

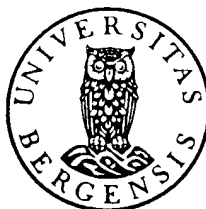


BROEGELMANN RESEARCH LABORATORY

*Department of Microbiology and Immunology
The Gade Institute*

Haukeland University Hospital - Faculty of Medicine

University of Bergen



ANNUAL REPORT

2000

"The Autoimmunity and Mucosal Immunobiology
Research Group (AMIR)"

Postal address:

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1. Administration - personnel - scientists

Administration
Technical and administrative personnel
Postdoctoral positions
Visiting scientists
Trainees

2. Teaching

Postgraduate teaching
Guestlectures

3. Scientific activity

Completed thesis work
Aims of research
Collaborating institutions
Major projects
Collaborating projects
Projects supported by the EU-Biomed 2

Publications

4. External activity

5. External funding

1. Administration - personnel - scientists

The Broegelmann Research Laboratory (BRL) is an immunology research unit at the University of Bergen and Haukeland University Hospital. The Laboratory was initiated in 1957 after a donation to the University of Bergen and is co-localised and integrated with the Department of Microbiology and Immunology, the Gade Institute. The core financial support comes from the Broegelmann Foundation. The main research activity is organized in the "Autoimmunity and Mucosal Immunobiology Research Group (AMIR).

RESEARCH AREAS:

Autoimmunity/chronic inflammation; molecular medicine; mucosal immunity; immunopathology; tumour immunology; nutrition and immunity.

HEAD OF LABORATORY (from 1991):

Roland Jonsson DMD, PhD, professor of medicine (immunology)

TECHNICAL/ADMINISTRATIVE PERSONNEL:

Kate Frøland (100% adm [55% BFL, 25% SJI, 20% EU])

Turid Tynning (50% BFL+ 50% ENT)

Marianne Eidsheim (80% BFL)(maternal leave from 06/99)

Hilde Garberg [100% (01-04/00 BFL + 05-07/00 Bjørge Bio)

+ 20% 08-12/00 H&R]

POSTDOCTORAL POSITIONS:

Anne Isine Bolstad DMD, PhD (molecular immunology/genetics)

Karl A. Brokstad PhD (molecular immunology/biology)

Kathrine Skarstein DMD, PhD (cellular immunology) (until 06/00)

Åke Davidsson MD, PhD (ENT – mucosal immunity)

Elisabeth Holen PhD (nutrition and immunity) (from 04/00)

VISITING SCIENTISTS:

Latisha Camp visiting student

Morris Reichlin visiting professor

TRAINEES:

Rheumatological immunology

Maria Ohlsson Msc, doctoral degree student
Konstantin Iakimtchouk MD, doctoral degree student

Principal supervisor(s)

Brokstad/Jonsson
Brokstad/Jonsson

Genetics in chronic inflammatory disease

Britt Nakken, cand mag, doctoral degree student

Bolstad/Jonsson

Mucosal immunobiology

Ivana Pereira Nunes DMD, doctoral degree student
Georg Tuwor

Jensen/Bakken/Jonsson
Lied

Mycobacterial immunity/vaccine development

Feseha Abebe MSc, doctoral degree student
Lise Schaug-Pettersen, cand scient/hovedfag student
Yoseph Haile Msc, doctoral degree student

Nerland/Bjune
Nerland
Nerland/Bjune/Wiker

Affiliated with Broegemann Research Laboratory (doctoral/master degree studies):

Tehmina Mustafa MD, Center for Int Health, UoB
Sabai Phyu MD, Center for Int Health, UoB
Jon-Helge Heimdal MD, Dept of ENT, UoB
Carla Olsnes, Dept of ENT, UoB
Lado Loko Loro DMD, Dept of Oral Pathol, UoB
Evelyn Neppelberg DMD, Dept of Oral Surgery, UoB
Tzige Weine Tesema MD, Center for Int Health, UoB
Jens-Christian Eriksson, Dept of ENT, UoB

Bjune/Nilsen
Bjune/Jonsson
Aarstad/Olofsson
Aarstad
Johannessen/Vintermyr/Jonsson
Johannessen/Jonsson
Bjorvatn
Davidsson/Brokstad

Affiliated with the laboratory (without current/immediate degree studies):

Pål Voltersvik MD, Dept of Medicine, UoB

Åsjö

Medical students (e.g. special reports):

Didrik Vestrheim (summer student fellowship)
Oddvin A. Bjørge
Ingrid Toft
Odd Børre Johansen

