BROEGELMANN RESEARCH LABORATORY
Department of Microbiology and Immunology
The Gade Institute

Haukeland University Hospital - Faculty of Medicine

University of Bergen

ANNUAL REPORT

2001
The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

http://www.uib.no/Broegelmann/
http://www.uib.no/Broegelmann/mcts/

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http://www.uib.no/Broegelmann/
1. **Administration - personnel - scientists**

   Administration
   Technical and administrative personnel
   Postdoctoral fellows
   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 and Quality of Life

   Publications

4. **Editorial Activities – Scandinavian Journal of Immunology**

5. **Lectures/seminars/other activity**

6. **External funding**
1. Administration - personnel - scientists

The Broegelmann Research Laboratory (BRL) is an immunology research unit with a focus on Autoimmunity and Mucosal Immunobiology 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-localized and integrated with the Department of Microbiology and Immunology, the Gade Institute. Internationally the unit is one of the leading groups on Experimental, Clinical and Genetic Studies of Sjögren’s syndrome and currently holds a EU funded Marie Curie Training Site. A broad repertoire of molecular and cellular methods in immunology and molecular biology has been established.

The core financial support comes from the Broegelmann Foundation. Other major funding agencies have been EU (four contracts), the Research Council of Norway (“miljøstøtte”) and the Foundation Health and Rehabilitation. Between 1962 and 2002 BRL has contributed to the finalization of 50 PhD/doctoral and 14 Master degrees. BFL has been the organizer of three international immunology meetings in Bergen 1997, 2001 and 2002. Since 1999 the unit is one of three Scandinavian Editorial offices for Scandinavian Journal of Immunology with Prof R. Jonsson as Editor-in-Chief.

RESEARCH AREAS:

The research activity at BRL has been devoted to the following areas:
- autoimmunity/chronic inflammation
- molecular medicine
- functional genomics
- mucosal immunity
- immunopathology
- tumour immunology
- nutrition and immunology

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)
Hilde Garberg (20% BFL)

POSTDOCTORAL FELLOWS:
- Anne Isine Bolstad DMD, PhD (molecular immunology/genetics)
- Karl A. Brokstad PhD (molecular immunology/biology)
- Åke Davidsson MD, PhD (ENT – mucosal immunity)
- Elisabeth Holen PhD (nutrition and immunity)

VISITING SCIENTIST:
Stina Salomonsson (Marie Curie Training Site PhD-student)
The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

TRAINED:

**Rheumatological immunology**
- Maria Ohlsson MSc, doctoral degree student
- Konstantin Lakintchouk MD, master degree student
- Peter Szodoray MD, doctoral degree student
- Ketil Moen DDS, doctoral degree student

Principal supervisor(s)
- Brokstad/Jonsson
- Brokstad/Jonsson
- Jonsson
- Brun/Jonsson

**Genetics in chronic inflammatory disease**
- Britt Nakken, cand mag, doctoral degree student

Principal supervisor(s)
- Bolstad/Jonsson

**Mucosal immunobiology**
- Ivana Pereira Nunes DMD, doctoral degree student
- Margret Owusu-Amoako MSc student
- Jens-Christian Eriksson MD, doctoral degree student

Principal supervisor(s)
- Jensen/Bakken/Jonsson
- Lied
- Davidsson/Brokstad

**Affiliated with Broegelmann Research Laboratory (doctoral/master degree studies):**
- 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
- Pål Voltersvik MD, Dept of Medicine, UoB
- Nancy Bletsa DDS, Dept of Physiology, UoB

Principal supervisor(s)
- Aarstad/Olofsson
- Aarstad
- Johannessen/Vintermyr/Jonsson
- Johannessen/Jonsson
- Bjorvatn
- Åsjö
- Heyeraas

**Medical students (e.g. special reports):**
- Didrik Vestrheim (summer student fellowship)
- Oddvin A. Bjørge
- Stig Jellestad
- Odd Børre Johansen

