Cholera and cholera toxin, mucosal immunity and development of mucosal vaccines and immunotherapies

Group leader: Jan Holmgren (Professor, M.D., Ph.D.)
Members: Carl-Fredrik Flach (postdoc, Ph.D.), Michael Lebens (senior scientist, Ph.D.), Anna Lundgren (shared postdoc, Ph.D.), Jia-Bin Sun (senior scientist, Ph.D.), Sukanya Raghavan (scientist, Ph.D.), Erik Nygren (postdoc), Margareta Blomquist (BMA, senior research technician), Annelie Ekman (research technician), Susanne Källgård (research engineer), Natascha Svensson (research engineer)

The mucosal immune system comprises ca 80% of all immunocytes and has developed effective, as yet incompletely understood means for protecting both against mucosal infections and harmful immune responses to ingested or inhaled antigens. There is currently great interest internationally in developing mucosal vaccines against many important microbial pathogens. Mucosally induced tolerance also is a promising form of immunomodulation for treating certain autoimmune diseases and allergies. Our research addresses these closely interlinked areas by studies in which cholera toxin or cholera toxin derivatives are often used as antigens, vectors or immunomodulating agents:

1. Mucosal immunity research aiming at improved ways of mucosal vaccination and immune response steering. We define mucosal regulatory mechanisms determining the outcome -- immunity or tolerance -- of local antigen exposure and work on developing ways for steering and maximizing the immune response in the desired direction. Specifically, we (1) Study the role of different subsets of mucosally induced antigen presenting cells (APC) for induction of immunity or tolerance, (2) Continue our development and testing of mucosal adjuvants based on cholera toxin or heat-labile enterotoxin (LT), and (3) (With C Czerkinsky, IVI) Analyze sublingual mucosal immunization as a novel approach for inducing strong systemic and exceptionally broadly disseminated mucosal B and T cell immune responses, and we also with a Dutch consortium work towards the development of a novel influenza vaccine for sublingual administration.

2. Development of oral vaccines against gastrointestinal infections. We have developed an internationally widely registered oral vaccine (Dukoral®) against cholera with efficacy also against diarrhea caused by enterotoxigenic E.coli (ETEC); this is the only original vaccine ever developed in Scandinavia. The further specific vaccine development objectives are: (1) (With M Lebens): To develop an improved single-component oral cholera vaccine based on a vaccine strain which is engineered to co-express the Inaba and Ogawa LPS serotype antigens and contains an adjuvant-active CTB/CTA formulation in the periplasm; (2) (With A-M Svennerholm): To develop a specific vaccine against ETEC diarrhea, the most common cause of diarrheal illness in both children in developing countries and in travellers, based on CFA-overexpressing vaccine strains and a hybrid LTB/CTB protein; and (3) (With S. Raghavan and C-F Flach): To advance the understanding of the balance between immune protection and immunopathology in experimental H. pylori infection and immunization and to generate specific vaccine candidates.

3. Research to develop therapeutic vaccines against autoimmune disease and allergic asthma based on oral tolerance induction. We have developed a novel concept for mucosal tolerance induction based on the use of recombinantly produced CTB fused chemically or genetically to a relevant antigen/tolerogen. This has given very promising results in the prevention and treatment in animal models of autoimmune diseases (e.g. MS-like encephalomyelitis, RA-like arthritis, diabetes and uveitis); IgE- and DTH-mediated allergies; and infection immunopathology (e.g. schistosomiasis). This novel treatment principle has also been tested clinically with promising results in patients with Behcet’s disease. Based on this we (1) (With M Lebens) Develop selected CTB-based fusion proteins for use in immune therapy in Behcet’s disease, diabetes, atherosclerosis and allergic asthma; (2) (With
J-B Sun) Further define immunological mechanisms and correlates to positive treatment effects and the special role and potential usefulness of B-cells as protective antigen-presenting cells.

4. Research on the molecular evolution of *V. cholerae* We participate in an international collaboration (with IVI-Korea, Sanger Centre -UK, and NICED-India) to: 1) Define genome changes, differences in virulence, adaptation to environment, and responses to vaccination in new, rapidly spreading hybrid El Tor/classical strains as compared with authentic El Tor strains.