Jonsson
Holen/Jonsson
Jonsson
Marcusson/Jonsson

ADDITIONAL SCIENTISTS/KEY-COLLABORATORS AFFILIATED WITH THE LABORATORY AND WITH E.G. SUPERVISION FUNCTIONS PLUS JOINT PUBLICATIONS:

professor Vidar Bakken, Laboratory for Oral Microbiology
professor Gunnar Bjune, Centre for Int Health, Univ of Bergen and Oslo
dr med Johan G. Brun, Div of Rheumatology, Med Dept B, Haukel Univ Hospital
professor Hans-Jacob Haga, Div of Rheumatology, Med Dept B, Haukel Univ Hospital
professor Anne C. Johannessen, Dept of Oral Pathology, The Gade Institute
professor Einar Lied, Directorate of Fisheries
professor Jan Marcusson, Department of Dermatology, Haukeland Univ Hospital
senior scientist Audun H. Nerland, Marine Research Institute
professor Rune Nilsen, Centre for International Health
professor Jan Olofsson, Department of Otolaryngology/Head & Neck Surgery, Haukeland Univ Hospital
assoc professor Hans-Jørgen Aarstad, Department of Otolaryngology/Head & Neck Surgery, Haukeland Univ Hospital
professor Birgitta Åsjö, Center for Virology

2. Teaching

POSTGRADUATE TEACHING:

Continuesly during the spring and fall semesters a *seminar series in immunology* was conducted every week with presentations from invited speakers. On a weekly basis seminars were given related to research areas of the students/trainees (*project-meetings*). *Guest lectures* are an important part of intellectual stimulation. The scientists were teaching immunological techniques, autoimmunity, mucosal immunity and oral medicine in postgraduate courses and at other invited situations both at national and international gatherings.

GUESTLECTURES AND VISITORS AT BRL:

- | | |
|-------|---|
| 04/05 | Stanley R. Pillemer MD, Sjögren´s syndrome clinic and Gene Therapy and Therapeutics Branch, NIDCR/NIH, Bethesda, USA “On the diagnosis of Sjögren´s syndrome” |
| 11/05 | Roy A. Fava PhD, Veterans Affairs Medical Center, Vermont, USA, “Possible roles of lymphotoxin beta and LIGHT in arthritis” |
| 15/05 | Morris Reichlin MD, Professor, Oklahoma Medical Research Foundation, Arthritis – Immunology Program, Oklahoma City, USA
“Defining the pathogenicity of autoantibodies in SLE”
(<i>The 4th Broegelmann Lecture</i>) |

- 18/08 Lars-Åke Hansson, MD, PhD, professor, Department of Clinical Immunology, University of Göteborg, Sweden
“The remarkable immunological relation between the mother and her fetus and newborn”
- 16/11 Marie Wahren MD, PhD, assoc prof, Karolinska Institute, Stockholm, Sweden
- 14/12 Elwaleed Mustafa DDS, Karolinska Institute, Stockholm, Sweden

3. Scientific activity

COMPLETED THESIS WORKS IN 2000 WITH CONTRIBUTIONS FROM BRL:

Tigalovna M: IgG receptors and cytokines in skin and serum from healthy individuals and patients with psoriasis; dr med, thesis defended feb 2000. *Principal Institutes: Department of Dermatology, Ullevaal Hospital, University of Oslo and Broegelmann Research Laboratory, Department of Microbiology and Immunology, The Gade Institute, UoB. Supervisors: Nils Roar Bjerke, Roald Matre*

Elagib KEE: Characterization of autoantibodies in primary Sjögren’s syndrome; Analysis of immunoglobulin variable region genes; dr phil (dr med), thesis defended 16/6 2000. *Principal Institutes: Institute of Immunology, The National Hospital, University of Oslo. Supervisor: Jacob B. Natvig, Keith Thompson*

Phyu S: Mouse models for latent and slowly progressive tuberculosis: host immune responses and importance of compartmentalization; dr med, thesis defended 6/10 2000. *Principal Institutes: Centre for International Health and Broegelmann Research Laboratory, UoB. Supervisors: Gunnar Bjune, Roland Jonsson*

Dyrhol-Riise AM: Human immunodeficiency virus type I (HIV-1) infection and highly active antiretroviral therapy; Virus dynamics and immune reconstitution in blood and tonsillar tissue; dr med, thesis defended 10/11 2000. *Principal Institutes: Centre for Research in Virology, Department of Microbiology and Immunology, The Gade Institute, UoB. Supervisor: Birgitta Åsjö*

Mustafa T: Murine models of chronic tuberculosis: significance of granuloma morphology, apoptosis and immune evasion; dr med, thesis to be defended 1/12 2000. *Principal Institutes: Centre for International Health, Broegelmann Research Laboratory, and Department of Odontology, UoB. Supervisors: Gunnar Bjune, Rune Nilsen, Roland Jonsson*

Lako Loro L: Apoptosis in oral squamous cell carcinoma; dr odont, thesis submitted dec 2000. *Principal Institutes: Department of Odontology – Oral Pathology and Forensic Odontology, Broegelmann Research Laboratory, and Centre for International Health, UoB. Supervisors: Anne Christine Johannessen, Olav K. Vintermyr, Roland Jonsson*

SPECIFIC AIMS OF THE RESEARCH AT BRL:

The laboratory targets its efforts within the fields of autoimmunity, mucosal immunity, immunopathology and tumour immunology. *The work is directed towards basic immunological questions incl. genetics in rheumatological and mucosal immunity as well as clinical immunological topics.* Furthermore, experimental autoimmune/rheumatological research is conducted in murine systems. The laboratory work is performed with immunomorphological and functional immunological techniques at both cellular and molecular levels in human and murine tissues, sera, and secretions as well as in tissue- and cell-cultures. Specific areas of interest are summarized below:

