

RESEARCH OVERVIEW AND PLAN FOR DEPARTMENT OF RHEUMATOLOGY, RIGSHOSPITALET AND ITS LABORATORY, INSTITUTE OF INFLAMMATION RESEARCH

CONTENT

General description of the department.....	2
Research vision	3
Aims of our research	3
Research description.....	4
Clinical research areas	4
Basic research areas.....	7
Ten mostly cited papers involving our research group	9
Research staff.....	9
Partners actively involved in our research.....	11
Internally, at Rigshospitalet	11
Externally, outside Rigshospitalet.....	11
Funding.....	12
Important research points within the next 5 years	12

GENERAL DESCRIPTION OF THE DEPARTMENT

Department of Rheumatology at Rigshospitalet is part of Clinic for Infectious Diseases and Rheumatology at Rigshospitalet, which is a highly specialized hospital organized under the Capital Region of Denmark. With a few exceptions Rigshospitalet covers all medical specialties. Rigshospitalet is a major provider of health care with 82.000 discharges and 450.000 outpatient visits annually and contributor to health science with more than 1.500 peer-reviewed publications annually.

Department of Rheumatology provides approximately 1.000 discharges and 10.000 outpatient visits annually. The department receives patients for specialist diagnostic evaluation and treatment from other hospitals, other departments at Rigshospitalet or from the primary sector. Patients admitted to the department are characterized by the following conditions or treatment needs:

- Autoimmune connective tissue diseases and vasculitides, such as
 - systemic lupus erythematosus and antiphospholipid antibody syndrome
 - systemic vasculitis and primary cerebral angiitis
 - scleroderma
 - polymyositis
- Rheumatologic complications to rare diseases
 - Complement deficiencies and immunogenetic defects
 - Hereditary and connective tissue diseases including
 - Marfan syndrome
 - Osteogenesis imperfecta
 - Ehlers-Danlos syndrome, excluding the hypermobility syndrome
- Rheumatologic diseases where diagnosis and treatment require supplementing clinical and/or paraclinical special functions within eg:
 - nephrology
 - neurology
 - thoracic surgery
 - otolaryngology
 - neurophysiology
 - clinical physiology
- Rheumatologic diseases requiring specific treatment or care
 - Pregnancies in autoimmune connective tissue disease patients
 - Complicated inflammatory rheumatologic diseases requiring highly specialist treatments, such as:
 - experimental treatment
 - plasmapheresis
 - advanced intensive therapy
 - Inflammatory rheumatologic diseases with serious complications that require close cooperation between several highly specialized units

- Rheumatologic diseases associated with severe prognosis in terms of survival or sequelae such as neurosarcoidosis

The research laboratory of the department holds facilities ranging from basic laboratory techniques to multichannel flow cytometry, multiplex analyses, and advanced microarray techniques. Our clinical research team and the laboratory act as core facilities for sampling biological material for clinical research and clinical trials.

Our research is aimed at the above mentioned diseases and conditions focusing on inflammatory, autoimmune rheumatic diseases by direct study, study of other autoimmune diseases and study of chronic inflammatory disease secondary to infections. The research comprises among others clinical cohort studies, epidemiological approaches, aberrant innate and adaptive immune responses, genetic and environmental disease associations, and predictive studies of biopharmaceuticals and immunomodulatory therapy; all resulting in approximately 50 peer-reviewed publications and two PhD dissertations annually.

3

RESEARCH VISION

Our research is to contribute with significant and internationally recognized scientific findings that will help patients with inflammatory rheumatic diseases to maintain quality of life and functionality.

AIMS OF OUR RESEARCH

The research vision is to be reached by early disease identification, effective, personalized and non-adverse treatment and understanding the patient related aspects of the diseases.

