

Director of the Research Center

Prof. Dr. Paul-Peter Tak

**Institution**

Division of Clinical Immunology and Rheumatology
Academic Medical Center/University of Amsterdam, F4-218
P.O. Box 22700
1100 DE Amsterdam
The Netherlands
Tel. +31 20 566 2171/ +31 20 566 8998
Fax +31 20 691 9658
E-mail: P.P.Tak@amc.uva.nl

Members of the Center***Rheumatologists and internists***

Dr. Dominique Baeten, MD PhD	d.l.baeten@amc.uva.nl
Dr. Huib Dinant, MD PhD	h.j.dinant@slz.nl
Dr. Danielle Gerlag, MD PhD	d.m.gerlag@amc.uva.nl
Dr. Liesbeth Hak, MD PhD	a.e.hak@amc.uva.nl
Dr. Philip Remans, MD PhD	p.h.remans@amc.uva.nl
Dr. Koen Vos, MD PhD	k.vos@amc.uva.nl
Dr. Niek de Vries, MD PhD	niek.devries@amc.uva.nl

Basic Scientists

Lisa van Baarsen, PhD	e.g.vanbaarsen@amc.uva.nl
Lisette Bevaart, PhD	bevaart@arthrogen.nl
Scott Loiler, PhD	loiler@arthrogen.nl
Cristina Lebre, PhD	c.lebre@amc.uva.nl
Margriet Vervoordeldonk, PhD	m.j.vervoordeldonk@amc.uva.nl
Kris Reedquist, PhD	k.a.reedquist@amc.uva.nl
Sander Tas, MD PhD	s.w.tas@amc.uva.nl

Current Fields of Research

The research in AMC's Division of Clinical Immunology and Rheumatology is organized in different teams with very close interactions. The teams focus on: innovative trials with synovial biomarkers; pathogenesis of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis; immunogenetics; signal transduction pathways; dendritic cell biology; and gene therapy.

Clinicians, basic researchers and technicians are working together on clinical research (pathogenetic studies and development of innovative treatment) and more basic research. Contacts between clinicians and basic researchers take place on a daily basis. Research in our group is performed at three different tiers:

Clinical studies: The aim of these studies is to provide more insight into the pathogenesis of various forms of arthritis by analysis of clinical samples of well defined patient groups. Examination of arthroscopic synovial tissue samples plays a key role in the research program. The use of serial synovial biopsies is also used to evaluate the effects of innovative treatment with targeted treatment. These studies give crucial information about the mechanism of action at the site of inflammation. Moreover, the use of biomarkers in the tissue samples is used to predict potential clinical efficacy in small proof of principle studies. This approach is also used to identify possible predictors of efficacy of biological treatment. We have set up a professional unit for arthroscopy, synovial tissue analysis, and digital image analysis for evaluation of stained sections. This unit is also very active in training international fellows.

In addition, we conduct pathogenetic and preventive/therapeutic studies in the earliest stages of rheumatoid arthritis. In these studies, we perform clinical evaluation as well as genetic studies, high throughput analysis of the T cell receptor and B cell receptor repertoire and examination of lymph node and synovial tissue biopsies from patients with rheumatoid arthritis, and pre-arthritis subjects.

Animal studies: We regularly perform studies in a variety of animal models of arthritis, including murine collagen-induced arthritis (CIA), rat adjuvant arthritis (AA), streptococcal cell wall induced arthritis (monoarticular and polyarticular), as well as antigen-induced arthritis in rabbits. These animal models are a feasible tool for studying the complex interplay of inflammation and joint destruction during arthritis and the effect of different therapies hereon.

In vitro studies: Fibroblast-like synoviocytes (FLS) isolated from synovial tissue biopsies of rheumatoid arthritis patients are of particular interest as they are highly activated and exhibit certain features of transformed cells. Furthermore, we use synovial fluid and peripheral blood mononuclear cells as well as synovial biopsy culture to perform in vitro/ex vivo experiments.

Combination of these three areas of research provides an excellent environment for the development of translational research.

Selected Publications

1. Tak PP, Rigby WF, Rubbert-Roth A, Peterfy CG, van Vollenhoven RF, Stohl W, Hessey E, Chen A, Tyrrell H, Shaw TM; for the IMAGE Investigators. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. *Ann Rheum Dis* 2011;70:39-46
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4. van Maanen MA, Stoof SP, Larosa GJ, Vervoordeldonk MJ, Tak PP. Role of the cholinergic nervous system in rheumatoid arthritis: aggravation of arthritis in nicotinic acetylcholine receptor alpha7 subunit gene knockout mice. *Ann Rheum Dis* 2010;69:1717-23

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7. Cantaert T, Brouard S, Thurlings RM, Pallier A, Salinas GF, Braud C, Klarenbeek PL, de Vries N, Zhang Y, Soulillou JP, Tak PP, Baeten D. Alterations of the synovial T cell repertoire in anti-citrullinated protein antibody-positive rheumatoid arthritis. *Arthritis Rheum.* 2009;60:1944-56
8. Lebre MC, Jongbloed SL, Tas SW, Smeets TJ, McInnes IB, Tak PP. Rheumatoid Arthritis Synovium Contains Two Subsets of CD83-DC-LAMP- Dendritic Cells with Distinct Cytokine Profiles. *Am J Pathol.* 2008 172:940-50
9. Tas SW, Vervoordeldonk MJ, Hajji N, Schuitemaker JH, van der Sluijs KF, May MJ, Ghosh S, Kapsenberg ML, Tak PP, de Jong EC. Non-canonical NF- κ B signaling in dendritic cells is required for indoleamine 2,3-dioxygenase (IDO) induction and immune regulation. *Blood.* 2007 110:1540-9
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Dutch Arthritis Association
EU Autocure
NWO and ZON-MW Research Foundations
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Training of Fellows in Research

We have established fellowships dedicated to training in arthroscopy, imaging techniques, immunohistochemistry, digital image analysis, and molecular biology

WebPages

<http://www.amc.nl>

<http://www.amc.nl/index.cfm?sid=525>

<http://www.arthrogen.nl>