- **AUTOIMMUNITY**

Autoimmune reactions are of central importance in the etiology of many somatic diseases. Different tissues can be affected in different ways but a common denominator is a chronic inflammation, which can result in tissue damage and accompanying loss of function. Our aim is to study disease mechanisms in connective tissue diseases (Sjögren's syndrome and rheumatoid arthritis) with special reference to exocrine gland and joint tissue. For this purpose we combine studies in both human and murine systems, which hopefully will help us in elucidating pathogenic mechanisms and more recently the genetic background as a basis for better diagnosis and therapy. The immunological aspect is concerned with cellular and molecular characterization of lesions, quantitation of humoral and cellular immune responses against endogenous and exogenous antigens, as well as attempts at immunomodulation. Special attention is given to programmed cell death (apoptosis) in relation to chronic inflammatory disorders (Sjögren's syndrome, rheumatoid arthritis, adult periodontitis).

- **MUCOSAL IMMUNITY**

Mucous membranes constitute important defence mechanisms for the body and contain important humoral effector functions via the humoral immune system. A change in the regulation of immunity can however give rise to undesirable side effects which may result in tissue lesions in mucous membranes of the oral cavity, the gastro-intestine, the vagina, the lungs, the exocrine glands etc. Furthermore, the body is normally confronted with the first antigen contact/stimulation through the mucous membranes. Our aim is to study antigen presentation in mucous membranes and to characterize defence mechanisms and pathological immunological situations. Knowledge obtained within this field is of particular importance for better diagnostic and preventive/treatment measures e.g. vaccines.

- **MYCOBACTERIAL IMMUNITY**

Tuberculosis is today the most important infectious disease world-wide. The currently used BCG vaccine has variable effect on primary tuberculosis, but little or no effect on reactivated tuberculosis. The aim of the project is to use molecular biology to characterize the individual antigens of *M. tuberculosis* and characterize the immune response at mucosal surfaces and in lymphoid organs in order to find suitable antigens for a future recombinant vaccine.

- **TUMOUR IMMUNOLOGY**

The immune system obviously has an important role in the development of malignant tumours. Our interests within this are: role of T-cells, macrophages, cytokines and apoptosis incl. regulating molecules in tumour development.

The scientific activity at BRL is concentrated much on an international profile with a vast network. Internationally BRL has kept and established contact with more than 10 foreign research institutions, mainly in Sweden, other European countries and USA. The work is characterized by "crossing" scientific fields aiming both towards clinical and basic research.

COLLABORATION IS ESTABLISHED WITH THE FOLLOWING LOCAL RESEARCH INSTITUTIONS:

- A. Department of Microbiology and Immunology, Sections for immunology, bacteriology and virology, The Gade Institute
 - B. Section of Rheumatology, Institute of Medicine
 - C. Department of Otolaryngology/Head & Neck Surgery
 - D. Department of Dermatology
 - E. Centre for Clinical Molecular Medicine/Dept of Medical Genetics
 - F. Centre for International Health
 - G. Department of Pathology and Oral Pathology, The Gade Institute
 - H. Laboratory for Oral Microbiology
- I. In addition, collaboration (joint grants/publications and/or sharing of reagents/materials) is established with the following laboratories/institutions:**
- 1. *Experimental rheumatic disease in murine models* (R. Holmdahl, Dept of Medical Inflammation Research, Lund Univ, Sweden)
 - 2. *Apoptosis and Fas antigen* (J. Mountz, Division of Clinical Immunology and Rheumatology, Univ of Alabama at Birmingham, AL, USA)
 - 3. *Immunology of rheumatic disease* (H. Carlsten & A. Tarkowski, Dept of Clinical Immunology, Univ of Göteborg, Sweden)
 - 4. *Potential viral etiology of autoantibody (Ro) production* (J. Harley, Arthritis and Immunology Program, Oklahoma Medical Research Foundation, OK, USA)
 - 5. *Anti-Ro and anti-La antibody studies* (M. Wahren, Dept of Medical Cell Genetics, Medical Nobel Institute, Karolinska Institute, Stockholm, Sverige)
 - 6. *Murine Ro and La antigens* (T. Gordon, Tissue Typing and Immunogenetics, Australian Red Cross Blood Transfusion Service, Adelaide, Australia)
 - 7. *Clinic/Epidemiology of inflammatory rheumatic disease* (J. Brun, H.J Haga, Division of Rheumatology, Medical Department B, UoB)
 - 8. *Calprotectin and its biology* (M. Fagerhol, Ullevål Hospital, Oslo)
 - 9. *Experimental models of Sjögren's syndrome* (Michael Humphreys-Beher, Univ of Florida, Gainesville, FL, USA)

Project supported by the European Union (EU) - Biomed II:

«Sjögren´s syndrome - A strategy for clarifying the disease process that underlies a chronic disorder of the mucous membranes»