Selected recent publications (among ca 540):

**Reviews:**


**Originals:**

Brief CV for Prof. Jan Holmgren, MD, PhD, University of Gothenburg, Sweden

BRIEF SCIENTIFIC BIOSKETCH

JH is Professor of Medical Microbiology at the Sahlgrenska Academy at University of Gothenburg (UG), Sweden; and Director of the UG Vaccine Research Institute (GUVAX). He has published more than 500 papers in the fields of microbiology, immunology and vaccinology. A large part of his research has been focused on the mechanisms of disease and immunity in cholera and other mucosal infections and on the development of mucosal vaccines. He discovered, for instance, the AB subunit structure and function of cholera toxin and identified the GM1 ganglioside as the cholera toxin receptor (then the first ever structurally defined biologic receptor molecule). In the field of vaccines, JH and coworkers have e.g. pioneered the development of methods for assessment of intestinal and other mucosal immune responses in humans; they have developed the now internationally widely licensed B subunit-whole cell oral cholera vaccine (Dukoral™) all the way from concept to final product (phase I to phase IV clinical trials) and also been active in technology transfer for local vaccine production in developing countries; they are actively working on vaccine development against ETEC diarrhea and H. pylori infection; and they are trying to develop novel immunotherapies against allergic and autoimmune diseases based on induction of antigen-specific “oral tolerance” with very promising results. In more basic aspects of mucosal vaccinology, JH’s laboratory has made important contributions in mucosal adjuvant development. JH has collaboration with many international research institutions and programs including e.g. IVI, WHO, GAVI, ICDDR,B (Bangladesh), PATH (USA) and big EU programs for mucosal vaccines (MUVAPRED, MUCIMM, MUCADJ).

CIVIL STATUS

Born March 25, 1944 in Borås, Sweden; Swedish nationality; Married to Professor Ann-Mari Svennerholm, 3 children.

EDUCATION/DEGREES

Medical candidate (M.B.) 1965 (UG); Doctor of Medicine Science (Ph.D.) 1969 (UG); Docent in medical microbiology and immunology 1970 (UG); Medical Licentiate (legislation as physician/ M.D) 1973.

EMPLOYMENTS AND OFFICES

Current:
1981- Professor of Medical Microbiology, UG
2002- Also Director of University of Gothenburg Vaccine Research Institute (GUVAX)

Recent additional appointments:
1981-2005 Head/Chairman (Prefect) of the Department of Medical Microbiology and Immunology, UG
2005-2007 Assoc. Dean for Research of Sahlgrenska Academy (Health Sciences faculty), UG

Board of Directors

Current/Recent:
• Knut and Alice Wallenberg Foundation 1995-
• International Vaccine Institute (Seoul) 2000-2006 (Vice chair 2002-2006 )
• Global Alliance for Vaccines and Immunization (GAVI) 2003-2006
• Göran Gustafsson Foundation for Natural Sciences and Medical Research 2009-

Previous (selection):
- International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) 1979-1983
- Swedish Medical Research Council, 1983-1989

Other Boards.
Selection:
- International SAB for Max-Planck Institute of Infection Biology, Berlin 2005-
- International SAB for HIV vaccine (Italy) 2009-
- Selection committees for major scientific prizes, e.g. Artois-Baillet (Belgium), Jahre (Norway) 2004-, Swedish Royal Academy Gustafsson medical prize(chair) 2003-
- GAVI’s Management Committee (Chair) for GAVI’s special vaccine development introduction programs (ADIPs) for rotavirus and pneumococcal vaccines 2003- 2008
- Steering committees for WHO programs: Diarrhoeal diseases; Enteric vaccines; New vaccine technologies (Chair).

Scientific Honours/Awards
- The Royal Swedish Academy of Science Prize in Medicine 1977 (“Hilda and Alfred Erikssons pris”)
- The Anders Jahre Prize II (young scientists) in Medicine 1982 (Norway)
- “Söderbergska Priset” 1994 (shared with A-M Svennerholm; biggest Prize of The Swedish Medical Society)
- The Louis Jeantet Prize for Medicine 1994 (Switzerland; shared with Thierry Boon and Philippe Sansonetti; biggest prize in Europe after Nobel)
- The Eric K. Fernström Big Nordic Prize in Medicine 2004 (Lund University, Sweden; together with the Jahre prize the biggest prize in Scandinavia)
- The International Society for Mucosal Immunology “Distinguished Science Achievement Award” 2007
- Elected member Swedish Royal Academy of Sciences (KVA), class VII (Medicine); Swedish Royal Academy of Technical Sciences (IVA), class X (biotechnology); Royal Society for Arts and Science in Göteborg; Honorary member of The Gothenburg Medical Society
- Organizer or co-organizer of >30 international scientific conferences; Invited honorary or keynote speaker at >50 international conferences; Invited speaker and/or chairman at >200 international conferences/symposia.

Publications
Editor of Books
- Nobel Symposium "Cholera and related diarrheal disease", Karger 1980;

Scientific papers
Author or co-author of more than 500 scientific publications in microbiology, immunology, infectious diseases and biotechnology
- Ca 350 peer-reviewed original papers & 185 reviews, book chapters etc.