



BROEGELMANN RESEARCH LABORATORY

The Gade Institute

University of Bergen



ANNUAL REPORT

2006

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<http://www.uib.no/Broegelmann/brsi/index.html>

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1. The Year in Review

2006 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. This year the Laboratory has also increased its efforts in tumor immunology.

Among the exciting events during the year have been the recruitment of new staff members (Silke Appel, Sussie Dalvin, Ewa Szyszko, Arnt-Ove Hovden, Karstein Haldorsen, Petra Vogelsang) and visits of scientists from University of Moscow (Ekaterina Rodionova) and University of Coimbra (Carina Madureira). 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 (Kvitfjell, Washington DC, Reykjavik and Sorrento). 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 major international journals. 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, Neuroimmunology, Infection & Immunity, and Rheumatology.

Our Editorial Office for *Scandinavian Journal of Immunology* has received continuous attention by obtaining a steady influx of manuscripts in 2006. The impact factor for *Scandinavian Journal of Immunology* is increasing and launch of electronic submission and handling of manuscripts was set to Feb 1, 2006 through <http://mc.manuscriptcentral.com/sji>.

The Laboratory has a track record of success in obtaining international funding (EU, NATO). One major success was the competitive approval and start of a new EU Marie Curie training project (Contract No: MEST-CT-2004-514483) coordinated from Bergen. Another success was the grant support from *the Translational Medical Research Consortium* to Silke Appel. Our grant support from *the Strategic Research Program at Helse Bergen*, continues.

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 additional international funding. Time and energy has during the year been spent on planning the laboratory facilities in the new Laboratory Building for 2008/2009.

2006 has also been a productive year for cementing and establishing translational clinical and scientific collaborations. As an initiative to further increase the Laboratory's activity, interaction and integration, for the Research School Program at the University of Bergen "*The Bergen Research School in Inflammation (BRSI)*" established 5 separate research courses/seminars (HUIMM901-905).

The Laboratory has a number of ongoing research projects including:

- Molecular studies of autoantibodies and biomarkers in Sjögren's syndrome
- Functional genomics and genetic basis of the autoimmune exocrinopathy (human/murine)
- Influenza and mucosal immunity
- Dendritic cells and tumor vaccines

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 (five contracts – four as coordinator), the Research Council of Norway (“miljøstøtte”), Helse Vest, the Foundation Health and Rehabilitation, and more recently the Strategic Research Program at Helse Bergen. Between 1962 and 2005 BRL has contributed to the finalization of 55 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 the 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; tumor immunology.

HEAD OF LABORATORY (from 1991):

Roland Jonsson DMD, PhD
Professor of medicine (The Broegelmann Chair in Immunology)
Director Bergen Research School in Inflammation

TECHNICAL/ADMINISTRATIVE PERSONNEL:

Kate Frøland (100% adm [70% BFL, 30% SJI])
Marianne Eidsheim (80% BFL)
Kjerstin Jacobsen (100% UiB) (incl. teaching)

POSTDOCTORAL/SENIOR RESEARCH FELLOWS:

Silke Appel PhD	(cellular/molecular immunology)
Oddmund Bakke PhD, (prof II)	(cellular/molecular immunology)
Anne Isine Bolstad DMD, PhD	(molecular biology/genetics)
Karl A. Brokstad PhD	(molecular immunology/cell biology)
Sussie Dalvin PhD (15/06-12/06)	(cell biology)
Åke Davidsson MD, PhD	(ENT – mucosal immunity)
Arnt-Ove Hovden PhD (since 10/06)	(cellular/molecular immunology)

VISITING SCIENTISTS:

Carina Madureria	(ERASMUS Master student), Coimbra, Portugal
Ekaterina Rodionova	(PhD student), Moscow, Russia

TRAINEES:

Rheumatological immunology

	Principal supervisor(s)
Elisabeth Sivy Nginamau MD, doctoral degree student	Jonsson
Tor Magne Madland MD, doctoral degree student	Brun/Jonsson
Nicolas Delaleu MSc, doctoral degree student	Jonsson
Sergio Carracedo Huroz, MSc, doctoral degree student	Gullberg/Jonsson
Carina Madureria, master degree student	Delaleu
Petra Vogelsang MSc, doctoral degree student	Appel/Jonsson
Ewa Szyszko MSc, doctoral degree student	Brokstad/Skarstein/Jonsson
Karstein Halvorsen MD, doctoral degree student	Brun/Appel/Bolstad

Genetics in chronic inflammatory disease

Trond Ove Hjelmervik MSc, doctoral degree student	Bolstad/Jonsson
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Mucosal immunobiology

Camilla Mittelholzer, MSc, doctoral degree student	Brokstad
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	Aarstad
Pål Voltersvik MD, Dept of Medicine, UoB	Åsjö
Nancy Bletsa DDS, Dept of Physiology, UoB	Heyeraas
Malin V. Jonsson DDS, Dept of Oral Pathol, UoB	Skarstein

Medical students (e.g. special reports):

Cecilie Ellingsen (summer student fellowship)	Brokstad/Jonsson
Oddleif Tjemsland	Jonsson
Stig Jellestad	Szodoray/Jonsson
Camilla Braathen	Brokstad
Arild Sæther	Brokstad

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 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, the Gade Institute
professor Harald G. Wiker, Section for Bacteriology, the Gade Institute
professor Donald Gullberg, Dept of Physiology, Inst of Biomedicine

3. Teaching

POSTGRADUATE TEACHING

Continuously 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.