Contract Nr.: BMH4-CT96-0595	Coordinator
Basic Research Project	
EU Contribution: 410,000 ECU	Prof Roland Jonsson
Starting date: spring/96	Tel: +47-55 97 46 48
Duration: 46 months	Fax: +47-55 97 58 17
EC Scientific Officer:	
Mr. Heikki Kallasvaara	
Fax: +32-2-295 5365	

Partners

Prof Josef S. Smolen	Vienna, Austria
Prof Joachim R. Kalden	Erlangen, Germany
Prof Haralampos M. Moutsopoulos	Athens, Greece
Prof Claudio Vitali	Pisa, Italy
Prof Jacob B. Natvig	Oslo, Norway
Dr Marie Wahren	Stockholm, Sweden
Prof Rikard Holmdahl	Lund, Sweden
Dr Rolf Manthorpe	Malmö, Sweden
Prof David Isenberg	London, United Kingdom

Project supported by the European Union (EU) - Biomed II:

«The genetics of systemic lupus erythematosus and Sjögren´s syndrome»

Contract Nr.: BMH4-CT98-3489	Coordinator
Basic Research Project	
EU Contribution: 1.200 Mill ECU	Prof. Ulf Gyllensten
	Dr Marta Alarcon-Riquelme
Starting date: spring/98	Tel: +46-18-513784
Duration: 36 months	Fax: +46-18-526849
EC Scientific Officer:	
Mr. Heikki Kallasvaara	
Fax: +32-2-295 5365	

Partners

Prof. Lars Klareskog	Stockholm, Sweden
Dr. Gunnar Sturfelt	Lund, Sweden
Prof. Paul A. Bacon	Birmingham, Great Britain
Dr. Kristján Steinsson	Reykjavik, Iceland
Dr. José Ma. Alvaro Gracia	Madrid, Spain
Prof. Roland Jonsson	Bergen, Norway
Prof Joachim R. Kalden	Erlangen, Germany
Daniel Commenges	Bordeaux, France
VP Mats Sundvall	Uppsala, Sweden

MAJOR SPECIFIC PROJECTS incl. progress report

- **Etiopathogenesis of autoimmunity with special reference to Sjögren's syndrome** (part of this is PhD thesis work for Ohlsson and Iakimchouk and student fellow Vestrheim)
(supported by EU/Biomed II and Research Council of Norway)

In the proposed studies we will investigate etiologic and pathogenic mechanisms in Sjögren's syndrome (SS), by focusing on a potential viral/microbial etiology of this autoimmune disease in exocrine glands. The project includes the following specific and long-term objectives: **I.** Characterization by immunological and molecular biological techniques the tissue distribution of viruses and/or their products at the site of tissue lesion, **II.** Investigation of the local and peripheral humoral response (antibody titers and quantitative evaluation of spontaneous immunoglobulin secretion at the single cell level) against endogenous antigens and viruses, **III.** Analysing the fine specificity of antibodies produced by using 'epitope scanning' and available databases, **IV.** Analysing antigen recognition by T-lymphocytes in salivary glands and peripheral blood using synthetic peptides of endogenous antigens and viral sequences, **V.** Performing polymerase chain reaction analyses on DNA and mRNA from human tissues and generated T-cell lines with the purpose of identifying any dormant versus active genomic viral sequences. It is anticipated that the proposed characterization and elucidation of potential viral etiology and related pathogenic mechanisms in this chronic inflammatory disease will yield direct important clinical insight into these disease processes. This may form a basis for therapeutic measures as well as contribute to our understanding of normal immune reactions in salivary glands.

Progress 2000: One paper has been published showing local production of anti-Ro/SSA and anti-La/SSB producing cells in salivary glands/saliva. Genomic HLA-typing of class II alleles of Norwegian anti-Ro/SS-A and anti-La/SS-B positive SS patients have been conducted and analyzed in relation to autoantibody phenotype; currently two papers submitted and one accepted. Studies have been conducted on potential etiologic agents/viruses in human material (serum, saliva, peripheral blood). Also, serological studies of Helicobacter pylori immunity has been conducted in SS and RA.

- **Apoptosis and its role in chronic inflammatory disease** (part of this is PhD thesis work for Ohlsson)
(supported by EU/Biomed II and Research Council of Norway)

The proposed study will focus on the possible role of Fas apoptosis antigen in the etiology and/or development of chronic inflammatory disease (CID) with special emphasis on Sjögren's syndrome. We will test the hypothesis that the abnormal expression of the Fas apoptosis antigen contributes to pathogenesis and development of autoimmune diseases, particularly of those characterized as lymphoproliferative disorders with a production of autoantibodies. To accomplish this goal, the proposal is to pursue four specific aims: **I.** characterize the constitutive and induced expression of Fas antigen in normal and inflammatory human tissue; **II.** determine the correlation of the secreted form of Fas antigen in pathogenesis and/or development of CID; **III.** determine if the abnormal proliferation of lymphocytes is due to defective Fas-mediated apoptosis; **IV.** identification of associations between Sjögren's syndrome and immune response genes. The significance of the proposed research is underlined by the high prevalence of CID in some of the more common autoimmune diseases. The results of the proposed research should let us understand the role of the secreted form of Fas antigen in Fas-Fas ligand mediated apoptosis. The method developed for detection of the secreted Fas antigen is important since the latter may have potential value as an additional marker for clinical diagnosis of CID patients. The conclusion of this research will shed light onto the development of therapies directed toward increasing apoptosis and elimination of these abnormal cells, which are present in the CID patients.