Principal supervisor(s)
- Jonsson
- Holen/Jonsson
- Szodoray/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
- dr med Johan G. Brun, 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
- 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
Continuously 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
13/6 Nikolai V. Guchiev, Institute of Gene Biology, Moscow
21/6 Eric Dabelsteen, Department of Diagnostics, Panum Institute, Copenhagen
19/7 Fritz Melchers, Basel Institute of Immunology, Switzerland
“B-cell development” (The 5th Broegelmann Lecture)

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13/6 Nikolai V. Gnuchev, Institute of Gene Biology, Moscow
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19/7 Fritz Melchers, Basel Institute of Immunology, Switzerland
“B-cell development” (The 5th Broegelmann Lecture)

SCIENTIFIC WORKSHOPS/MEETINGS ORGANIZED BY BRL
Feb 2-4 the unit organized a NOS-M Workshop at Lysebu, Oslo with 25 Nordic attendees.

July 19-21 the unit organized a Satellite Meeting to the 2001 International Conference in Immunology. This Satellite Meeting was organized in Bergen and had the embracing theme: “B Cells and Autoimmunity: New Concepts and Therapeutic Perspectives” with 16 invited speakers and gathered the international experts in the field. A report was subsequently published:

3. Scientific activity

COMPLETED THESIS IN 2001 WITH CONTRIBUTIONS FROM BRL:

Iakimtchouk Konstantin: A possible viral etiology of primary Sjögren’s syndrome; Master Sc, thesis defended June 8. Principal Institute: Broegelmann Research Laboratory, UoB. Supervisors: Karl A. Brokstad, Roland Jonsson

Lako Loro Lado: Apoptosis in oral squamous cell carcinoma; dr odont, thesis defended June 20. 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

Owusu-Amoako Margaret: Nutritional status and humoral immune response in Ghanaian children; Master Sc, thesis defended Aug. Principal Institute: Institute of Nutrition, Directorate of Fisheries and Broegelmann Research Laboratory, UoB. Supervisor: Einar Lied.

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.

• TUMOUR IMMUNOLOGY

The immune system obviously has an important role in the development of malignant tumours. Our interests within this area: 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
The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

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

1. **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. *Genetic Studies in Sjögren’s syndrome and 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, Sweden)
6. *Murine Ro and La antigens* (T. Gordon, Tissue Typing and Immunogenetics, Flinders University Hospital, Adelaide, Australia)
7. *Clinic/Epidemiology of inflammatory rheumatic disease* (J. Brun, Section of Rheumatology, Institute of Medicine, UoB)
8. *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»

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<th>Contract Nr.: BMH4-CT96-0595</th>
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<td>Basic Research Project</td>
<td>Prof Roland Jonsson</td>
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- Prof Joachim R. Kalden Erlangen, Germany
- Prof Haralampus 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»

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<td>Prof. Ulf Gyllensten Dr. Marta Alarcon-Riquelme</td>
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- 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 Iakimtchouk 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 2001:** 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. Studies have been conducted on potential etiologic agents/viruses in human material (serum, saliva, peripheral blood). Also, serological studies of Helicobacter pylori immunity have been conducted in SS and RA. Studies of aquaporin-5 have been conducted in collaboration with Australia. A revised version of the EU criteria has been worked out after discussion in a EU-US consensus group.

- **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 2001: One paper regarding Fas/FasL expression and in situ apoptosis in SS has been published. In vitro apoptotic inductive studies have been conducted with regard to relocalization of the autoantigens Ro52, Ro60 and La48. Additional studies on the role of apoptosis has been: 1/ The effect of cytokine therapy on apoptosis-susceptibility of peripheral blood mononuclear cells in RA patients; 2/ the association between B cell activating factor (BAFF, BlyS, TALL-1) and autoimmune processes concerning programmed cell death in Sjögren’s syndrome patients, (both in peripheral blood B cells and salivary gland tissue); 3/ the role of B cell activating factor and programmed cell death in the pathogenesis of lymphoma development in Sjögren’s syndrome; 4/ the investigation of pro- and antiapoptotic molecules in Sjögren’s syndrome patients’ salivary gland biopsy tissues.

