



BROEGELMANN RESEARCH LABORATORY

The Gade Institute

University of Bergen



ANNUAL REPORT

2004

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1. The Year in Review

2004 has been another exciting year for the Broegelmann Research Laboratory and its staff. The Laboratory has continued to bond its place in the top league of international laboratories investigating systemic autoimmune diseases with a focus on Sjögren's syndrome. Among the exciting events during the year have been the visits of scientists from University of Florida (Janet Cornelius), Karolinska Institutet (Mathula Thangarajh), University of Southern Australia (Sue Lester) and University of Moscow (Ekaterina Rodionova). Professor Jonsson's standing in the field of Sjögren's syndrome research was recognized by invitations to give a number of key-note lectures and/or chair scientific sessions worldwide (Berlin, Beijing, Jeju, Göteborg, Birmingham (USA), Paris). Laboratory members were invited to speak at other national and international meetings or author articles and/or chapters in scientific publications/books.

The Laboratory has published extensively this year in top international journals; a mean impact factor of 5.2 was reached for the top five publications. The breadth of the Laboratory's approach to study autoimmunity and mucosal immunity is reflected in the diversity of fields in which publications have appeared, including immunology, infection & immunity, nutrition, pharmacology, physiology, and rheumatology.

Our Editorial Office for *Scandinavian Journal of Immunology* has received continuous attention by obtaining approx. 100 manuscripts in 2004. While the 2003 impact factor for most immunology journals in the middle field did go down, the impact factor for *Scandinavian Journal of Immunology* increased, indeed 2 years in a row.

The Laboratory has a track record of success in obtaining international funding (EU, NATO). One major success was the competitive approval of a new EU Marie Curie training grant. A major challenge will be to establish modern and up to date laboratory equipment and infrastructure. This is essential for being eligible and competitive for international funding.

2004 has also been a productive year for cementing and establishing clinical and scientific collaborations. As an initiative to further increase the Laboratory's activity, interaction and integration, an application for the Research School Program at the University of Bergen "The Bergen Research School in Inflammation (BRSI)" was submitted.

The Laboratory has a number of ongoing research projects including:

- Molecular studies of autoantibodies and biomarkers in Sjögren's syndrome
- Functional genetics of the autoimmune exocrinopathy
- Characterization of animal models for Sjögren's syndrome
- Genetic basis of human and murine Sjögren's syndrome
- Influenza and mucosal immunity

Roland Jonsson
Head of Broegelmann Research Laboratory

2. 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"), Helse Vest and the Foundation Health and Rehabilitation. Between 1962 and 2004 BRL has contributed to the finalization of 53 PhD/doctoral and 15 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 *Editorial offices for Scandinavian Journal of Immunology* with Prof R. Jonsson as Editor-in-Chief. Currently, the major activity of the Journal is localized to Bergen.

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 (The Broegelmann Chair in immunology)

TECHNICAL/ADMINISTRATIVE PERSONNEL:

Kate Frøland (100% adm [50% BFL, 30% SJI, 20% EU])

Marianne Eidsheim (80% BFL)

POSTDOCTORAL/SENIOR RESEARCH FELLOWS:

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

Karl A. Brokstad PhD (molecular immunology/biology)

Åke Davidsson MD, PhD (ENT – mucosal immunity)

VISITING SCIENTISTS:

Nicolas Delaleu	(Marie Curie Training Site PhD-student), Switzerland
Camilla Mittelholzer	(Marie Curie Training Site PhD-student), Sweden
Janet Cornelius	Florida, USA
Mathula Thangarajh	Stockholm, Sweden/India
Sue Lester	Adelaide, Australia
Ekaterina Rodionova	Moscow, Russia

TRAINEES:

Rheumatological immunology

Elisabeth Sivy Nginamau MD, master degree student
Peter Szodoray MD, doctoral degree student
Ketil Moen DDS, doctoral degree student
Tor Magne Madland MD, doctoral degree student
Nicolas Delaleu MSc, doctoral degree student

Principal supervisor(s)

Brokstad
Jonsson
Brun/Jonsson
Brun/Jonsson
Jonsson

Genetics in chronic inflammatory disease

Trond Ove Hjelmervik MSc, doctoral degree student

Bolstad/Jonsson

Mucosal immunobiology

Jens-Christian Eriksson MD, doctoral degree student

Davidsson/Brokstad

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

Carla Olsnes Msc, Dept of ENT, UoB
Pål Voltersvik MD, Dept of Medicine, UoB
Nancy Bletsa DDS, Dept of Physiology, UoB
Stanley Mogga MD, Centre for International Health, UoB
Malin V. Jonsson DDS, Dept of Oral Pathol, UoB

Aarstad
Åsjö
Heyeraas
Nilsen/Mustafa/Jonsson
Skarstein

Medical students (e.g. special reports):

