BROEGELMANN RESEARCH LABORATORY

Department of Microbiology and Immunology
The Gade Institute

Haukeland University Hospital - Faculty of Medicine

University of Bergen

ANNUAL REPORT

1999

"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
Abstracts

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 [30% BFL, 50% EU, 20% NFR])
Turid Tynning (50% BFL+ 50% ENT)
Marianne Eidsheim (80% BFL)(maternal leave from 06/99)
Hilde Garberg (100% BFL) (from 06/99)

POSTDOCTORAL POSITIONS:

Anne Isine Bolstad DMD, PhD	*(molecular immunology/genetics)*
Karl A. Brokstad PhD	*(molecular immunology/biology)*
Kathrine Skarstein DMD, PhD	*(cellular immunology)*
	(maternal leave until 08/99)

VISITING SCIENTISTS:

Åke Davidsson MD, PhD, Örebro County Hospital, Örebro, Sweden	*01/99*
Thomas P. Gordon MD, PhD, Flinders Medical Centre, Adelaide, Australia	*06/99*

TRAINEES:

Rheumatological immunology (Jonsson)	*Principal supervisor(s)*
Anne-Kristine Halse MD, doctoral degree student	*Jonsson*
Maria Ohlsson Msc, doctoral degr student	*Brokstad/Jonsson*
Konstantin Iakimtchouk MD, doctoral degree student	*Brokstad/Jonsson*

Genetics in chronic inflammatory disease (Bolstad)	
Britt Nakken, cand mag, doctoral degree student	*Bolstad/Jonsson*

Mucosal immunobiology (Jonsson)	
Ivana Pereira Nunes DMD, doctoral degree student	*Jensen/Bakken/Jonsson*
Georg Tuwor	*Lied*

Mycobacterial immunity/vaccine development (Nerland)	
Feseha Abebe MSc, doctoral degree student	*Nerland/Bjune*
Lise Schaug-Pettersen, cand scient/"hovedfag" student	*Nerland*
Ingunn Sommerset, cand scient/"hovedfag" student	*Nerland/Bakken*
Yoseph Haile Msc, doctoral degree student	*Nerland/Bjune/Wiker*

Affiliated with Broegelmann Research Laboratory (doctoral/master degree studies):	
Tone Skeie Jensen MD, Dept of Gynecology, UoB	*Matre*
Tehmina Mustafa MD, Center for Int Health, UoB	*Bjune/Nilsen*
Sabai Phyu MD, Center for Int Health, UoB	*Bjune/Jonsson*
Pia Tengnér MD, Karolinska Inst, Sweden	*Wahren-Herlenius/Jonsson*
Jon-Helge Heimdal MD, Dept of ENT, UoB	*Aarstad/Olofsson*
Carla Olsnes, Dept of ENT, UoB	*Aarstad*
Lado Loko Loro DMD, Dept of Oral Pathol, UoB	*Johannessen/Vintermyr/Jonsson*
Evelyn Neppelberg DMD, Dept of Oral Surgery, UoB	*Johannessen/Jonsson*
Selemawit Tadezze, Center for Int Health, UoB	*Bjune*
Tzige Weine Tesema MD, Center for Int Health, UoB	*Bjorvatn*

Affiliated with the laboratory (without current/immidiate degree studies):	
Roland Jureen MD, Dept of Microbiol/Immunol, UoB	*Nerland*
Pål Voltersvik MD, Dept of Medicine, UoB	*Åsjö*

Medical students (e.g. special reports):	
Lisbeth Homlong	*Bolstad*
Didrik Vestrheim	*Jonsson*
Oddvin A. Bjørge	*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 Lars R. Haaheim, Inst of Molecular Biology
dr med Knut Hordnes, Dept of Obstetrics and Gynecology
assoc professor Eystein Husebye, Medical Dept B, Haukeland Univ Hospital
professor Einar Lied, Directorate of Fisheries
senior scientist Audun H. Nerland, Marine Research Institute
professor Harald Jensen, Inst of Molecular Biology
professor Anne C. Johannessen, Dept of Oral Pathology, The Gade 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.