Progress 2000: One paper regarding Fas/FasL expression and in situ apoptosis in SS has been accepted

for publication. Screening for mutations in the Fas and FasL genes has been performed and a paper published.

- **Autoimmunity and pathogenesis of murine sialadenitis**
(supported by EU/Biomed II and Research Council of Norway)

Studies proposed will investigate the immunopathogenesis of sialadenitis in spontaneous and congenic murine models of Sjögren's syndrome. Local responses to potentially immunogenic and endogenous constituents in salivary glands will be investigated. An enzymatic dissociation method evaluated/assessed at this laboratory will permit detailed cellular and molecular analysis of resident and infiltrating lymphoid cell populations present in involved tissue. This project includes the following specific and long-term objectives: **I.** Characterization, by immunomorphological techniques, of the architecture of immunocompetent cells in salivary glands, **II.** Investigation of the characteristics of antigen presentation in murine sialadenitis; in particular, the capacity of salivary glands to generate an immune response after systemic or intraglandular immunization, **III.** Evaluation of infiltrating T cells during the evolution of sialadenitis for patterns of expression of T cell markers and T cell receptors incl. TCR a/b and TCR g/d gene expression and production of various lymphokines, **IV.** Analysis of autoreactivity/pathogenicity among infiltrating mononuclear cells by cell transfer and antigen specific T cell proliferation, **V.** Carrying out immunomodulation in order to prevent sialadenitis. The availability of autoimmune murine strains, the MRL/Mp-lpr/lpr and the NOD mouse, with spontaneous infiltration of mononuclear cells in salivary glands makes these models uniquely suited for the study of the pathogenesis of sialadenitis. The proposed studies should yield important insights concerning the pathogenesis of Sjögren's syndrome in humans as well as contribute to our understanding of normal immune responses in salivary glands.

Progress 2000: Phenotypic work (apoptosis, regulating molecules, T cell phenotypes) are under way in MHC congenic NOD strains.

- **Shared gene analysis and autoimmunity**
(part of this is PhD thesis work for Nakken)
(supported by EU/Biomed II and Research Council of Norway)

The longterm goal of the current murine studies is to obtain information about the influence of different genes in the development of sialadenitis as compared to arthritis, encephalomyelitis and diabetes. This is part of a wider approach also involving human genetic studies (candidate genes and whole genome scanning). The current aim is feasible due to already performed backcrossing and breeding of the NOD strain at the University of Lund, Sweden. More specifically the working plan is as follows: **1/** Different NOD congenic strains will be tested for susceptibility to diabetes, sialadenitis, arthritis and encephalomyelitis in order to initially determine the role of MHC/H-2 for the sensitivity of these diseases. **2/** Secondly, there will be done F1 hybrids between the strains in order to determine whether MHC plays a disease down-regulatory role. **3/** From these data another strain will be selected to analyse non-MHC genes. The goal is finally to determine the genes controlling susceptibility to autoimmune sialadenitis which might help in identifying the genetic background for human Sjögren's syndrome.

Progress 2000: Full genome scanning has been conducted and results are currently being analyzed as a basis for phenotypic/genotypic correlates. One paper on arthritis have been accepted and another one will shortly be submitted.

- **The genetics of Sjögren's syndrome; Identification of susceptibility genes**
(part of this is PhD thesis work for Nakken)
(supported by EU/Biomed II and Research Council of Norway)

Sjögren's syndrome (SS) is an autoimmune disease of unknown etiology and uncertain pathogenesis affecting predominantly women. Regardless of the actual mechanistic aspects of autoimmunity,

population, family and twin studies have clearly shown that genetic factors exert the most significant influence on autoimmune disease predisposition. Current understanding of the genetic factors that contribute to autoimmune disease predisposition indicate that multiple genes contribute to induction of pathogenic autoimmunity, and that no single genetic abnormality is sufficient in itself to induce disease. The ultimate objective of this project is to identify genes involved in the susceptibility for SS. To accomplish this goal, the proposal is to pursue four specific aims: **I.** clinical and immunological assessment of family material; **II.** identification of the chromosomal regions involved in the susceptibility to SS; **III.** identification of the genes involved in the susceptibility of SS and their genetic interactions; **IV.** development of diagnostic risk and risk assessment markers for clinical use. The experimental approach will include immunological assessment of family material and study of candidate genes parallel with genome scanning approaches, such as development of dense chromosomal maps based on polymorphic microsatellite DNA. Computer analysis will be performed for statistical and linkage analysis. The proposed project will yield important information concerning pathogenesis in SS and shed light on the genetics behind the disease.

