Establishing tolerance

Professor Roland Martin is fascinated by the interplay of the immune and nervous systems in multiple sclerosis. In the following discussion, he explains the challenges of researching this incompletely understood disease and his hopes to halt its progression

What is your background in multiple sclerosis (MS) research?

Following medical school, I pursued a postdoctoral position in virology and immunology at the University of Wuerzburg, Germany, working on T cell-mediated immune responses in viral infections of the brain in children. Besides learning new techniques, I became interested in neuroimmunology. Afterwards, during my residency in neurology, also in Wuerzburg, I worked on nervous system manifestations of Lyme disease and thereafter pursued a second postdoctoral position at the US National Institutes of Health (NIH)'s Neuroimmunology Branch of the National Institute of Neurological Disease and Stroke (NINDS), Bethesda, USA. From then on, I have continuously worked on the immunological, clinical and translational aspects of MS.

Could you provide an insight into the pathological events underlying this condition?

MS is a prototypical autoimmune disease in individuals with a complex genetic trait, but also involves environmental triggers such as viral infection, smoking and low vitamin D3 levels. The most relevent genetic risk factor is a set of histocompatibility antigens that are important, for example, for transplantation – the so-called human leukocyte antigen haplotype (HLA-DR15). However, our understanding of precisely how HLA-DR15 contributes to risk of MS is limited. The major mechanism is likely the presentation of viral peptides to CD4 helper T cells. Once triggered by a virus, these cells can cross-react with central nervous system molecules, such as myelin peptides, and start the disease process that leads to damaged brain tissue.

Furthermore, the inflammatory process in the brain involves multiple other cell types and immune mediators, and the exact cascade of events is not fully understood. These are the questions that interest our laboratory; which antigens are recognised by T cells and how the HLA-DR15 haplotype contributes.

Can you explain immune system tolerisation and how it was employed in the Establish Tolerance In MS with Peptide-Coupled Blood Mononuclear Cells (ETIMS) trial published in 2013?

Immune tolerance operates at two levels. Central tolerance mechanisms generate a functioning T cell repertoire in the thymus, positively selecting T cells that should leave self-tissue alone but effectively respond to infectious agents. Once these cells enter the peripheral immune system they need to be controlled, and these mechanisms are referred to as peripheral tolerance.

The ETIMS approach and methods to re-establish peripheral tolerance aim to eliminate autoreactive T cells that have lost control by silencing them or changing their function. A number of mechanisms can achieve this, including regulatory T cells and tolerogenic antigen presentation. Since a large number of our cells die by programmed cell death (apoptosis), the body must not mount an immune response to these dying cells. This maintains immune system tolerance and involves presentation of apoptotic cells in certain tolerogenic organs, such as the liver and spleen, where the dying cells are degraded and presented (or 'shown') to T cells in a way that keeps them silent. This is the mechanism we think works in the trial.

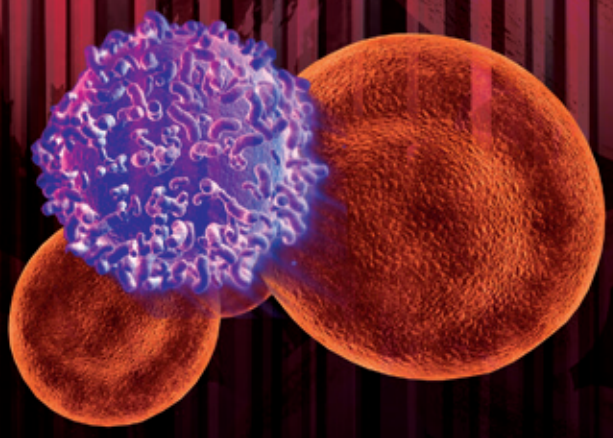
Have there been any particular challenges you have faced in your research?

Medical education and subsequent specialisation during residency, is a long process and leaves little room for basic science education. Therefore, actively translating knowledge into clinical care, better understanding human physiology and pathological conditions, and keeping pace with methodological advance is not easy, and training does not foster that bridge.

I am fascinated by the intricacies and challenges of the two most enigmatic systems of our body – the immune and central nervous systems. In MS, they intersect in a disease that affects young individuals, leads to uncertainties about their future and compromises their private and professional lives. Therefore, it is highly motivating, not only from a scientific, but also from a personal, point of view, to better understand this disease and develop new treatments.

How do you expect to see the fight against autoimmune diseases advance in the next decade?