• 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 2001: Phenotypic work (apoptosis, regulating molecules, T cell phenotypes) are have been conducted in MHC congenic NOD strains as part of PhD thesis work for Britt Nakken.

• The genetics of Sjögren’s syndrome; identification of susceptibility genes

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 the autoimmune predisposition. Current understanding of the genetic factors that contribute to autoimmune disease predisposition indicate that multiple genes contribute to the 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 different approaches have been and will be applied, including studies on human material as well as on murine models: The proposal is to pursue the following specific aims:

A. HUMAN STUDIES:
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 to SS and their genetic interactions. IV. profiling gene expression of inflammatory salivary glands of SS patients. 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. Gene
expression studies on salivary glands will be performed by quantitative PCR and microarray. The
tissue localization of the expressed proteins will be detected by immunohistochemistry.

Progress 2001:

Candidate genes: Two papers on candidate genes have been published this year. First, we performed a
complete screen of the Ro52 gene in pSS patients, and a SNP was found to be strongly associated with
the presence of anti-Ro52 autoantibodies in pSS. This finding is interesting in light of the fact that an
alternative mRNA is made by deleting exon 4, which contains a putative leucine zipper domain,
generating a shorter version of the Ro52 protein (Ro52\textsuperscript{b}). Second, we wanted to explore the
association between HLA genotypes and clinical and immunological characteristics in Caucasians with
pSS. No significant associations were seen between HLA markers and histopathological or clinical
features of pSS. Significant positive associations with HLA class II markers were restricted to the
formation of different autoantibodies. Formation of an anti-Ro/SSA- and anti-La/SSB autoantibody
response, was positively associated with DRB1*03, DQB1*02 and DRB1*03/DRB1*15-
DQB1*02/DQB1*0602 heterozygosity. Considering the contribution of individual DQA1 and DQB1
amino acids and sequence motifs to the formation of anti-Ro/SSA and anti-La/SSB autoantibodies, a
dose-dependent positive influence was detected for DQ\textsuperscript{-}34Q and DQ\textsuperscript{-}26L. For DQ\textsuperscript{-}DI, the largest
difference between patients and controls was seen for the presence of a single copy of this motif after
selecting patients with either anti-Ro/SSA or anti-La/SSB autoantibodies.

Gene expression studies: One paper is submitted where we have assessed pSS salivary gland tissue
for their gene expression profile of the candidate genes Fas, FasL, Ro52\textsuperscript{a}, Ro52\textsuperscript{b}, La, CTLA4, PD-1
and Orm2, selected on the basis of their putative participation in salivary gland inflammation. The
study demonstrated a substantial increase in expression of the negative regulator molecules PD-1 and
CTLA-4, and the apoptotic signal molecules Fas and FasL in pSS patients which corresponded with
the immunomorphological pattern, and strongly indicates these molecules as central actors in the
inflammatory process of salivary glands in pSS. Gene expression profiling by microarray is initiated.

Family studies: Family material is collected continuously parallel to the other ongoing projects as part
of a more long-term strategy, and a full genome scan will be performed as soon as there are enough
families to give acceptable statistical power.

B. MURINE STUDIES:

Shared gene analysis and autoimmunity.
The long-term 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 involving human genetic studies as described above. 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: I. 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; II. There will be done F1 hybrids between the strains in order to determine whether MHC
plays a disease down regulatory role; III. 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 SS.