Day of Immunology, May 19 - Program:

Autoimmunitet – en ultimativ forklaring; Elling Ulvestad
Regulatoriske T celler; immunsystemets dirigent; Einar Kristoffersen
Immunologens verktøykasse; Karl A. Brokstad
Dendritiske celler; immunsystemets vektore; Silke Appel

GUESTLECTURES AND VISITORS AT BRL

- 19/5 JOHN F. KEARNEY, Birmingham, AL, USA - *The 10th Annual Broegelman Lecture: B cells and natural autoantibodies*
- 22/6 PIERRE YOUINOU, Brest, France: CD5 regulates B cells and B cells regulate tolerance
- 13/9 ELISABETH HULTGREN-HÖRNQUIST, Göteborg, Sweden: T cell ontogeny and effector functions in inflammatory bowel disease.

4. Scientific activity

COMPLETED THESIS IN 2006 WITH CONTRIBUTIONS FROM BRL:

Mittelholzer C: Influenza virus – protection and adaption; Philosophiae doctor (PhD), thesis defence April 6, 2006. *Principal Institutes: Microbiology and Tumorbiology Center, Karolinska Institute, The Swedish Institute for Infectious Disease Control and Broegelman Research Laboratory, The Gade Institute, University of Bergen. Supervisors: Annika Linde and Karl Brokstad.*

Rodionova E: Immunophenotype studies of minor salivary gland cells under *Chlamydia trachomatis* and *Mycoplasma pneumoniae* effect in Sjögren's syndrome; PhD thesis, thesis defence April 23, 2006. *Principal Institute: Peoples' Friendship University of Russia, Moscow.*

Jonsson MV: Ectopic germinal center formation in Sjögren's syndrome – significance of lymphoid organization; Doctor odontologiae (dr odont), thesis defence June 23, 2006. *Principal Institutes: Department of Oral Sciences – Oral Pathology and Forensic Odontology and Broegelman Research Laboratory, The Gade Institute, University of Bergen. Supervisor: Kathrine Skarstein.*

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.

- **TUMOR IMMUNOLOGY**

The immune system obviously has an important role in the development of malignant tumors. Our interests within this are: role of dendritic cells, T cells, macrophages, cytokines and apoptosis incl. regulating molecules in tumor 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, laying the ground for truly translational medicine.

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)
8. *Integrins and matrix biology* (Donald Gullberg, Section for Physiology, Institute of Biomedicine, UoB)
9. *Mycobacterial immunity and vaccine development* (Harald G. Wiker, Section for Bacteriology, the Gade Institute, UoB)
10. *Design of tumor specific immunotherapies* (Hans-Jørgen Aarstad, Dept of Otolaryngology/Head & Neck Surgery, Haukeland University Hospital)

MAJOR PROJECTS

Antigen induced immune modulation and autoimmunity (PhD thesis work for Nicolas Delaleu)

Role of dendritic cells in primary and experimental Sjögren's syndrome (PhD thesis work for Petra Vogelsang)

B cells, autoantigens and autoantibodies in Sjögren's syndrome (PhD thesis work for Elisabeth Nginamau and Ewa Szyszko)

Autoimmunity and pathogenesis of murine sialadenitis – lymphoid neogenesis (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)

OTHER COLLABORATIVE PROJECTS:

- **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 2006

Bergeland T, Tewinkel M, Bakke O. Precise calculation of photoactivation kinetics. *Nat Methods*, 3: iii-iv, 2006.

Centola M, Frank MB, Bolstad AI, Alex P, Szanto A, Zeher M, Hjelmervik TO, Jonsson R, Nakken B, Szegedi G, Szodoray P. Genome-scale assessment of molecular pathology in systemic autoimmune diseases using microarray technology: A potential breakthrough diagnostic and individualized therapy-design tool. *Scand J Immunol* 64:236-242, 2006.

Cox RJ, Brokstad KA, Haaheim LR. Pandemic influenza vaccine development: time is of the essence. *Expert Rev Vaccines* 5:603-606, 2006.

Cox RJ, Haaheim LR, Ericsson J-C, Madhun AS, Brokstad KA. The humoral and cellular responses induced locally and systemically after parenteral influenza vaccination in man. *Vaccine* 24:6577-6580, 2006.

Cox RJ, Hovden AO, Brokstad KA, Szyszko E, Madhun AS, Haaheim LR. The humoral immune response and protective efficacy of vaccination with inactivated split and whole influenza virus vaccines in BALB/c mice. *Vaccine* 24:6585-6587, 2006.