COURSES PROVIDED by BRL:

Immunological methods , March 17-19, 1999

Autoimmune disease - from molecular mechanisms to clinical practice ; May 10-12, 1999 together with E. Husebye and H.-J. Haga.

GUESTLECTURES AND VISITORS AT BRL:

05/02 *Med. Dr. Åke Davidsson, ENT, Regionsjukhuset i Örebro, Sweden "The cytokine network in allergic rhinitis and nasal polyposis. Interleukins 2,4,5,6,12 and RANTES"*

12/05 *Prof. Argyrios N. Theofilopoulos, The Scripps Research Institute, La Jolla, USA "The genes of systemic autoimmunity" (The 1999 Broegelmann Lecture)*

16/06 *Prof. Tom P. Gordon, Flinders University of South Australia*
"Anti-Ro and anti-La autoantibodies in patients with primary Sjögren's syndrome: epitope spreading, clinical subsets and immunogenetics"

29/06 *Prof. Constantin Bona, Mount Sinai Medical Center, New York*
"Dimeric soluble antigen presenting molecules in treatment of IDDM"

02/07 *Assoc.prof. Hal Scofield, Oklahoma Research Foundation, Oklahoma City*
"Human and experimental anti-Ro/SSA immunity"

3. Scientific activity

COMPLETED THESIS WORKS IN 1999 WITH CONTRIBUTIONS FROM BRL:

Steinmoen H: Optimalisering av plasmid for DNA-immunisering med fomA gen fra Fusobacterium nucleatum ; hovedfagsoppgave, thesis defence feb 1999. Principal Institute: Odontological Institute - Oral Microbiology, UoB. Supervisors: Vidar Bakken and Audun Nerland.

Tengnér P: Immune responses to the Ro and La autoantigens; med dr, thesis defence 28/5 1999. Principal Institute: Karolinska Institutet, Stockholm, Sweden and Broegelmann Research Laboratory, UoB. Supervisor: Marie Wahren-Herlenius.

Skeie Jensen T: Complement regulatory protein and factors with immunomodulatory properties in human reproduction; dr med, thesis defence 8/6 1999. Principal Institute: Broegelmann Research Laboratory, and Department of Microbiology and Immunology, The Gade Institute, UoB. Supervisor: Roald Matre.

Sommerset I: Molekylærbiologisk søk etter antigen-kodande sekvenser i «region of difference 1» (RD1) hjå Mycobacterium tuberculosis ; hovedfagsoppgave, thesis defence 29/9 1999. Principal Institute: Broegelmann Research Laboratory. Supervisor: Audun Nerland.

Halse A-K: Autoimmunity to Ro/SSA and La/SSB in Sjögren's syndrome; dr med, thesis defence 17/12 1999. Principal Institute: Broegelmann Research Laboratory, Department of Microbiology and Immunology, The Gade Institute, UoB. Supervisor: Roland Jonsson.

Tadesse S: TGF- β expression in slowly progressive primary and latent murine tubeculosis. Master Sc. Thesis defence 20/12 1999, pp. 1-56, University of Bergen, 1999. ISBN: 82-7815-030-3. Principal Institutes: Centre for International Health and Broegelmann Research Laboratory, Department of Microbiology and Immunology, The Gade Institute, UoB. Supervisors: Gunnar Bjune and Audun Nerland.