Progress 2000: Polymorphisms/mutations have been detected in the Fas and FasL gene of primary SS patients; one paper is published. A large sample of primary SS patients have been analyzed in Germany for HLA-alleles, being part of a more than 300 patients and European study; one paper has been submitted and accepted. A Norwegian family material of Sjögren's syndrome and systemic lupus erythematosus has been collected (incl. clinical data, DNA and serum) and is now ready for gene scanning. Fine mapping of the hSLE2 locus involved in susceptibility to systemic lupus erythematosus, including the Norwegian material has been done in Uppsala; one paper will shortly be submitted.

- **Induction of cervico-vaginal mucosal immunity against group B streptococci** (PhD thesis work for Hordnes)

Group B streptococci (GBS) often colonize the birth channel of pregnant women leading to infection of the new-born. This type of infection represents a substantial health problem in many countries world-wide. In preliminary experiments of mice we have found that rectal vaccination can produce antibodies in serum and production of specific antibodies against GBS in local secretions. The purpose of this project is to characterize the systemic and local immune response, and map the region of the bacterium, which acts as a stimulus to immunity i.e. antigenic determinants. With this as a background the aim is to construct a vaccine to be tested in mice by analysing the obtained protection against infection of GBS in cervix/vagina after delivery of the vaccine per anally. In parallel with the murine experiments the immune response in humans will be monitored. If the analysis provide evidence for protection and safety it might be feasible to start phase-I vaccine studies in non-pregnant volunteers. If this proposed immunization will be effective it suggests that infection of new-borns can be prevented.

Progress 2000: Work is currently in preparation of a phase I vaccine trial using intra-nasal route of immunization. No major progress in 2000 due to a current contract in Saudi-Arabia for Knut Hordnes.

- **Molecular biology related to mycobacteria** (part of this is thesis work for Abebe, Haile, Schaug-Pettersen).

Tuberculosis is one of the major global health problems today with more than 8 million registered new cases and around 3 million registered deaths yearly (1992). To combat this disease there is a need for 1) faster and more sensitive diagnostic methods, 2) new antibiotics and 3) more efficient vaccines.

The aim of the project is development of improved vaccines and sensitive diagnostic methods that can discriminate between different mycobacterial infections.

The strategy is cloning of genes encoding relevant antigens of *M.tuberculosis* into vectors for expression in *E.coli*, followed by testing out the recombinant antigens for immune stimulation (lymphocyte stimulation test/skin test) and protection in an animal model (mice). In addition, the

Progress 2000: The gene encoding mpt64, an antigen present in *M.tuberculosis* but not in the *M.bovis* BCG strain, has been cloned into an *E.coli* expression vector. This antigen may be suitable to differentiate between vaccinated persons and persons infected with tuberculosis. The gene has also been cloned into an eukaryotic vector, and we are presently testing it for expression in eukaryotic cells (Cos-cells) *in vitro*. Cytokine studies in murine Tb has been performed.

- **Immune responses to *Fusobacterium nucleatum***
(PhD thesis work for Nunes)

Fusobacterium nucleatum is an anaerobic bacterium commonly isolated from sites of periodontal disease. The cell wall of this bacterium has been extensively studied and purified preparations of the outer membrane are available. The purpose is to compare different antigen preparations for their capacity to elicit a systemic immune response in mice. The second goal is to quantitate at the single cell level the local and peripheral immune response against *F. nucleatum* in adult periodontitis. Furthermore, the aim is to characterize stimulatory properties of this bacterium and/or derived proteins on T cells. The characterization of the immune response against *F. nucleatum* will help to elucidate its role in the microbial etiology of adult periodontitis.

Progress 2000: No progress due to maternal leave.

- **Immune responses to influenza; studies of mucosal immunity and vaccine responses**
(PhD thesis work for Eriksson, post doc project Davidsson)

The aim of this project is to examine immune competent cells and immune responses in the mucosa of the upper respiratory tract. We have chosen influenza virus as a model system to examine stimulation of the mucosal immune responses, either by stimulation by nasal/oral/mucosal route or by systemic route (parenteral vaccination).

Progress 2000: Clinical vaccine studies have been conducted and 2 papers submitted for publication.

- **Immunology and oligonucleotides**
(Postdoc project for Holen)

This project aims to clarify if there is interaction between the immune system and oligonucleotides in broad term.

Progress 2000: In vitro studies are ongoing.

OTHER COLLABORATIVE PROJECTS:

- **Humoral immunity and protein-deficiency** (Lied)

Progress 2000: Work for «master» thesis has been conducted and a thesis defended. Additional work is in progress.

- **Effects of orthodontic forces on immune cells in the periodontal ligament**
(Vandevska)

Progress 2000: Additional studies regarding osteoclastic activity during orthodontic move are in preparation.

- **Clinical evaluation and symptoms of the upper respiratory tract in patients with Sjögren's syndrome** (Hultén)

Progress 2000: One study related to reliability and sensitivity of diagnostic tests has been published. Further collection of clinical and laboratory data is ongoing.

- **Relations between immune functions/cytokines, psychological status and cancer development** (Heimdal/Aarstad)

Progress 2000: The work is focused at leukocyte studies from peripheral blood of cancer patients. Work on biology of metastases is being initiated; interactions between monocytes and spheroids. Two papers are in press.