Cecilie Ellingsen (summer student fellowship)
Oddleif Tjemsland
Stig Jellestad

Brokstad/Jonsson
Jonsson
Szodoray/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
assoc prof Johan G. Brun, Div of Rheumatology, Med Dept B, Haukel Univ Hospital
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 prof Kathrine Skarstein, Dept of Oral Pathology, The Gade Institute
professor Hans-Jørgen Aarstad, Department of Otolaryngology/Head & Neck Surgery, Haukeland Univ Hospital
professor Birgitta Åsjö, Center for Virology

3. Teaching

POSTGRADUATE TEACHING

Continuesly during the spring and fall semesters a *seminar series in immunology* was conducted every week with presentations from research fellows or 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

- | | |
|-------|---|
| 02/04 | A potential assay for anti-muscarine receptor autoantibodies in Sjögren's syndrome - Janet Cornelius, University of Florida |
| 14/05 | Gene transfer as a tool for understanding and managing organ-directed autoimmunity - Bruce Baum, Gene Therapy and Therapeutics Branch NIDCR/NIH, USA. (The 8th Broegelman Lecturer) |
| 25/10 | Immunogenetics in rheumatic disease - Sue Lester, University of Southern Australia |
| 2/9 | BAFF in multiple sclerosis and myasthenia gravis - Mathula Thangarajh, Karolinska Institutet |
| 13/10 | Potential infectious agents connected to primary Sjögren's syndrome - Ekaterina Rodionova, Univ of Moscow |

4. Scientific activity

COMPLETED THESIS IN 2004 WITH CONTRIBUTIONS FROM BRL:

Salomonsson S: The role of Ro52 autoantibodies in congenital heart block; dr med sci, thesis defended May 28, 2004. *Principal Institute: Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockhom Sweden. Supervisor: Marie Wahren-Herlenius.*

Nedrebø T: The effect of tumour necrosis factor- α and interleukin-1 β on interstitial fluid pressure and microvascular exchange in acute inflammation; dr med, thesis defended Nov 26, 2004. *Principal Institute: Section for Physiology, Institute of Biomedicine, University of Bergen. Supervisor: Rolf K. Reed*

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 the 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 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, Australia 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:

University of Bergen – Haukeland University Hospital

- 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. 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. *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)
3. *Anti-Ro and anti-La antibody studies* (M. Wahren, Centre for Molecular Medicine, Department of Rheumatology, Karolinska Institute, Stockholm, Sverige)
4. *Human/murine Ro and La antigens, aquaporins and muscarinic receptors* (T. Gordon, Tissue Typing and Immunogenetics, Flinders University Hospital, Adelaide, Australia)
5. *Muscarinic receptors and autoimmunity* (Ammon B. Peck, University of Gainesville, FL, USA)
6. *Clinic/Epidemiology of inflammatory rheumatic disease* (R. Omdal, Section for Clinical Immunology, Stavanger Hospital)
7. *Experimental model of Sjögren's syndrome* (Hal Scofield, Arthritis and Immunology Program, Oklahoma Medical Research Foundation, OK, USA)

MAJOR PROJECTS

- **Etiopathogenesis of autoimmunity with special reference to Sjögren's syndrome and rheumatoid arthritis** (part of this is PhD thesis work for Moen)
- **Apoptosis and its role in chronic inflammatory disease** (part of this is PhD thesis work for Szodoray)
- **Autoimmunity and pathogenesis of murine sialadenitis** (part of this is PhD thesis work for MV Jonsson)
- **The genetics of Sjögren's syndrome; identification of susceptibility genes and global gene expression studies** (part of this is PhD thesis work for Hjelmervik)
- **Influenza and mucosal immunobiology group (FLUMID)** (PhD thesis work for Eriksson and Mittelholzer, post doc project Davidsson)
- **Immunology and oligonucleotides** (Postdoc project for Holen, medical student project Bjørge)

OTHER COLLABORATIVE PROJECTS:

- **Clinical evaluation and symptoms of the upper respiratory tract in patients with Sjögren's syndrome** (Hultén)
- **Relations between immune functions/cytokines, psychological status and cancer development** (Heimdal/Aarstad)
- **B-cell activity (anti-p24 and anti-gp120) in tonsils and peripheral blood from humans with HIV infection** (Voltersvik)

PUBLICATIONS from the LABORATORY in 2004

Mean (tentative) impactfactor (2003) for the top 5 publications = 5.21

Cox RJ, Brokstad KA, Ogra PL. Influenza Virus: Immunity and Vaccination Strategies. Comparison of the Immune Response to Inactivated and Live, Attenuated Influenza Vaccines. *Scand J Immunol* 2004 Jan; 59(1): 1-15.

Delaleu N, Jonsson MV, Jonsson R. Disease mechanisms of Sjögren's syndrome. **Drug Discov Today** 1:329-336, 2004. (IF=4.943)

Davidsson Å, Uddman R. Persisterande (perenn) allergisk rinit. In: Allergologiska sjukdomar. Internetmedicin i Göteborg (www.internetmedicin.se). 2004. pp.17-20.

Davidsson Å, Uddman R. Vasomotorisk rinit (VMR). In: Allergologiska sjukdomar. Internetmedicin i Göteborg (www.internetmedicin.se). 2004. pp.21-24.