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 accompaning 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. Centre for Clinical Molecular Medicine/Dept of Medical Genetics
E. Centre for International Health
F. Department of Pathology and Oral Pathology, The Gade Institute
G. Laboratory for Oral Microbiology
H. Department of Obstetrics and Gynecology

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)*
10. *Vaccine development and mucosal immunity (B. Haneberg, National Institute of Public Health, Oslo, Norway)*

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 Halse, Tengnér, Ohlsson and lakimtchouk) (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 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 1999: Three papers have been published or in press showing local production of anti-Ro/SSA and anti-La/SSB producing cells in salivary glands/peripheral blodd with in situ detection and ELISPOT techniques, respectively. Another study of the frequency of cytokine production in peripheral blood of SS patients is in press. Two thesis on Ro/SSA and La/SSB immunity in Sjögren´s syndrome has been finalized; one in Bergen and one in Stockholm. 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 will be analyzed in relation to autoantibody phenotype; currently in the writing phase. Studies are ongoing on potential etiologic agents/viruses in human material (serum, saliva, tissues).

- ***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 lympho-proliferative 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 1999: One paper regarding Fas/FasL expression and in situ apoptosis in SS is in preparation. Screening for mutations in the Fas and FasL genes has been performed and a paper submitted.

- *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 α/β and TCR γ/δ 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 1999: Phenotypic work (apoptosis, regulating molecules, T cell pheotypes) are under way in different 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 1999: Full genome scanning has been conducted and results are currently being anlayzed as a basis for phenotypic/genotypic correlates.

- *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 1999: Polymorphisms/mutations have been detected in the Fas and FasL gene of primary SS patients; one paper is submitted. Studies on the Ro 52 and La genes has been conducted and summarized in a paper. A large sample of primary SS patients are currently being analyzed in Germany for HLA-alleles, being part of a more than 300 patients and European study; one paper has been prepared. 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 hSLE1 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 1999: Work is currently in preparation of a phase I vaccine trial using intra-nasal route of immunization.

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

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 same DNA sequences will be cloned into suitable vectors and tested out as «DNA vaccines».

Progress 1999: 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. One master thesis and one "hovedfag" has been finalized.

• *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 1999: The work has been continued and a human study is in the planning stage. One "hovedfag" has been finalized. Work has been partly delayed due to maternal leave.

OTHER COLLABORATIVE PROJECTS:

- *Emotional stress effects on immunity, periodontitis and gingivitis (Breivik)*

Progress 1999: Research has been summarized in one paper concerning phenotyping of rat periodontal tissues. The cytokine profile work has been delayed.

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

Progress 1999: Work for «master» thesis has been conducted and a thesis will shortly be finalized. Additional work is in progress.

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

Progress 1999: One paper has been published concerning immune-phenotyping in orthodontically manipulated periodontal tissues of the rat. Additional studies regarding osteoclastic activity during orthdontic move are in preparation.

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

Progress 1999 : 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 1999: 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 have been published and two are in press.

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

Progress 1999: Two papers have published during the year. Another study has been conducted regarding CD40/CD40L in oral squamous cell carcinoma and is currently prepared for publication.

- *B-cell activity (anti-p24 and anti-gp120) in tonsils and peripheral blood from humans with HIV infection (Voltersvik)*

Progress 1999: 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 conucted.

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

Progress 1999: Apoptotic and phenotypic studies are ongoing and are currently summarized.

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

Progress 1999: 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). A total of 3 papers have been published, 2 papers are in press and 2 papers have been submitted.

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

Progress 1999: A study of the rate of apoptosis in mucosal biopsies is in the writing phase.

PUBLICATIONS from THE BROEGELMANN RESEARCH LABORATORY 1999

- Bolstad AI, Nakken B: Genetics of Sjögren´s syndrome. In: The 100-Year Anniversary of Henrik Sjögren, eds. Eriksson P, Jonsson R, 1999, pp. 74-77.

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Sundler M, Johansson Å, Skarstein K, Kjellén P, Jonsson R, Holmdahl R: Genetic influence on the development of spontaneous autoimmune disease in NOD congenic strains. Printed in: Clin Exp Rheumatol 18; (1) abstr # A-3, 2000.