Main areas and purposes of our research include

- Characterization and detailed description of clinical problems
 - With the aim to identify research needs
- Estimate the extent and influence on patient outcomes
 - With the aim to prioritize research needs
- Gaining insight of disease mechanisms
 - With the aim to facilitate early diagnostics and specific intervention.
- Development of new and optimization of known treatment modalities.
 - With the aim to increase quality of life, functionality and life span

Further, it is important that research in our department

- Has its main focus within areas that correspond to our clinical responsibilities

- Bridges between clinical and basic science
- Facilitates and is facilitated by collaboration with national and international research networks
- Supports further development of evidence-based diagnostics and treatment
- Contributes to the recruitment and retainment of qualified and talented researchers and other staff members
- Is a shared responsibility and concern for all professional groups in the department

RESEARCH DESCRIPTION

CLINICAL RESEARCH AREAS

I. AUTOIMMUNE CONNECTIVE TISSUE DISEASES

This section comprises in particular systemic lupus erythematosus, anti-phospholipid antibody syndrome and systemic sclerosis. Our clinical section has a large tertiary referral obligation to these diseases and has established clinical cohorts, which are being followed over time.

1. Systemic lupus erythematosus
 - a. Cohort studies comprising 100 to 700 patients studying genetic risk factors, clinical phenotypes, comorbidities and mortality, eg.
 - i. Nephritis and cardiovascular complications
 - ii. Clinical correlates to genetic variations of innate immunity components
 - iii. Contributing to pathogenetic studies
 1. Epigenetic alterations
 2. Apoptotic microparticles
 - b. SLICC contributor (Systemic Lupus International Collaborating Clinics). International cohort study comprising 1800 patients studying cardiovascular disease, nephritis and neuropsychiatric complications. Specific current studies focus on:
 - i. Classification criteria validation
 - ii. Development of flare definitions
 - iii. Cancer risk factors
 - iv. Lupus nephritis predictors
 - v. Lupus headache
 - c. IRBIS contributor (International Registry of Biologics in SLE). International cohort study comprising 500 patients studying use and effects of biologics in SLE.
 - d. BIOLUPUS. International study of genetic risk factors in SLE
 - i. Genome wide association studies
2. Anti-phospholipid antibody syndrome (APS)
 - a. EURO-phospholipid. European cohort study of 1000 APS patients studying clinical phenotypes, comorbidities and mortality.

3. Systemic sclerosis

- a. Copenhagen scleroderma cohort in collaboration with Department of Dermatology, Bispebjerg Hospital comprising 400 patients
- b. ESOS – European Scleroderma Observational Study focussing on patients with early diffuse systemic sclerosis and their treatment outcomes.
- c. SCTC – Scleroderma Clinical Trials Consortium. International network working with disease classification, comorbidities and trials in scleroderma.

4. Pregnancy in autoimmune CTDs

- a. Development of a risk stratified care algorithm focussing on improved outcome

Primary internal investigators: Søren Jacobsen, Mikkel Faurschou, Niels Tvede, Per Brown Frandsen, Claus H Nielsen

5

II. VASCULITIDES

Vasculitides comprise a variety of inflammatory disorders that involve small, medium-sized and large vessels. Clinically these disorders are mainly characterized by signs of systemic inflammation and end-results of the vessel inflammation. Our department has a particular focus on granulomatous inflammation of small vessels (granulomatosis with polyangiitis (Wegeners) and large vessels (giant cell arteritis and Takayasu arteritis) and is involved in both local and collaborative projects:

1. ANCA associated small vessel vasculitis
 - a. Genome wide association studies
 - b. Cancer risk factors
2. Large vessel vasculitis
 - a. Genome wide association studies
 - b. National register based epidemiological studies on incidence and mortality
3. EUVAS contributor (European Vasculitis Study Group). European initiative primarily promoting studies with focus on
 - a. Treatment
 - b. Development of vasculitis assessment tools
 - c. Guidelines

Primary internal investigators: Bo Baslund, Mikkel Faurschou.

