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Current Fields of Research

Autoantibodies

Anti-citrullinated proteins-specific antibodies (ACPA) are the only antibodies that display a strong RA-specificity and have been shown to be able to exacerbate arthritis in mice. Therefore, ACPA are thought to be involved in RA-pathogenesis. Therefore, one of the goals of the research is to understand the biology and relevance of ACPA in Rheumatoid Arthritis. In the past we have shown that, genetically, ACPA-positive and negative RA are distinct, indicating that these RA-subforms represent two distinct disease-etiologicals. Moreover, we demonstrated that the immune response against citrullinated antigens is not "static", but involves a continuous reactivation of naïve ACPA-directed B cells. These observations offer hope to the endeavors aiming to inhibit the ACPA-reaction in a specific fashion as ongoing immune-responses are easier to manipulate as completed immune-reactions.

(Immuno)genetics

A 2nd line of research pursued in the laboratory is the identification of the genes that predispose to RA-susceptibility and severity. Important new insights into the understanding of the association between RA and the HLA-system, the most prominent genetic risk factor, has been obtained by demonstrating that the predisposing HLA-alleles are exclusively associated with ACPA-positive RA and that they represent a risk factor for ACPA-development, rather than for RA itself. More recently, by taking a candidate gene-approach, we identified, next to the long-known risk factors HLA and PTPN22, the TRAF/C5-region as the third genetic risk factor for RA.

Cellular Immunity

As T-cell responses are likely to play a pivotal role in the pathways that initiate and/or drive RA, a third research line operational in the laboratory involves the study of T-cell-mediated immune-regulation. Especially, regulatory T-cells (Tregs) have gained considerable interest as a misbalance in Treg activity could lead to autoimmune diseases, such as RA. In a mouse model that closely resembles human RA, we have demonstrated that Tregs modulate the outcome of arthritis. Likewise, we revealed that Tregs have the potential to be used therapeutically, most likely through shedding of TNF-receptors as we have shown that Tregs inhibit the action of TNF through release of these receptors. Together, these data indicate that Tregs can be used for the treatment of arthritis and current research therefore investigates the possibility if- and how these T-cells can be targeted in the treatment of RA.

Personalized medicine in RA

During the last decade major advances have been taken place in the field of rheumatoid arthritis (RA). New genetic risk factors for the development of RA have been identified and a major paradigm shifts have occurred in the treatment of RA. Additionally, a number of studies showed that Treatment schedules that are based on metric instruments that objectively aims to reduce disease activity in a tightly controlled manner, improves the outcome of RA. Moreover, it has been demonstrated on a group level that combination therapy with multiple antirheumatic drugs (DMARDs), steroids or biologicals results in better outcome than monotherapy with methotrexate. In contrast, in practice >95% of RA-patients starts with methotrexate monotherapy which is ineffective in 66% of patients. This discrepancy is generally explained by the concern to harm with potential toxic mediation. This underlines the need for a good metric model that is able to identify the patients that will develop a severe disease course, in order to prevent undertreatment as well as overtreatment. Thus, the aim is to translate the identified risk factors to a prediction of the disease course to guide treatment decisions in individual patients.

Furthermore, research is carried out to predict the severity of the disease course in individual patients with RA. As the currently known clinical and immunological risk factors for a destructive RA insufficiently predict the disease outcome, the aim of these investigation is to identify additional predictive markers that combined with the already identified factors allow individualized treatment decision.

Osteoarthritis

Osteoarthritis will be one of the key topics in pharmacological research for the coming decades. Since 2000 in collaboration with Clinical Epidemiology several osteoarthritis projects are started with the objective to create a base for rational interventions and drug development. The focus is twofold: 1] which risk factors are important for development and progression of osteoarthritis, and 2] which tools can be developed to enable the monitoring of disease progression.

In collaboration with several hospitals in the region a cohort of sib pairs with familial osteoarthritis at multiple joint sites was started, the so-called GARP-study. The objective of this cohort is to determine genetic risk factors, in collaboration with the department of Molecular Epidemiology, and to investigate the value of MRI of the knee in predicting and monitoring disease progression, in collaboration with the department of Radiology.

Clinical studies

Clinical research focuses on identifying the best therapeutic strategy to treat arthritis, including the optimal timing of combinations of drugs and innovative therapies in a setting of intensive follow up with goal orientated treatment adjustments. These studies are LUMC coordinated multicenter studies, in cooperation with the majority of rheumatology clinics in the southwest of the Netherlands.

Recent analysis of our studies has shown that with intensive therapy, up to 20% of patients with rheumatoid arthritis in the earliest stages can be spared from developing a chronic and destructive disease. Some of the findings have already been translated from trial to daily practice and introduce a new paradigm in the treatment of RA.

Our research aims at using the 'window of opportunity' for early identification of patients at risk and individualized therapy with optimal use of available therapeutic interventions.

Non-pharmacologic treatment strategy

The research line "Models of care in rheumatic diseases" is aimed at the development, evaluation and implementation of various non-pharmacologic treatment strategies in rheumatic diseases.

Apart from the development, optimization and evaluation of multidisciplinary team care programs for RA and other diseases such as systemic sclerosis and systemic lupus erythematosus, the research is aimed at the evaluation and implementation of interventions designed to enhance physical activity. Examples of such studies are an implementation study of intensive group exercise therapy (funded by the Reumafonds), a study on self-management and self-regulation related to physical activity among patients with rheumatoid arthritis and various health professionals (rheumatologists, clinical nurse specialists and physical therapists), and an update of a systematic review on dynamic exercise therapy in RA (funded by the Koninklijk Nederlands Genootschap voor Fysiotherapie KNGF). Recently, the development and evaluation of an innovative, integrated care model for patients with osteoarthritis was started, in co-operation with Prof.dr. R. Nelissen, from the department of Orthopaedics.