Progress 2001:

One paper is published and one is submitted where we have analysed shared genes and autoimmunity
in congenic murine models. A full genome scan using microsatellite markers were performed. In the
first paper we identified a NOD locus in an F2 cross with the H\textsuperscript{2}\textsuperscript{o} congenic NOD (NOD.Q) and
C57/Bl/10.Q (B10.Q) strains that promoted susceptibility to collagen-induced arthritis. Genetic control
of collagen induced arthritis in a cross with NOD and C57Bl/10 mice was found to be dependent on
gene regions containing complement C5 and FcgrII genes, and was not associated with loci controlling
diabetes. In the second paper, the genetic control of sialadenitis in mice was compared to that of
arthritis. The sialadenitis in NOD.Q showed a similar histological phenotype as in NOD, whereas no
submandibular gland infiltration was found in B10.Q. The development of sialadenitis was
independent of immunization with type II collagen and established arthritis. To identify the genetic
control of sialadenitis, a gene segregation experiment was performed on an (NOD.QxB10.Q)F2 cross and genetic mapping of 353 F2 mice revealed one significant locus associated with sialadenitis on chromosome 4, LOD score 4.7. The NOD.Q allele mediated susceptibility under a recessive inheritance pattern. The genetic control of sialadenitis seemed to be unique in comparison to diabetes and arthritis, as no loci associated with these diseases have been identified at the same location.

**Gene expression analyses** of sialadenitis in salivary glands of congenic mice by microarray have been initiated.

In addition to these experimental reports, two review papers and an invited correspondence have been published on related subjects. Also, the paper on Fas/FasL expression and *in situ* apoptosis in SS was published early this year.

- **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 2001:** No progress.

- **Influenza and mucosal immunology group (FLUMI)** (PhD thesis work for Eriksson, post doc project Davidsson)

  The aim of the project is to study the effect of influenza vaccination and natural infection on immune competent cells in the local lymphoid and mucosal tissue. Additionally, the mechanisms responsible for protection against influenza infection are investigated. We are also interested in the processes behind initiation and establishment of humoral and cellular immune memory in local mucosal and lymphoid tissue. Our main advantage is a well established collaboration between the clinics (ENT clinic) and the experimental immunology laboratory (Broegelmann) to investigate unique tissue samples in novel and relevant fashion.

**Progress 2001:** Clinical vaccine studies have been conducted and 2 papers submitted for publication.

- **Immunology and oligonucleotides**
  (Postdoc project for Holen, medical student project Bjørge)

  **Background** Purines and pyrimidines are building blocks for DNA and RNA synthesis. Tissues with rapid synthesis and degradation of cells, such as the immune system and the intestine, are heavily dependent on these nucleic acids for proliferation and protein synthesis. Emerging evidence suggests that nucleotide free diets induce immune suppression and may seriously influence intestine growth, maturation and function. **Aims** The aim of this study was to utilise a novel DNA-Na+ salt prepared from fish soft roe as well as sperm nuclei from salmon and RNA from baker's yeast (S. cerevisiae), investigating intestinal growth effects under optimal and nutrition depleted in vitro conditions and mononuclear cell growth and function. In addition, growth effects of the various deoxymono-nucleotides have been clarified.

**Conclusions**

- The results clearly show that DNA-Na+ from fish soft roe and specific deoxymono-nucleotides
are involved in growth regulation and influence cell function in intestinal and epithelial cell lines as well as in human immune cells. DNA-Na+ and specific nucleotides have clearly beneficial effects on intestinal cell growth.

- Of special interest is the observed modulation of mononuclear proliferation coupled to INF-gamma secretion, important for immunisation regimes and protection against pathogens.
- Also the tendency to reduce high "unwanted" responses as well as increase low to medium "wanted" responses, possible giving DNA-Na+ adjuvancing features.
- Similarities but also differences were observed investigating DNA and nucleotide effects on RA- and psoriatic patients PBMC, revealing differences in the immune cells of the two patients group. Amount or type of functional receptors, signalling pathways and so on, featuring the immune cells of a particular patients group, may be responsible for these divergent observations. Therefore, it is crucial to determine nucleotide-binding sites on various cell types to elucidate their mechanisms of action and signalling pathways, and thereby be able to create DNA-fragments, which specifically could be used in various disease conditions, or to manipulate various cell types.