III. ARTHRITIDES

Patients with inflammatory arthritides are mostly followed at our department in the event of treatment failures or extra-articular complications. Clinical studies mainly comprise patients with

1. Rheumatoid arthritis
 - a. Dose reduction of biologics in inactive disease
 - b. Contribution to specific studies of pathogenesis or immunomodulatory response
 - c. Contribution to studies in the Danish Biologics Register DANBIO
 - d. Meta-analyses of treatment regimes, mixed treatment comparisons
 - e. Genetic polymorphism as predictors of clinical response to treatment with therapeutic monoclonal antibodies, e.g. the influence of IL-6-receptor polymorphism on the clinical response of rheumatoid arthritis patients to treatment with the IL-6-receptor antagonist tocilizumab. Two patent applications based on this principle have been filed.
2. Spondylarthropathies
 - a. Contribution to biomarker and imaging studies
 - b. Contribution to studies in the Danish Biologics Register DANBIO

Primary internal investigators: Henrik Nordin, Niels Graudal, Per Brown Frandsen, Claus Henrik Nielsen, Søren Jacobsen

IV. INFLAMMATORY AND METABOLIC MUSCLE DISEASE

This section focuses on the pathogenesis of muscle dysfunction in autoimmune diseases, metabolism and possible inflammation in degenerative and metabolic muscle diseases.

1. Inflammatory muscle diseases, including polymyositis and dermatomyositis (PM/DM)
 - a. National cohort study of clinical phenotypes of PM/DM.
 - b. Cardiac involvement in PM/DM.
2. Polymyalgia rheumatica (PMR)
 - a. Gene expression in muscle of patients with PMR.
 - b. Circadian variation in clinical presentation and immune function in PMR.
3. Putative muscle inflammation in patients with mitochondrial myopathy.
4. Fat and carbohydrate muscle metabolism in patients with
 - a. Late-onset Pompe disease (α -glucosidase deficiency)
 - b. Debrancher deficiency

Primary internal investigators: Henrik Galbo, Søren Jacobsen, Niels Tvede.

V. OTHER CHRONIC IMMUNOINFLAMMATORY DISEASES

The spectrum of autoimmune and inflammatory diseases treated in our department is very broad and also involves conditions not strictly confined to the rheumatology specialty. However, due to the overlap between such diseases and several rheumatologic conditions, our department has gained a large experience within some of these diseases, in particular

1. Sarcoidosis and other granulomatous diseases
 - a. Pulmonary involvement
 - b. Cerebral involvement
2. Orbital pseudotumours

Primary internal investigators: Bo Baslund, Niels Graudal, Niels Milman

VI. GENERAL INTERNAL MEDICINE

High dietary salt intake is traditionally linked to excess risk of heart disease, but low intake may have the same effect. This has been addressed by meta-analyses and participation in the forming of an international white-paper.

Glucocorticosteroids are important tools in treating various immunemediated diseases and condtions, including inflammatory rheumatic diseases. Their mechanism of action, effects and optimal therapeutic usage are studied in vitro and in vivo.

Primary internal investigators: Niels Graudal, Bo Baslund

BASIC AND TRANSLATIONAL RESEARCH AREAS

A. AUTOIMMUNE HOMEOSTASIS AND DISORDERS

This section focuses on autoimmune homeostasis in healthy conditions versus immunopathogenic mechanisms in rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, autoimmune thyroid disease. Immune responses to disease-relevant self-antigens are examined in ex vivo cultures of patient cells or cells from healthy blood donors.