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4. External activity

LECTURES/SEMINARS/OTHER ACTIVITY

Roland Jonsson:

19/1	*Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB*
9/2	*Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB*
17/2	*Lecture in oral medicine: "Sjögren's syndrome", Faculty of odontology, UoB*
19/2	*Chairman doctoral thesis committee, UoB*
25-28/2	*Attending and session chairman at «The 19th European Workshop for Rheumatology Research», Oslo*
1/3	*Attending Research Conference "The Foundation Health and Rehabilitation" Oslo*
17-19/3	*Course leader and own lectures/presentations «Immunological Methods», UoB*
22/3	*Lectures at specialist course "Immunological diagnosis": "The secretory immune system" and "Autoimmunity – immunemediated tissue destruction", Haukeland University Hospital*
10-12/5	*Co-chairing course "Autoimmunity – from basic mechanisms to clinical diagnosis", Haukeland University Hospital, Bergen*
12/5	*Organizer of the 3rd Broegelmann Lecture, Haukeland University Hospital*
28/5	*Invited lecture "Sjögren´s syndrome" for Oral surgeons from Linköping, Sweden, at Haukeland University Hospital*
6/6-10/6	*Invited lecture "Recent Advances in the Treatment of Sjögren´s syndrome" and session chairman at the EULAR conference, Glasgow, Scotland*
22/6	*Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB*
23-27/6	*Attending and session chairman at «The Henry Kunkel Symposium», Oslo*
24/6	*Chairing Organizing Meeting on the EU Concerted Action «Sjögren´s syndrome», Oslo*
19-21/7	*Evaluating grant proposal for the European Commission, Brussels, Belgia*
25-29/8	*Attending and session chairman at the XXXth Annual Scandinavian Society for Immunology Meeting, Council Meeting and Editorial Board Meeting of Scandinavian Journal of Immunology; Lund, Sweden*

3-5/9 *Attending and session chairman "The 100 year anniversary of Henrik Sjögren", Jönköping, Sweden*

9/9 *Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB*

24-26/9 *Attending workshop on diagnostic criteria for Sjögren´s syndrome, Denver, CO, USA*

28/9 *Lecture in course "Immunology of infectious disease" on "Mucosal immunology", Haukeland University Hospital*

22/10 *Lecture in «Oral Mucosal and Salivary Gland Disease» for dental students in course Oral Pathology, UoB*

29/10 *Opponent on odont dr thesis, Univ of Stockholm*

3/11 *Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB*

5/11 *Lecture in «Oral Mucosal and Salivary Gland Disease» for dental students in course Oral Pathology, UoB*

13-17/11 *Invited lecture State of the art : "Sjögren´s syndrome", American College of Rheumatology, Boston, USA (recorded on CD)*

25/11 *Invited lecture "Recent developments in Sjögren´s syndrome", Zurich, Switzerland*

1-5/12 *Invited lectures and session chairman "The VII International Symposium on Sjögren´s syndrome", Venice, Italy*

R. Jonsson was in 1999 appointed 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.

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

During this year R. Jonsson has been a member of five Organizing Committees of International Scientific Meetings:

- *«The 19th European Worskhop for Rheumatology Research», Feb 25-28, 1999, Oslo*
- *«Autoantibodies and Autoimmunity», June 24-27, 1999, Oslo*
- *«The 100-Year Anniversary of Henrik Sjögren», Sept 3-5, 1999, Jönköping*
- *«The VII International Symposium on Sjögren´s syndrome», Venice, Dec 2-5, 1999*
- *«ICI-2001 Sponsor Committee Advisory Group», July 22-28, 2001*

Anne Isine Bolstad:

Febr.	*Seminar: EBV-transformering at Center for Molecular Medicine*
17-19/03	*Seminar :Immunologiske metoder: Genteknologiske metoder, PCR, sekvensering, mikrosatellitt analyse*
29/04	*Seminar: Familial mediterranian fever*
3-5/9	*Invited speaker "The 100 year anniversary of Henrik Sjögren", Jönköping, Sweden*
08/10	*Seminar: Microarrays*
28/10	*Seminar: Monozygotic twins with primary Sjögren´s syndrome*
09/12	*Seminar: Report from the VII International Symposium on Sjögren´s syndrome, Venice, Italy.*
Spring/ Autumn 99	*Responsible for research seminars at Center for Molecular Medicine* *Co-responsible for project seminars at Broegelmann Research Laboratory*

During this year A. I. Bolstad has been a member of "Sturingsgruppa" at Center for Molecular Medicine.