DNA-Na+ from fish soft roe and the deoxy mono-nucleotides investigated, have application potentials in human and animal immunity, modulating immune cell proliferation responses and cytokine secretion as well as intestinal growth.

Progress 2001: In vitro studies have been conducted and are currently summarized for publication.

OTHER COLLABORATIVE PROJECTS:

• Humoral immunity and protein-deficiency (Lied)
  Progress 2001: Work for a «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 2001: Additional studies regarding osteoclastic activity during orthodontic move are in progress.

• Clinical evaluation and symptoms of the upper respiratory tract in patients with Sjögren's syndrome (Hultén)
  Progress 2001: Further collection of clinical and laboratory data is ongoing with a short review paper published.

• Relations between immune functions/cytokines, psychological status and cancer development (Heimdal/Aarstad)
  Progress 2001: 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.
- 15 -

The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

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

  *Progress 2001:* A doctoral thesis have been defended.

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

  *Progress 2001:* 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.

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

  *Progress 2001:* 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). One paper published.

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

  *Progress 2001:* A study of the rate of apoptosis in mucosal biopsies has been published.

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

  *Progress 2001:* Patientmaterial has been collected and analysed. Data are being summarized.
Mean impact factor (2001) for the top 5 publications = 8.34


**ABSTRACTS**


4. EDITORIAL ACTIVITIES – Scandinavian Journal of Immunology

Since 1999 BRL serves as the central Editorial Office for Scandinavian Journal of Immunology. This activity means a great number of international contacts in addition to the reviewing of scientific immunology papers. K. Frøland is part-time employed as Editorial Assistant with responsibilities for contacts with the publisher Blackwell Science, address lists for subscribers, economy etc.

In 2001, R. Jonsson initiated and produced an ICI2001 volume (double-issue) of Scandinavian Journal of Immunology which was printed in 6000 copies and distributed to all participants at the International Conference of Immunology in Stockholm. Papers received for publication in this issue was of very high standard.
5. LECTURES/SEMINARS/OTHER ACTIVITY

Roland Jonsson

29/1 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB

2-4/2 Organizer of NOS-M seminar on Mucosal Immunity at Lysebu, Oslo (25 participants)


27-28/2 Opponent doctoral thesis, University of Tromsø

16/3 Attending "Revmaklubb Vestland", Stavanger

3/4 Meeting with Bjørge Biomarin, Bergen

24-26/4 Evaluation of EU proposals – Ageing, Brussels, Belgia (expert)

8/5 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB

29/5 Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB

1/6 Meeting at the Research Council of Norway, Oslo

5/6 Meeting of the Steering Board for the "Vivarium", Faculty of Medicine, UoB

28/6 Meeting with Bjørge Biomarin, Bergen

18/7 Planning of Genetic Studies in Sjögren’s syndrome with John Harley et al., Bergen

19-21/7 Organizer of ICI2001 Satellite Meeting "B cells and Autoimmunity”, Bergen

22-27/7 Attending the ICI 2001 Conference, Stockholm, Sweden

27/7 Chairing Editorial Board Meeting "Scandinavian Journal of Immunology”, Stockholm, Sweden

23-26/8 Invited speaker “Etiopathogenesis of autoimmune rheumatic disease – what have we learned from animal models?”, The 84th Annual Meeting of NOF/IADR division, Copenhagen, Denmark;

31/8 Midterm Review on EU grant, Edinburgh, Scotland (expert)

10/9 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB

28/9 Attending "Revmaklubb Vestland”, Bergen

11/10 Lecture in immunology: "Autoimmunity", for medical students, Faculty of medicine, UoB

6/11 Attending Board Meeting The Foundation Health and Rehabilitation, Oslo

10-15/11 Invited Speaker «Oral manifestations of rheumatic disease», State-of-the-Art lecture at American College of Rheumatology Congress, San Fransisco, USA (=8.000 delegates); Attending Editorial Board Meeting Arthritis and Rheumatism and Sjögren's study Group session
The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