1. The ability of human B cells to present antigen and produce cytokines. In this context, the recently described IL-10 producing B-cell subset, Bregs or B10 cells, is examined.
2. T-cell responses to self-antigen: Th1-, Th2- and Th17 responses to various self-antigens are examined ex vivo in human cell cultures.
3. Natural autoantibodies and disease-associated autoantibodies. The ability of autoantibodies to modulate B- and T-cell responses in health and autoimmune disease.
4. The role of protein citrullination in chronic inflammatory disease
5. The role of microparticles in elicitation of autoimmune responses in systemic lupus erythematosus.
6. Influence of phthalates on autoimmune thyroid disease
7. The immunomodulatory role of platelets and B cells in healthy individuals and patients with immune trombocytopenic purpura

Primary internal investigators: Claus Henrik Nielsen, Søren Jacobsen, Bo Baslund.

B. IMMUNOMODULATORS; PERSONALIZED MEDICINE AND POTENTIAL DRUGS

This section focuses on treatment with 'biologics' and natural products. The intention is to develop useful tools to personalize treatment and to discover or develop new drugs. The investigations include:

1. The ability of pre-existing anti-mouse immunoglobulin antibodies to predict clinical responses of relevant patient groups to treatment with monoclonal therapeutic antibodies including infliximab, rituximab, basiliximab, cetuximab, natalizumab, bevacizumab (Avastin), trastuzumab (Herceptin), adalimumab, certolizumab pegol and ofatumumab. A patent application based on this principle has been filed.
2. The influence of benzoxazinoids (natural compounds found in e.g. rye) on the immune system. In collaboration with Inge Fomsgaard (Århus University), a grant of 13.5 million DKR has been given from the Danish Strategic Research Council, of which IIR is endowed with 1.5 million DKR.
3. Anti-peptidylarginine deiminase 2 (anti-PAD2) as novel treatment of rheumatoid arthritis. 35 monoclonal antibodies have been generated against PAD2, and investigations concerning their therapeutic potential are pursued. A patent application based on this principle has been filed.

Primary internal investigators: Claus Henrik Nielsen, Søren Jacobsen, Bo Baslund.

C. MOLECULAR MEDICINE

Association between gene polymorphisms and pathogenesis of autoimmune disease

1. Association of polymorphism in TLR7, -8 and -9 with systemic lupus erythematosus
2. The role of IFI16 in induction of type I interferon responses
3. Association of IFIH1 and IFI16 with systemic lupus erythematosus
4. Association of IL-6R polymorphism with chronic periodontitis

Primary internal investigators: Claus Henrik Nielsen, Søren Jacobsen.

D. INFLAMMATORY RESPONSES TO MICROBIAL PATHOGENS AND SURGICAL TRAUMA

This section comprises studies that investigate the inflammatory mechanisms and response to extrinsic factors, which may play a role in the pathogenesis of some inflammatory rheumatic diseases.

1. Evasion of immune responses by periodontal pathogens
2. Association between periodontal pathogens and cardiovascular disease
3. Identification of bacterial taxa/clusters in health and odontological disease
4. The role of complement receptors in the induction of "neutrophil extracellular traps" (NETs)

5. Characterisation of the postoperative inflammatory response after endovascular treatment of aorta aneurysm

Primary internal investigators: Claus Henrik Nielsen, Søren Jacobsen.