- **Apoptosis in oral cancer** (Lado Loko Loro)

Progress 2000: A study has been conducted regarding CD40/CD40L in oral squamous cell carcinoma has been accepted for publication.

- **B cell activity (anti-p24 and anti-gp120) in tonsils and peripheral blood from**

humans with HIV infection (Voltersvik)

Progress 2000: Studies of B-cell activity in tonsils and peripheral blood of HIV patients is being summarized. Studies of cytokine production at the single cell level is in the writing phase. Additional studies regarding effects of treatment with HAART has been conducted.

- **T cell phenotypes and apoptosis in HIV infected tonsillar tissue** (Åsjö)

Progress 2000: Apoptotic and phenotypic studies are ongoing and are currently summarized. This is part of a doctoral thesis.

- **Immunohistopathology and mucosal/cellular immunity in experimental *M. tuberculosis*** (Phyu/Mustafa)

Progress 2000: Work has been finished but is also ongoing related to differential function of lung and spleen cells in normal and infected mice (Phyu). Furthermore, phenotypic and functional analysis incl. apoptosis of infiltrating cells during experimental tbc infection is currently studied in mice (Mustafa). Two doctoral thesis have been submitted and defended.

- **Immunohistopathology and apoptosis in oral lichen planus** (Neppelberg)

Progress 2000: A study of the rate of apoptosis in mucosal biopsies has been submitted.

- **Apoptosis in psoriasis and its relation to treatment** (Johansen, Marcusson)

Progress 2000: Patientmaterial has been collected and will be subject to laboratory analysis.

**PUBLICATIONS from THE BROEGELMANN RESEARCH LABORATORY
2000**

- Bolstad AI, Haga H-J, Wassmuth R, Jonsson R: Monozygotic twins with primary Sjögren's syndrome. *J Rheumatol* 27: 2264-2266, 2000.
- Bolstad AI, Wargelius A, Nakken B, Haga H-J, Jonsson R. Fas and FasL gene polymorphisms in primary Sjögren's syndrome. *J Rheumatol* 27: 2397-2405, 2000.
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In press

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- Nakken B, Jonsson R, Bolstad AI. Polymorphisms of the Ro52 gene associated with anti-Ro52 autoantibodies in patients with primary Sjögren´s syndrome. *Arthritis Rheum* 44: in press.
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4 External activity

LECTURES/SEMINARS/OTHER ACTIVITY

Roland Jonsson

- 6/1 Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB
- 10-14/1 Evaluation of EU proposals – Generic Activities, Brussels, Belgia (expert)
- 27/1 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB
- 2/2 Meeting at Norwegian Research Council
- Feb Evaluation abstracts for EULAR Meeting, Nice.
- 22-24/3 Attending the European Workshop of Rheumatology Research, Oxford, UK
- 29/3 Attending the Annual Education Meeting at CIH, UoB
- 28/4 Meeting at Bjørge Biomarine, Ellingsøy, Ålesund
- 2/5 Meeting at Norwegian Research Council
- 15/5 Organizer of the 4th Broegelmann Lecture, Haukeland University Hospital
- 24/5 Lecture at specialist course, University of Göteborg: "Sjögren´s syndrome"
- 26/5 Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB
- 31/5 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB
- 7/6 Opponent on med dr thesis (immunology), Univ of Göteborg
- 20/6 External examiner Master of Science thesis, Univ of Bergen
- 10-13/7 Evaluation of EU proposals – Accompanying measure, Brussels, Belgia (expert)
- 23-27/8 Attending the XXXIth Annual Scandinavian Society for Immunology Meeting, Council Meeting and Editorial Board Meeting of *Scandinavian Journal of Immunology*; Helsinki, Finland
- 4/9 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB
- 7-10/9 Invited lecture "Pathogenesis of Sjögren´s syndrome" and session chairman at the Scand Congress of Rheumatology, Turku, Finland
- 23/9 Invited lecture "Pathogenesis and Implications for Treatment of Sjögren´s syndrome" Continues Education Conference at NIDCR/NIH, Bethesda, USA
- 25-26/9 Worskhop on Genetics of Sjögren´s syndrome, NIDCR/NIH, Bethesda, USA
- 28/10-2/11 Attending American College of Rheumatology Meeting, Philadelphia, USA
- 6/11 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB

R. Jonsson has in 2000 (since 1999) served as Managing Editor (one of three Editors in chief) of *Scandinavian Journal of Immunology*. Further, he serves on the Editorial Board of *European Journal of Oral Sciences* and was appointed as advisory editor for *Arthritis and Rheumatism* and *Scandinavian*

R. Jonsson is currently (since 1998) Chairman of the Study Section/Peer Review Committee for Clinical Research, The Research Council of Norway

R. Jonsson is member of the Steering board for the "Vivarium", Faculty of Medicine, UoB and has served as a Board member of the Foundation Health and Rehabilitation.