Selected Publications

1. Wang. J., H. van Dongen. H.U. Scherer, T.W.J. Huizinga and R.E.M. Toes. 2008. Suppressor activity among CD4+,CD25++ T cells is discriminated by membrane-bound tumor necrosis factor alpha. *Arthritis & Rheum.* 58: 1609-1618.
(IF: 7.8)
2. Van Mierlo G.J., H.U. Scherer, M. Hameetman, M.E. Morgan, R. Flierman, T.W.J. Huizinga and R.E.M. Toes. 2008. Cutting Edge: TNFR-Shedding by CD4+CD25+ Regulatory T Cells Inhibits the Induction of Inflammatory Mediators. *J. Immunol.* 180: 2741-2751.
(IF: 6.3)
3. Feitsma A.L., J. Worthington, A.H.M. van der Helm-van Mil, D. Plant, W. Thomson, J. Ursum, D. van Schaardenburg, I.E. van der Horst-Bruinsma, J.J. van Rood, T.W.J. Huizinga, R.E.M. Toes and R.R.P. de Vries. 2007. Protective effect of noninherited maternal HLA-DR antigens on rheumatoid arthritis development. *Proc. Natl. Acad. Sci. U.S.A.* 104: 19966-19970.
(IF: 9.6)
4. Kurreeman F.A., L. Padyukov, R.B. Marques, S.J. Schrodi, M. Seddighzadeh, G. Stoeken-Rijsbergen G, A.H. van der Helm-van Mil, C.F. Allaart, W. Verduyn, J. Houwing-Duistermaat, L. Alfredsson, A.B. Begovich, L. Klareskog, T.W. Huizinga and R.E.M. Toes. 2007. A candidate gene approach identifies the TRAF1/C5 region as a risk factor for rheumatoid arthritis. *Plos Medicine* 4, e278.
(IF: 13.7)
5. Van Dongen H., J. van Aken, L.R. Lard, K. Visser, H.K. Runday, H.M. Hulsmans, I. Speyer, M.L. Westedt, A.J. Peeters, C.F. Allaart, R.E.M. Toes, F.C. Breedveld and T.W.J. Huizinga. 2007. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis & Rheum.* 56: 1424-1432.
(IF: 7.8)
6. Verpoort K.N., E.A.M. Papendrecht-van der Voort, A.H.M. van der Helm-van Mil, C.M. Jol-van der Zijde, M.J.D. van Tol, J.W. Drijfhout, F.C. Breedveld, R.R.P. de Vries, T.W.J. Huizinga and R.E.M. Toes. 2007. Association of smoking with the constitution of the anti-cyclic citrullinated peptide response in the absence of HLA-DRB1 shared epitope alleles. *Arthritis & Rheum.* 56: 2913-2918.
(IF: 7.8)
7. Goekoop-Ruiterman Y.P.M., J.K. de Vries-Bouwstra, C.F. Allaart, D. van Zeben, P.J.S.M. Kerstens, J.M.W. Hazes, A.H. Zwinderman, A.J. Peeters, J.M. de Jonge-Bok, C. Mallée, W.M. de Beus, P.B.J. de Sonnaville, J.A.P.M. Ewals, F.C. Breedveld and B.A.C. Dijkmans. 2007. Comparison of Treatment Strategies in Early Rheumatoid Arthritis: a Randomized Controlled Trial. *Ann Intern Med Mar* 20;146(6):406-15.
(IF: 15.5)
8. Van der Helm-van Mil A.H., S. le Cessie, H. van Dongen, F.C. Breedveld, R.E. Toes and T.W. Huizinga. 2007. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum.* Feb;56(2):433-40.
(IF: 7.8)

9. Botha-Scheepers S., I. Watt, E. Slagboom, I. Meulenbelt, F.R. Rosendaal, F.C. Breedveld and M. Kloppenburg. 2007. Influence of familial factors on radiologic disease progression over two years in siblings with osteoarthritis at multiple sites: A prospective longitudinal cohort study. *Arthritis Rheum* 57(4): 626-632.
(IF: 7.8)
10. Riyazi N., E. Slagboom, A.J.M. de Craen, I. Meulenbelt, J.J. Houwing-Duistermaat, H.M. Kroon, C. van Schaardenburg, F.R. Rosendaal, F.C. Breedveld, T.W.J. Huizinga and M. Kloppenburg. 2005. Association of the risk of osteoarthritis with high innate production of interleukin-1 β and low innate production of interleukin-10 ex vivo, upon lipopolysaccharide stimulation. *Arthritis Rheum.* 52: 1443-1450.
(IF: 7.8)
11. Goekoop-Ruiterman Y.P., J.K. de Vries-Bouwstra, C.F. Allaart, D. van Zeben, P.J. Kerstens, J.M. Hazes, A.H. Zwinderman, H.K. Rondag, K.H. Han, M.L. Westedt, A.H. Gerards, J.H. van Groenendael, W.F. Lems, M.V. van Krugten, F.C. Breedveld and B.A. Dijkmans. 2005. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* Nov; 52(11):3381-90.
(IF: 7.8)

Current Funding

Dutch Arthritis Foundation
EC Autocure
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Training of Fellows in Research

The department is certified to provide the training to become a rheumatologist. The training programme consists of three year internal medicine, 2.5 year training within the LUMC and 0.5 year training in the Haga-hospital in The Hague. During the training period, the fellows can follow training periods in pediatric rheumatology and hand surgery. All fellows will follow training periods for integrated team care programmes.

WebPages

<http://www.lumc.nl/rep/cod/redirect/2096/>