TEN MOSTLY CITED PAPERS INVOLVING OUR RESEARCH GROUP

1. Cervera R, et al (SJ). EURO-phospholipid project: clinical and immunologic characteristics of 1,000 patients with the antiphospholipid syndrome (APS). *Arthritis Rheum* 2002;46:1019-27 [51.1 cites/yr]
2. Hetland ML, et al (SJ). MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2 year randomized controlled trial (CIMESTRA). *Ann Rheum Dis* 2009;68:384-90 [18.2 cites/yr]
3. Gislason G, et al (SJ). Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and non-selective non-steroidal anti-inflammatory drugs after acute myocardial infarction: a population-based study. *Circulation* 2006; 113: 2906-13 [18.1 cites/yr]
4. Szkudlarek M, et al (SJ). Interobserver agreement of ultrasonography of rheumatoid arthritis finger and toe joints. *Arthritis Rheum* 2003;49:955-62 [16.1 cites/yr]
5. Cervera R, et al (SJ). EURO-phospholipid project group. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicenter prospective study of 1,000 patients. *Ann Rheum Dis* 2009;68:1428-32 [15.0 cites/yr]
6. Baslund B, et al. Targeting interleukin-15 in patients with rheumatoid arthritis - A proof-of-concept study. *Arthritis Rheum* 2005;52:2686-92 [14.6 cites/yr]
7. Lyons PA, et al (BB). Genetically distinct subsets within ANCA-associated vasculitis. *New England J Med* 2012;367:214-23 [14.0 cites/yr]
8. Øhlenschläger T, et al (SJ). Mannose-binding lectin variant alleles and risk of arterial thromboses in systemic lupus erythematosus. *NEJM* 2004; 351:260-7 [12.3 cites/yr].
9. Fosbøl E, et al (SJ). Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: A nationwide cohort study. *Clin Pharm Ther* 2009;85:190-7 [11.8 cites/yr]
10. Faurischou M, et al. Malignancies in Wegener's granulomatosis: Incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol* 2008;35:100-5 [11.2 cites/yr].

RESEARCH STAFF

SENIOR STAFF

- Bo Baslund, consultant physician, associate professor, PhD

- Claus H Nielsen, consultant physician, associate professor, PhD
- Henrik Galbo, professor, consultant physician DMSc
- Klaus Müller, consultant physician, DMSc
- Mikkel Faurschou, consultant physician, PhD
- Niels Graudal, consultant physician DMSc
- Niels Tvede, consultant physician
- Per Brown Frandsen, MD
- Søren Jacobsen, professor, head of department, DMSc

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- Marie K Brimnes, PhD
- Tania Køllgaard, PhD
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- Constance Jensina Ullf-Møller, MD
- Daniel Belstrøm, Odont
- Dres Damgaard, MSc
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- Janni L Larsen, RN
- Line Kjær, MD
- Louise de la Motte, MD
- Marie-Louise Hermansen, MD
- Sif Gudbrandsdottir, MD

STUDENTS

- Christina Aniol-Nielsen, science student
- Helene Bisgaard, medical student
- Katrine Kielsen, medical student
- Nana Rue, human nutrition student
- Nima Tanha, medical student
- Sanja Arnautovic, science student
- Simi Yousafzai, science student

TECHNICAL STAFF

- Lisbeth Kall
- Ole Christiansen

- Pia Meinke
- Winnie Hansen

PARTNERS ACTIVELY INVOLVED IN OUR RESEARCH

INTERNALLY, AT RIGSHOSPITALET

- Cardiology: Lars Køber
- Cardiovascular surgery: Henrik Sillesen, Torben Schrøder, Lars Lönn
- Clinical biochemistry: Finn Cilius Nielsen
- Clinical immunology: Peter Garred, Lone Troelsen, Lars Ryder
- Endocrinology: Ulla Feldt-Rasmussen
- Infectious diseases: Niels Obel
- Nephrology: Anne-Lise Kamper, Søren Schwartz Sørensen
- Neurology: Finn Sellebjerg, John Vissing
- Pathology: Claus Andersen, Birgitte Grønhøj
- Pediatrics: Carsten Heilmann, Klaus Müller