19/11 Lecture in ENT: "Oral disease" for medical students in course Otolaryngology, Faculty of medicine, UoB

22/11 Attending “Supervisor” Seminar, Faculty of Dentistry, Bergen

5-6/12 Attending Course for Scientific Journal Editors, Stockholm, Sweden

7/12 Attending Meeting for Nordic Editors, Stockholm, Sweden

17/12 Attending Meeting in The Broegelmann Foundation, Bergen

18/12 Meeting with Bjørge Biomarin, Ålesund

19/12 Lecture «Oral manifestations of rheumatic disease», Dept of Rheumatology, Haukeland University Clinic

R. Jonsson has in 2001 (since 1999) served as Managing Editor (one of three Editors in chief) of the Scandinavian Journal of Immunology. Further, he serves on the Editorial Board of European Journal of Oral Sciences, advisory editor for Arthritis and Rheumatism and Scandinavian Journal of Rheumatology.

R. Jonsson has been a 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 2001 Member of a committee evaluating applicants for a professor/assoc. prof position at the Faculty of Dentistry, Bergen

Spring 2001 Lectures and examination in periodontal pathogenesis for dental students at Faculty of Dentistry

Spring 2001 Member of the local organizing committee arranging the satellite meeting "B cells and autoimmunity: New concepts and therapeutic perspectives", Bergen, 20-21/7

23-27.02.01 Attended International Congress on Oral Immunology: "New frontiers in Oral Immunological Diseases, Lillehammer,

08.03.01 Seminar at BRL

28.03.01 Laboratory meeting with staff at Det norske Radiumhospital, Oslo, planning of the use of microarray in Bergen

June 2001 External examiner of a Master of Philosophy at Faculty of Dentistry and evaluation of the thesis.

22-27.07.01 Attending The 11th International Congress of Immunology, Stockholm

4-6.10.01 Attended the Annual Meeting of Norwegian Dental Association, Bergen

31.10.01 Seminar at Center for Medical Genetis and Molecular Medicine (Gentics of Sjögren’s syndrome)
The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

01.11.01 Seminar at BRL (Real Time PCR and gene expression)
10.12.01 Seminar at Center for Medical Genetis and Molecular Medicine (BAFF)

Autumn 2001 Member of the scientific committee arranging The XXXII Scandinavian Society of Immunology Meeting, April 24-28, 2002, Bergen

Jan-Dec 2001 Responsible for weekly project-seminars 2001 at BRL

Supervisor For Dr. philos. student


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


Deltagande i Svenska läkarälskapets läkarstämma, Stockholm Sverige 011128-30.


Eget föredrag och deltagande vid möte med möte för Allergicentrum USÖ, 011206, Örebro, Sverige.

Eget föredrag och deltagande vid möte med Allergicentrum i Uppsala. 011217. Uppsala, Sverige.


Under rapporteringsperioden 15/8 2001- 14/8 2002 hade Å. Davidsson även artikelgranskningsuppslag för tre olika vetenskapliga tidskrifter.

Medlem av allergicenturmens styrelse och ansvarig för utbildning inom allergi, av läkare under vidareutbildning, vid Universitetssjukhuset i Örebro, Sverige.

Undervisning och utbildning av medicine studerande vid ÖNH kliniken, Universitetssjukhuset i Örebro, Sverige.
The Autoimmunity and Mucosal Immunobiology Research Group (AMIR)

Elisabeth Holen

Joined Broegelmann Research Laboratory 1/4-2000

28/4 Meeting at Bjørge Biomarine, Ellingsøy, Ålesund


Participant in an ongoing project : Allergy Drugs, Allergy Research Group, UoB.
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<th>Collaborating Institutions</th>
<th>Period</th>
<th>Budget</th>
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<td>University of Bergen, University of Oslo, University of Madrid, University of Birmingham, Lund University Hospital, Karolinska Hospital, University of Uppsala</td>
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