During this year R. Jonsson has been involved in organizing the following International Scientific Meeting(s):

- "ICI-2001 (Sponsor Committee Advisory Group)", July 22-28, 2001 (Stockholm)
- "B cells and Autoimmunity – Satellite Meeting", July 19-21, 2001 (Bergen)
- "The XXXII Scandinavian Society of Immunology Meeting, April 24-28, 2002 (Bergen)

Anne Isine Bolstad

Spring/
Autumn

Responsible for weekly research seminars/seminar-program at Center for Medical Genetics and Molecular Medicine (about 60 employees)

Spring/
Autumn

Responsible for weekly project-seminars at BRL

Spring/
Autumn

Given seminars, a.o. advantages and disadvantages with the use of macroarrays; results from pilot studies

27-30/01

Attending the Biochemical Wintermeeting, Lillehammer

24-26/02

Attending NorFA meeting in Uppsala, Sweden

27-31/10

Attending American College of Rheumatology Meeting, Philadelphia, USA

2-3/11

Opponent on dr scient thesis (biochemistry/microbiology), Faculty of Mathematics and Natural Sciences, Bergen High Technology Centre

Karl Brokstad

Spring/autumn Responsible for the weekly seminars in Immunology at BRL

Computer coordinator for

- Broegelmann Research Laboratory, AHH
- Dept of Microbiology and Immunology, AHH
- Dept of Oral Microbiology, AHH
- Center for Virology, HIB

During this year KA Brokstad has been involved in organizing the following International Scientific Meeting(s):

- "B cells and Autoimmunity – Satellite Meeting", July 19-21, 2001 (Bergen)
- "The XXXII Scandinavian Society of Immunology Meeting, April 24-28, 2002 (Bergen)

Åke Davidsson

000205 Course in research strategy administered by University of Linköping, at Örebro Medical Centre Hospital, Örebro, Sweden.

Participation in American Academy of Allergy Asthma & Immunology. 56th Annual Meeting. March 2000. San Diego, USA.

Member of advisory discussion group in nasal corticosteroid therapy, Schering-Plough, March 2000, San Diego, USA.

000414. Invited to and attended ALLIS-meeting, Malmö, Sweden.

000426. Invited to and attended meeting organised by the Allergycenter at University of Linköping, Linköping, Sweden.

000427. Organised and lectured at meeting: Allergy in the airway, organised by the Center for Allergy at Örebro Medical Centre Hospital, Örebro, Sweden.

May 2000. Attended annual springmeeting of Swedish Society of Otolaryngology Head and Neck surgery.

May 2000. Attended meeting of Swedish ORL specialist education inspection board.

000913-15. Attended annual autumn meeting of the Swedish society of Otolaryngology Head and Neck surgery.

000913. Attended meeting of Swedish ORL specialist education inspection board.

000928-29. Attended and organised the annual meeting of the Swedish Rhinologic Society, Gothenburg, Sweden.

001129-001201. Participated at the annual meeting of the Swedish Medical Society, Gothenburg, Sweden.

Consultant at Dept. of ORL, Haukeland University Hospital, Bergen, Norway.

Consultant at Dept. of ORL, Örebro, Medical Centre Hospital, Örebro, Sweden.

Member of the educational group at Dept. of ORL, Örebro, Medical Centre Hospital, Örebro, Sweden. Teaching medical students in ORL at Dept. of ORL, Örebro, Medical Centre Hospital, Örebro, Sweden.

Member of the board of Center for Allergy, Örebro Medical Centre Hospital, Örebro, Sweden. Responsible for education in allergy for residents at Örebro Medical Centre Hospital, Örebro, Sweden. Responsible for the organisation of the meeting and meeting: Allergy in the airway 000427. Örebro Medical Centre Hospital, Örebro, Sweden.

Responsible for organising the annual meeting of the Swedish Rhinologic Society, 000928-29, Gothenburg, Sweden.

Secretary of the Swedish Rhinologic Society.

Member of the board of the Swedish Rhinologic Society.

Member of the Swedish ORL specialist education inspection board.

Åke Davidsson had during the year 2000 review assignments for three different scientific journals: Acta Otolaryngol (Stockh), Scandinavian Journal of Immunology Journal of Interferon & Cytokine Research.

Invited lecturer

Davidsson, Å. Cytokiner, har de en framtid på kliniken ? Ett kliniskt perspektiv på cellkommunikation. Allergi under ett nytt millenium. Framtiden ur ett näsvist perspektiv. Allismöte. 000414. Malmö. Sweden.

Davidsson, Å. Näsan som "homing" organ vid inflammation och antigenpresentation. Inflammation i luftvägsslemhinnan och allergisk inflammation på cellnivå. 000426. Linköping. Sweden.

Elisabeth Holen

Joined Broegelmann Research Laboratory 1/4-2000

28/4 Meeting at Bjørge Biomarine, Ellingsøy, Ålesund

5-9/6 Invited speaker in: Kurs nr. B-1536: Allergologi og immunologi ved sykdommer i luftveiene, UiB: Immunsystemet-Antigener-Allergener, Generelle egenskaper.

Participant in an ongoing project : Allergy Drugs, Allergy Research Group, UoB.