Karl Brokstad

Spring 99	*Responsible for the weekly seminars in Immunology at BRL*
19-22/8	*Invited speaker "Den artiske tonsillen", Svalbard, Norway*
25-29/8	*Attending the XXXth Annual Scandinavian Society for Immunology Meeting, Lund, Sweden*
Autumn 99	*Teaching dental students in immunology including examination and marking of the students*

K. A. Brokstad has been involved in planning and installing a new structured computer and telephony network in the AHH building

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

Kathrine Skarstein

Autumn 99	*Co-responsible for project seminars at Broegelmann Research Laboratory*

Broegelmann Research Laboratory, University of Bergen

Externally Funded Research Programmes 1999

Funding	Coordinator	Subject	Collaborating Institutions	Period	Budjet Total (1999)
EU	Roland Jonsson	Sjögren's syndrome - pathogenesis and immunogenetics (BMH4-CT96-0595)	University of Vienna University of Erlangen National University Athens Universita di Pisa University of Oslo Karolinska Institutet Lund University University Hospital Malmö University College London	1996-99	3.280.000,- (1.312.000,-)
EU	Roland Jonsson (coordinator at UoB)	Genetics of SLE and Sjögren's syndrome (BMH4-CT98-3489)	University of Uppsala Karolinska Hospital Lund University Hospital University of Birmingham Reykjavik University Hospital University of Madrid University of Erlangen Université d'Bordeaux NORDIC GENOMICS AB	1998-2001 total sum of funding 1.200.000,- ECU = 9.720.000,- NOK for all 10 groups/3 years	 (≈500.000,-)

Funding	Coordinator	Subject	Collaborating Institutions	Period	Budjet Total (1999)
NorFA	Roland Jonsson (coordinator at UoB)	Genetics of SLE and Sjögren's syndrome	University of Uppsala Reykjavik University Hospital Statens Seruminstitut, CPH Hvidovre Hospital, CPH Odense University Karolinska Hospital Lund University	1997-2001	(276.000,-)
NFR	Hans-Jacob Haga/ Roland Jonsson	Connective tissue disease in females	Dept of Rheumatology, UoB	1997-99	2.340.000,- (800.000,-)
Helse og Rehab	Roland Jonsson	Genetics of experimental Sjögren's syndrome	Lund University Univ of Uppsala	1998-2000	(440.000,-)
Helse og Rehab	Roland Jonsson	doctoral stipend (1) (Maria Ohlsson)	-	1999-2001	(410.000,-)
NFR	Roland Jonsson	Genetics of Sjögren's syndrome	(Instrumentation) Microarray Instrumentation	1999/00/?€	1.000.000,-)
NFR/SND	Roland Jonsson Einar Lied	Nukleotider fra fiskekmelke	Bjørge BioMarin A/S CIH, UiB Fiskeridirekt. Ernær. Inst	1999-2001	1.302.000,- (650.000)

NorFA = Nordic Academy for Advanced Study
NFR = The Research Council of Norway

Broegelmann Research Laboratory is a major collaborator of the following externally funded programmes at UoB:

Funding	Coordinator	Subject	Collaborating Institution(s)	Period
EU	Gunnar Bjune	Murine model for latent Tb (ERBIC-18-CT96-0066)	Center for Int Health	1996-99
NUFU	Einar Lied	Processing of Protein Foods to Improve Nutrition and Health	Center for Int Health/ Direct of Fisheries	1996-99
Kreftfor.	Jan Olofsson, Hans Jørgen Aarstad	Oropharyngeal cancer	Ear-Nose-Throat Department	1996-99
NFR + Kreftfor.	Birgitta Åsjö	HIV and tonsillar studies	Center for virology	1996-99