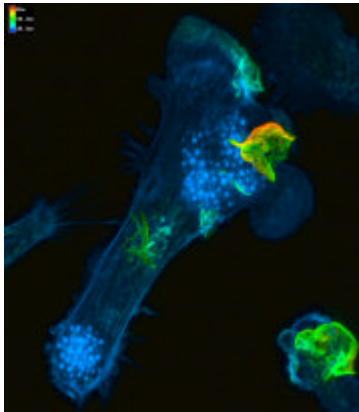


## Immunology

Immunology is one of the prioritized areas of the Karolinska Institute and there is a strong research tradition in this discipline. This is based on studies of basic mechanisms as well as on translational research in e.g. transplantation, infectious diseases, chronic inflammatory diseases, allergy and cancer. The immunological research is therefore conducted in several different departments of the university. The Karolinska Institutet network in Inflammation and Immunology ([www.kiim.ki.se](http://www.kiim.ki.se)) connects these different research groups through a common home page, scientific symposia, seminars and mailing lists for exchange of reagents and methods. It also acts to bridge experimental, clinical and epidemiological approaches (e.g. in studies of immunogenetics in chronic inflammatory diseases). This network is closely associated with the Ph.D. program for Allergy, Immunity and Inflammation ([www.aii.ki.se](http://www.aii.ki.se)) organizing advanced theoretical and methodological courses as well as laboratory rotations for new students.



Some departments and centers within Karolinska Institutet put a particular emphasis on immunology, thus forming central nodes in the network. These include the Strategic Research Center for studies of Integrative Recognition in the Immune System, The Center of Infectious Medicine and The Center of Molecular Medicine. Prioritized research interests include molecular, cellular and physiological aspects of NK-cells, dendritic cells, NK/T-cells; innate immunity in rheumatoid arthritis, inflammatory bowel disease and parasite infections; T-cell regulation in multiple sclerosis, transplantation, viral infections and cancer; Ig switch mechanisms in B-cells, vaccine development in HIV infection, malaria and cancer; interference with immunity by viruses in the Herpes-family; immunogenetics of inflammatory diseases.

*Dendritic cells are essential in the early immune reactions. From a Karolinska Institutet publication in Science (2004) 305:1153-1157.*

At Karolinska Institutet, groups are studying a number of factors that shape the immune response during infection. Thus, T-cell responses can be visualized and monitored with respect to antigen specificity and molecular effector function. New subsets of cells can be more precisely defined and understood at the molecular level. With new flow cytometry and imaging techniques, cells can be monitored with high resolution with respect to their interactions during the infectious response, *in vivo* and *in vitro*. New disease associated genetic polymorphisms mapped by molecular epidemiologists are explored functionally.

### Examples of three potential PhD projects:

#### 1. Molecular genetics of inflammatory and allergic disorders

This project focuses on finding new molecular pathways in inflammatory and allergic diseases, such as asthma, systemic lupus and psoriasis. Genetics are used as a primary strategy to find genomic regions and then genes that influence the risk to develop inflammatory diseases. The genes thus discovered may implicate new molecular mechanisms in disease pathogenesis. The discoveries made so far include the identification of GPR154 (GPR154) as an asthma susceptibility gene, studies on SLE candidate genes, and study of HCR1 (CCHCR1) as a susceptibility gene in psoriasis.

## **2. From abortive to effective NK- and T-cell recognition in HIV infection and cancer**

This project spans from basic research around “microbial strategies” and “host responses” to clinical research around intervention. It requires the becoming graduate student to be participating in a collaboration between groups specializing in T-cells, NK-cells, apoptosis and vaccination. The aim is to understand and develop methods to alter the inhibitory or abortive immune recognition of virus infected cells that often dominate the host-virus interactions in chronic infections (e g HIV). There is evidence that in such chronic virus infections, the infected cells do not avoid recognition completely by these effector cells; rather, the virus induce the host cell to present molecules or a profile of molecules that can inhibit or even induce apoptotic signals in effector cells. In the project the basic mechanisms behind abortive recognition will be studied by identifying critical components in the integrative pathways, and by developing tools to interfere with these, thus restoring effective recognition. The proposed studies may lead to new approaches to the treatment of and vaccination against these infections. Two parallel project investigates similar mechanisms in cancer (NK-cells and leukemia; T-cells and prostate cancer), aiming to restore effector function as an immunotherapeutic tool.

## **3. Studies of the inflammatory mediator HMGB1 in inflammation and arthritis**

HMGB1 is historically known as an abundant, non-histone, architectural chromosomal protein, that is extremely conserved across species. As a nuclear protein HMGB1 stabilizes nucleosomes and allows bending of DNA that facilitates gene transcription. Unexpectedly, recent studies identified extracellular HMGB1 as a potent macrophage-activating factor, inducing inflammatory responses. HMGB1 occupies a critical role as a proinflammatory mediator passively released by necrotic, but not apoptotic cells. Necrotic HMGB1-/- cells mediate minimal inflammatory responses. Stimulated macrophages actively secrete HMGB1 to promote inflammation, and in turn stimulate production of multiple pro-inflammatory cytokines. HMGB1 mediates endotoxin lethality, acute lung injury, arthritis induction, activation of macrophages, smooth muscle cell chemotaxis and epithelial cell barrier dysfunction. HMGB1 is structurally composed of three different domains, two homologous DNA-binding sequences entitled box A and box B and a highly negatively charged C-terminus. The B box domain contains the proinflammatory cytokine functionality of the molecule, whereas the A box region has an antagonistic, anti-inflammatory effect with therapeutic potential. Administration of highly purified, recombinant A box protein or neutralizing antibodies against HMGB1 rescued mice from lethal sepsis, even when initial treatment was delayed for 24 hours after the onset of infection, establishing a clinically relevant therapeutic window that is significantly wider than for other known cytokines. Analogous beneficial therapy results have recently been demonstrated in collagen-induced arthritis using either anti-HMGB1 antibodies or A box protein.

A generation of neutralizing anti-HMGB1 mAb is in good progress and these antibodies will be used for further therapy studies initially in experimental arthritis and later in a clinical setting. Such reagents will also be required for further quantitative assessments of HMGB1 in disease.

**For more information on the Immunology projects, please contact:**



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