reduce the frequency and severity of respiratory tract infections (RTIs). To test this hypothesis we performed a randomised and placebo-controlled trial where 4000 IU vitamin D3 or placebo was given to patients for one year. The main result was that patients given vitamin D exhibited a reduced infectious burden related to RTIs and a lower antibiotic consumption compared with the placebo-group. Interestingly, in vitro experiments have shown that another compound, phenylbutyrate (PBA), is able to potentiate the effects of vitamin D. Thus, the combination of Vitamin D and PBA could potentially have even better clinical effects than vitamin D alone. My current research focus is to study the mechanisms involved in Vitamin D/PBA mediated effects on immunity and to perform additional clinical trials.

Central nervous system viral "escape" and neuronal damage in HIV-1 infection

Antiretroviral therapy (ART) has had a major impact in reducing HIV-1 related disease in the CNS, including HIV-associated dementia, but milder forms of neurocognitive impairment remains prevalent. Although ART is usually effective in lowering HIV-1 RNA in cerebrospinal fluid (CSF) as well as in plasma, cases of viral “escape” in CSF have been described. We have previously shown that 10% of effectively treated patients had detectable levels of HIV-1 RNA in CSF despite having undetectable levels in plasma, suggesting that some individuals may have a continuous low grade CNS infection. Our current research project will evaluate the occurrence of detectable CSF HIV-1 RNA longitudinally, in relation to immune activation and neuronal damage.
The MIMS Clinical Research Fellows recruitment 2013

Strategies against antibiotic resistant bacterial infections: novel antibacterial compounds and rapid diagnosis with infection specific metabolites

To identify novel drug candidates targeting the obligate intracellular bacteria *Chlamydiae* we are using high content screening of chemical compound libraries, modification of identified compounds and investigation of mode of action. The project involves development of a compound class with drug like properties and low toxicity identified in a recent screening. Chemical probes will be used for target identification as well as selection of resistant mutants. We are using high sensitive masspectrometry and chemometrical modeling to look for novel biomarkers for infections and treatment effects.

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Antimicrobial resistance in a One Health perspectives

My studies focus on different aspects of antimicrobial resistance: 1. development of resistance of influenza A viruses in the environment; 2. antibiotic resistance in the human/animal/environment interface; and 3. unknown resistance mechanisms against PTC-antibiotics. I believe that a multi-disciplinary, One Health-oriented approach is essential to grasp the full extent of the antimicrobial resistance problem. Therefore, I have close collaborations with scientists from many different areas such as environmental chemistry, veterinary medicine, zoonotic ecology and molecular biology.

Josef Järhult
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The MIMS Clinical Research Fellows recruitment 2013

Bacterial manipulation of host defence systems in sepsis

*Streptococcus pyogenes* sometimes causes invasive infections with very high mortality. Severe sepsis is often accompanied by thrombocytopenia. We have, in a model, shown that induced thrombocytopenia reduces the dissemination of infection. We plan to further characterize the platelet-pathogen interaction and its consequences for the host.

*Streptococcus agalactiae* causes life-threatening infections in neonates but has also an increasing incidence among elderly. sPLA2-IIA (group IIA secreted phospholipase A2) is one of the members in the family of phospholipases A2. *S. agalactiae* has proven to be extremely sensitive to sPLA2-IIA. In our studies we investigate if this enzyme modulates the course of *S. agalactiae* infections.

Fredrik Kahn
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Immunomodulatory effects exerted by HIV-1 on dendritic cells and the induction of regulatory suppressor T cells

New evidence indicates that HIV-1 has immune modulatory effects on DCs. In this study an in vitro model that aim to mimic in vivo situations of DC-T cell interaction in the presence of HIV-1 is used to study the effect HIV-1 exerts on DCs ability to prime T cells. We have shown that high doses of HIV-1 impaired DC priming of allogeneic and autologous T cells. The impairment of T cell proliferation was cell-contact dependent, involving inhibitory molecules and transcriptional repressors. The new knowledge regarding HIV pathogenesis made from this project can be translated into new ways to block viral dissemination and immune impairment. The model for HIV-1 induced T cell impairment will be used to test strategies to enhance the capacity of the host response to control HIV infection.

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