

Director of the Research Center

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Current Fields of Research

Our center is focused on translational research in inflammatory rheumatic diseases. This means that we have three major arms in our research and we focus on a few inflammatory rheumatic diseases, mainly arthritis (focus on rheumatoid arthritis, responsible Lars Klareskog), SLE (responsible Elisabet Svenungsson and Iva Gunnarsson), Sjögrens syndrome (responsible Marie Wahren Herlenius) and myositis (responsible Ingrid Lundberg), with some emerging activities in sclerodermia and vasculitis. We also conduct basic research related to inflammatory diseases within immunology, genetics and epidemiology.

Our research is conducted in three collaborating units; in the clinic where we conduct careful IT-based surveillance of longitudinal course of disease on a large group of patients with arthritis, SLE and myositis. In this work we also capture biological material for further large scale analyses of genetics, biomarkers etc that determine onset and course of the rheumatic diseases. We also have an advanced clinical trials unit, (headed by Ronald van Vollenhoven), where both investigator initiated and industry sponsored trials are conducted.

In the laboratory, which is situated at the Center for Molecular Medicine, adjacent to the rheumatology clinic, 10 different research groups lead by different senior investigators, conduct immunological and genetic research related to arthritis, myositis, Sjögrens disease and SLE. We also conduct basic research on inflammatory mechanisms that may contribute to inflammatory diseases in general. Also animal models are used (PI Helena Erlandsson Harris) and the animal work is also conducted in close collaboration with the other center of excellence in Stockholm, headed by Rickard Holmdahl.

Epidemiology research and genetic epidemiology is the third arm of our rheumatology research center. Epidemiology research is conducted both at the institute for environmental medicine (PI Lars Alfredsson) where the secretariat of the EIRA-study is located. EIRA is aimed at understanding how genes and environment determine the onset and course of arthritis as well as myositis. Epidemiology research is also conducted at the unit for Clinical Epidemiology which is the center where the surveillance of drug utilization, safety of drugs and health economics are performed under the leadership of Johan Askling. Here we are coordinating the ARTIS (Anti Rheumatic Therapy In Sweden) registry which is in charge of the surveillance of biologics in arthritis in Sweden.

Support and informatics structures are being developed in order to fuse the different parts of our research structure and the registers and management is being coordinated by Staffan Lindblad (also affiliated with the unit for Medical Management at Karolinska Institutet).

A major strategy in our work is to combine the different competences in the different research groups with the rheumatology unit and the rheumatology clinic, and enhance a number of different national and international collaborations within our focus areas. Major efforts in this respect are national collaborations funded by the national research foundations in Sweden (all together 8 million Euros over 5 years, beginning autumn 2008). In addition we are

coordinating the AutoCure project for rheumatology research in Europe and we are also members of the EU FP7 funded program Masterswitch. We also have extensive international collaborations, primarily with the Feinstein Institutet in New York (Peter Gregersen), the Harvard School of Medicine and Broad Institute (Robert Plenge), Boston and the Genome Institute of Singapore (Mark Seielstad).

Selected Publications

1. Klareskog L, Rönnelid J, Lundberg K, Padyukov L, Alfredsson L. Immunity to citrullinated proteins in rheumatoid arthritis. *Annu Rev Immunol.* 2008;26:651-75
2. Dastmalchi M, Alexanderson H, Loell I, Ståhlberg M, Borg K, Lundberg IE, Esbjörnsson M. Effect of physical training on the proportion of slow-twitch type I muscle fibers, a novel nonimmune-mediated mechanism for muscle impairment in polymyositis or dermatomyositis. *Arthritis Rheum.* 2007 Oct 15;57(7):1303-10.
3. Alfredsson L, Criswell LA, Amos CI, Seldin MF, Kastner DL, Klareskog L, Gregersen PK. TRAF1-C5 as a risk locus for rheumatoid arthritis--a genome-wide study. *N Engl J Med.* 2007 Sep 20;357(12):1199-209. Epub 2007 Sep 5
4. Askling J, Fored CM, Geborek P, Jacobsson LT, van Vollenhoven R, Feltelius N, Lindblad S, Klareskog L. Swedish registers to examine drug safety and clinical issues in RA. *Ann Rheum Dis.* 2006 Jun;65(6):707-12.
5. Samuelsson B, Morgenstern R, Jakobsson PJ. Membrane prostaglandin E synthase-1: a novel therapeutic target. *Pharmacol Rev.* 2007 Sep;59(3):207-24.
6. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, Rönnelid J, Harris HE, Ulfgren AK, Rantapää-Dahlqvist S, Eklund A, Padyukov L, Alfredsson L. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006 Jan;54(1):38-46.
7. Palmblad K, Sundberg E, Diez M, Söderling R, Aveberger AC, Andersson U, Harris HE. Morphological characterization of intra-articular HMGB1 expression during the course of collagen-induced arthritis. *Arthritis Res Ther.* 2007;9(2):R35
8. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martín Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet.* 2004 Feb 28;363(9410):675-81
9. Salomonsson S, Sonesson SE, Ottosson L, Muhallab S, Olsson T, Sunnerhagen M, Kuchroo VK, Thorén P, Herlenius E, Wahren-Herlenius M. Ro/SSA autoantibodies directly bind cardiomyocytes, disturb calcium homeostasis, and mediate congenital heart block. *J Exp Med.* 2005 Jan 3;201(1):11-7.
10. Vällerskog T, Heimbürger M, Gunnarsson I, Zhou W, Wahren-Herlenius M, Trollmo C, Malmström V. Differential effects on BAFF and APRIL levels in rituximab-treated patients with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Res Ther.* 2006;8(6):R167

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EU FP7, Masterswitch

Söderbergska foundations

Swedish Research Foundations (Vinnova, Stratfo, KK, Vardal, Invest in Sweden agency)

NIH – 2 grants (co-PI)

Training of Fellows in Research

As part of our international collaborations we are keen to develop exchange with students, post docs and senior scientists from all over the world.

WebPages

www.ki.se

www.autocure.org

www.combinesweden.se