11

EXTERNALLY, OUTSIDE RIGSHOSPITALET

- Agroecology, Aarhus University: Inge Fomsgaard
- Ann Arbor, Michigan: Terry Smith, Ray Douglas
- Biomedicine, Aarhus University: Knud Poulsen
- Biomolecular Chemistry, Nijmegen: Ger Pruijn
- Cardiology, Gentofte Hospital: Peter Riis Hansen
- Clinical Immunology, Odense University Hospital: Torben Barington
- Dentistry, Aarhus University: Jesper Reinholdt
- Dentistry, Copenhagen University: Palle Holmstrup
- Endocrinology, Odense University Hospital: Laszlo Hegedüs
- Exercise Epidemiology, SDU: Lars Bo Andersen
- Gastroenterology, Herlev Hospital: Jørgen Brynskov
- Harvard University, Bruce Paster
- Hematology, Roskilde Hospital: Hans Hasselbalch
- Microbiology, Copenhagen University: Michael Givskov
- Molecular Medicine, SDU: Yeseelan Palarasah
- Molecular Medicine, Tromsø University: Ole Petter Rekvig
- Næstved Hospital, Mikel Alberdi-Saugstrup.
- Novo Nordisk A/S: Dorthe Lundsgaard, Lars Hornum, Frederik Kreiner.
- Rheumatology, Aarhus University Hospital: Ulrik Tarp
- Rheumatology, Gentofte Hospital: Troels Mørk-Hansen, Lene Dreyer
- Rheumatology, Glostrup Hospital: Merete Hetland, Mikkel Østergaard, Lene Terslev

- Rheumatology, Lund University: Anders Bengtsson, Gunnar Sturfelt, Ola Nived
- Rheumatology, Odense University Hospital: Anne Voss, Helle Laustrup, Louise Diderichsen, Hanne Lindegaard
- Statens Serum Institut: Niels Heegaard

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- Rigshospitalet Research Funds
- Capital Region of Denmark
- Danish Rheumatism Association
- Novo Foundation
- Danish Strategic Research Council
- Ministry of Science, Innovation and Higher Education

12

IMPORTANT RESEARCH POINTS WITHIN THE NEXT 5 YEARS

- Current research in our department supports well the areas in which we have clinical responsibilities as well as basic research in aberrant and normal immune mechanisms. Several findings and research ideas represent novel paths and some of these form base for patent applications.
- As to published research results from our group, clinical cohort studies seem to have the highest impact as rated by number of yearly citations. Further efforts in bridging our clinical and laboratory resources would have the potential to increase the impact of our translational research.
- Studies combining epidemiological approaches with laboratory science are a realistic research scenario and will be supported as well as contributions to international collaborative efforts and networks.
- Our own research facilities and unique opportunities for collaboration with highly competent internal and external partners have put us in a leading position within research on disease mechanisms of systemic lupus erythematosus and rheumatoid arthritis. Pathogenetic research within vasculitides would supplement the above and specific work plans are to be developed. Studies on pathogenetic mechanisms support the development of diagnostic biomarkers and therapeutic interventions.
- Comorbidities such as cardiovascular disease and cancer are major contributors to poor health in patients with inflammatory rheumatic diseases and will continuously be addressed by epidemiologic, clinical and mechanistic studies.
- Maintaining a high academic and scientific standard is a key factor for the continuous attraction of highly qualified staff. Our department offers many opportunities for such a

staff, but it is also a responsibility for the staff actively to support the creation of new scientific knowledge.

Important goals to have achieved within the next 5 years are

- Expanding participation in international cohorts within
 - Systemic lupus erythematosus
 - ANCA associated small vessel vasculitis, WG
- Maintaining and developing databases and biobanks of clinical cohorts within
 - Systemic lupus erythematosus, to be expanded into a national database
 - Small vessel vasculitis, in particular granulomatous polyangiitis, Wegeners
- Further bridging between clinical and laboratory research within the department, but also with other departments at Rigshospitalet, given the systemic nature of inflammatory rheumatic diseases
- Significant scientific results candidating for high-end publication within
 - Pathogenesis of systemic lupus erythematosus
 - Comorbidities of systemic lupus erythematosus and rheumatoid arthritis
 - New treatment principle within rheumatoid arthritis
 - The role of B-cells in the pathogenesis of autoimmune diseases
- Securing development of the high academic standard in the clinical and laboratory sections by full professorships, post-doctoral positions, continuous recruitment of new PhD students, and for clinicians the possibility of part-time research positions.