Gao J, Cha S, Jonsson R, Opalko J, Peck AB. Detection of anti-type-3 muscarinic acetylcholine receptor autoantibodies in sera of Sjögren's syndrome patients using a transfected cell line assay. **Arthritis Rheum** 50:2615-2621, 2004. (IF=7.190)

Holen E, Jonsson R. Dietary nucleotides and intestinal cell lines. I. Modulation of growth. *Nutrition Res* 24:197-207, 2004.

Jarvis JN, Dozmorov I, Jiang K, Frank MB, Szodoray P, Alex P, Centola M. Novel approaches to gene expression analysis of active polyarticular juvenile rheumatoid arthritis. **Arthritis Res Ther** 6:R15-R32, 2004. (IF=5.036)

Jonsson MK, Wahren B. Sexually transmitted herpes simplex viruses. *Scand J Inf Dis* 36: 93-101, 2004.

Jonsson R. Germinal Centres in Sjögren's syndrome. Proceedings APLAR 2004 pp. 54-56, 2004. MediMedia, Korea. www.aplar2004.com

Jonsson R. Tableau clinique et biologique et approche thérapeutique du syndrome de Sjögren. Quintessence du congrès 2004, Association dentaire française (ADF), pp. 30-32, 2004. ISSN: 1274-8293.

Jonsson R, Szodoray P, Moen K, Jonsson MK. Comparison of the lacrimal and salivary glands. In: *Immunology of the Lacrimal Gland and Tear Film*, eds. Zierhut M, et al., 2004, in press.

Madhun A, Cox R, Haaheim LR, Jonsson R, Brokstad KA. The kinetics of the systemic and local immune response to parenteral influenza vaccination. In: Options for the control of influenza V. International Congress Series 1263 (2004) 515-518.

Nedrebø T, Reed RK, Jonsson R, Berg A, Wiig H. Differential cytokine response in interstitial fluid and serum during experimental inflammation. **J Physiol** 556:193-202, 2004. (IF=4.352)

Szodoray P, Alex P, Brun JG, Centola M, Jonsson R. Circulating cytokines in primary Sjögren's syndrome determined by a multiplex cytokine array system. *Scand J Immunol* 59:592-599, 2004.

Szodoray P, Alex P, Dandapani V, Nakken B, Wilson PC, Jonsson R, Centola M. Apoptotic effect of Rituximab on peripheral blood B cells in rheumatoid arthritis. *Scand J Immunol* 60:209-218, 2004.

Szodoray P, Jellestad S, Alex P, Zhou T, Centola M, Brun JG, Jonsson R. Programmed cell death of peripheral blood B cells in Sjögren's syndrome with a special emphasis on BAFF determined by laser scanning cytometry. **J Clin Immunol** 24:600-611, 2004. (IF=2.591)

5. EDITORIAL ACTIVITIES – *Scandinavian Journal of Immunology*

Since 1999 BRL has been serving as the central Editorial Office for *Scandinavian Journal of Immunology*. This activity means a 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.

Jonsson - Editor-in-Chief (shared responsibility): *Scandinavian Journal of Immunology* (1999 - present)
Jonsson - Editorial Board Member/Advisory Editor: *Scandinavian Journal of Immunology* (1995 - 1999); *European Journal of Oral Sciences* (1999 - present); *Scandinavian Journal of Rheumatology* (2000 – present); *Arthritis & Rheumatism* (2000 – present); *Current Rheumatology Reviews* (2004 – present).

Referee: *Annals of the Rheumatic Diseases*, *Arthritis Research*, *Arthritis & Rheumatism*, *Clinical and Experimental Rheumatology*, *Journal of Oral Pathology & Medicine*, *Journal of Rheumatology*, *Rheumatology*, *Scandinavian Journal of Immunology*, *Scandinavian Journal of Rheumatology*, *The Vaccine*.

6. LECTURES – SEMINARS - OTHER ACTIVITY

Roland Jonsson - 2004

Invited speaker:

- 2004 “Immunopathology of Sjögren’s syndrome”, at the Annual European Congress of Rheumatology “EULAR2004”, Berlin, Germany
“Clinical and Experimental Sjögren’s syndrome”, at Department of Rheumatology and Immunology, Beijing University Medical School, Beijing, China
“Sjögren’s syndrome”, at the 30th Scandinavian Congress of Rheumatology, Göteborg, Sweden
“Germinal Centers in Sjögren’s syndrome”, at Asian Pacific League Against Rheumatism Meeting, Jeju, South Korea
“Sjögren’s syndrome”, Grand Round at Arthritis Center, Univ of Alabama at Birmingham and the Lowe Conference, Birmingham, AL, USA
“Sjögren’s syndrome: clinical presentation, biology and therapeutic approach”, at the Annual French Dental Association Meeting, Paris, France

Evaluation of Professorship in Rheumatology, Univ of Göteborg

R. Jonsson has served as a Board member of the Foundation Health and Expert evaluator for the Research Council of Norway.

During this year R. Jonsson has been involved in organizing the following International Scientific Meeting(s): The Scientific Committee of “The 8th World Congress of Inflammation”, Copenhagen 2007.