Danielsen A, Tynning T, Brokstad KA, Olofsson J, Davidsson A. Interleukin 5, IL6, IL12, IFN-gamma, RANTES and Fractalkine in human nasal polyps, turbinate mucosa and serum. *Eur Arch Otorhinolaryngol.* 263:282-289, 2006.

Gupta SN, Kloster MM, Rodionov DG, Bakke O. Re-routing of an invariant chain-TfR chimera to the direct sorting pathway by introduction of an AP3-binding motif from LIMPII. *Eur J Cell Biol* 85:457-467, 2006.

Jonsson MK, Levi M, Rudén U, Wahren B. Minimal change in HSV-2 seroreactivity – a cross-sectional Swedish population study. *Scand J Inf Dis* 38:357-365, 2006.

Jonsson MV: Ectopic germinal center formation in Sjögren's syndrome – significance of lymphoid organization. Thesis for doctoral degree. ISBN: 82-308-0176-2

Jonsson MV, Delaleu N, Brokstad KA, Berggren E, Skarstein K. Impaired salivary gland function - association with changes in cytokine profile but not with salivary gland histopathology. *Arthritis Rheum* 54:2300-2305, 2006.

Jonsson R, Ljunggren HG: Editorial. *Scand J Immunol* 64:171, 2006.

Mittelholzer CM: Influenza virus – protection and adaption. Thesis for doctoral degree. ISBN: 91-7140-656-5

Mittelholzer CM, Brokstad KA, Pauksens K, Jonsson R, Brytting M, Linde A. Human cell lines used in a micro neutralisation test for measuring the influenza neutralising antibodies. *Scand J Immunol* 63:257-263, 2006.

Moen K, Brun JG, Valen M, Skartveit L, Eribe ERK, Olsen I, Jonsson R. Synovial

inflammation in active rheumatoid arthritis and psoriatic arthritis favours a trap of a variety of oral bacterial DNAs. *Clin Exp Rheumatol* 24: 656-663, 2006.

Szodoray P, Alex P, Frank B, Turner M, Turner S, Cadwell C, Dozmorov I, Tang Y, Wilson PC, Jonsson R, Centola M. A genome-scale assessment of peripheral blood B-cell molecular homeostasis in patients with rheumatoid arthritis. *Rheumatology* 45:1466-1476, 2006.

Szodoray P, Jonsson R, Brun JG, Zeher M. Polymyalgia rheumatica in primary Sjögren's syndrome. *Rheumatol Int* 26:401-403, 2006.

Szyszkowski E, Brokstad KA, Cox RJ, Hovden AO, Madhun A, Haaheim LR. Impact of influenza vaccine formulation – a detailed analysis of the cytokine profile. *Scand J Immunol* 64:467-475, 2006.

Thangarajh M, Masterman T, Helgeland L, Rot U, Jonsson MV, Eide G, Pirskanen R, Hillert J, Jonsson R. The thymus is a source of B-cell survival factors – APRIL and BAFF - in myasthenia gravis. *J Neuroimmunol* 178:161-166, 2006.

Vogelsang P, Jonsson MV, Dalvin ST, Appel S. Role of dendritic cells in Sjögren's syndrome. *Scand J Immunol* 64:219-226, 2006.

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 - 2005); *Scandinavian Journal of Rheumatology* (2000 – present); *Arthritis & Rheumatism* (2000 – 2004); *Current Rheumatology Reviews* (2004 – present); *Up-to-date Rheumatology* (2005 – present).

Referee: *Annals of the Rheumatic Diseases*, *Arthritis & Rheumatism*, *Clinical and Experimental Rheumatology*, *Journal of Oral Pathology & Medicine*, *Journal of Rheumatology*, *Rheumatology*, *Scandinavian Journal of Immunology*, *Scandinavian Journal of Rheumatology*, *European Archives of Oto-rhino-laryngology*.

6. LECTURES – SEMINARS - OTHER ACTIVITY

Roland Jonsson - 2006

Course master: Basic Course in Medical and Health Related Research, Faculty of Medicine, UoB (weeks 3+4, 22+24, 45+46)

Invited speaker:

Sjögren's syndrome: can we expect new molecular markers in the diagnosis? – Kvitfjell, Norway
ETIOPATHOGENESIS OF SJÖGREN'S SYNDROME: Part I - Genetics + Panel discussion -

Washington DC, USA

Mucosal Membranes in Rheumatology, (Selected) NEWS AND VIEWS ABOUT SJÖGREN'S SYNDROME, Techniques in immunology serving rheumatology – Reykjavik, Iceland

Sjögrens syndrom: hva er nytt? – Stavanger, Norway
Current concepts on Sjögren's syndrome - Sorrento, Italy

Evaluation of dr thesis – opponent: Stavanger 13/10

Evaluation of professorship in immunology (19 applicants): Univ of Örebro, Sweden

Evaluation of research grant proposals:

The Danish Research Agency – International Expert Evaluator 2006
Tromsø Univ Hospital

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.

Appointed vice-chairman, the Gade Institute, with main responsibility for teaching, from 2005.