While substantial progress has been made with conventional drugs, efficacy often comes at a price: damaging side-effects. This issue is particularly important in a chronic disease, such as MS, that begins at a young age. Our goal is to halt and prevent disease activity as much and as early as possible. There is little doubt in my view that antigen-specific tolerisation could come close to an ideal treatment, enabling us to readjust the immune system in a very specific way. Despite many setbacks, there remains much optimism that sooner or later practicable and efficacious tolerisation approaches will be developed.



Immune trickery

Researchers from **University Hospital Zurich** are investigating the complexities of multiple sclerosis, with a view to developing a novel immune tolerisation approach. This could present a revolutionary new treatment – perhaps even a cure – for the disease, as well as other similar autoimmune conditions

WHILE IT IS designed to protect us from foreign invaders, sometimes the immune system can go awry, working against the very tissues it is meant to defend. When the body fails to recognise its own tissue as self, it is attacked. This is the basis of autoimmune conditions such as multiple sclerosis (MS). Here, as a result of mistaken attack, myelin sheath – the membrane wrapped around nerve cells that enables fast conduction – is gradually lost throughout the central nervous system. This prevents neurons from effectively communicating with one another and results in progressive symptoms ranging from fatigue to paralysis and loss of vision.

MS is one of the most common neurological disorders and a primary cause of disability in young adults – affecting 2.5 million people worldwide. Although some patients never experience disability, over half are no longer able to walk unaided 20 years after disease onset. This clearly has a profound impact on quality of life, impeding sociality and the ability to work. Considered alongside the healthcare costs, MS represents a major personal and financial burden to society.

Crucially, however, the causes of this inflammatory process are not fully understood, and Professor Roland Martin, Senior Consultant at the University Hospital Zurich's Department of Neurology, and his team hope to amend this situation. Their work involves searching for antigens wrongly targeted by the immune system (autoantigens) and potential foreign triggers; ultimately, they aim to halt the progression, more effectively treat and perhaps even prevent this debilitating condition.

COMPLEX INTERPLAY

MS is an archetypal autoimmune disease, mediated by white blood cells called T cells, but with a complex genetic basis involving over 100 genetic risk factors. Although considerable progress has been made in understanding the condition in recent years – both in terms of its genetics and pathophysiology – many questions remain about this multifactorial disease.

> Re-establishing tolerance could contain or even stop the inflammatory components of MS

What is known, however, is that the basis of MS lies in the activity of T cells, as Martin explains: "In MS an immune repertoire is shaped in the thymus that generates T cells that not only protect from infectious agents but, under certain conditions, also begin to attack tissue in the brain and spinal cord". The major genetic risk factors in MS – two alleles of the so-called HLA-DR15 haplotype of the human leukocyte antigen complex – likely select a harmful T cell repertoire, which is prone to respond to central nervous system autoantigens. Martin and his group have shed new light on this process, revealing that HLA-derived self-peptides may alter the proliferation and dynamics of T cells.

Although genetic predisposition is a requirement for developing MS, it is not sufficient. Environmental risk factors, such as viral infection, are thought to initiate the disease. Exposure to such triggers leads to a deleterious immune response, characterised by a cross reaction with myelin peptides in the brain. After repeated stimulation, the T cells become proinflammatory and are more easily activated.

These autoreactive T cells proceed to enter the brain where they recognise the target antigen (myelin peptides and probably other as yet unknown target antigens) and begin an inflammatory process, producing harmful immune mediators. "Since the brain can only be repaired to a limited extent, this tissue damage is permanent," states Martin. "While damaged areas may be compensated at the functional level for some time, neurological symptoms and disability are the long-term result, and steadily increase from the point when compensation is no longer sufficient."

FIRST-IN-HUMAN TRIAL

The crux of MS is the patient's own immune cells attacking self-antigens in the central nervous system. Martin believes tolerisation – leveraging the body's attempt to prevent autoimmunity – could be the key to solving this. Re-establishing tolerance could contain or even stop the inflammatory components of MS and inducing antigen-specific tolerance in mouse models has been remarkably successful.


THE MARTIN LAB

Translating this to human patients, last year Martin co-led a phase I trial to 'reset' the immune systems of people with MS. The trial – Establish Tolerance In MS with peptide-coupled blood mononuclear cells (ETIMS), was the result of the efforts of many investigators, a clinical team, scientists, nurses, technicians and collaboration between the University Medical Centre Hamburg-Eppendorf in Germany and Northwestern University in the US. Key individuals besides Martin were Andreas Lutterotti, Mireia Sospedra and Stephen Miller, who had pioneered the approach on which the ETIMS project was based in animal studies.

Using patients' own white blood cells, which had been treated with myelin peptides and a coupling agent, the team was able to inject these antigen-coupled and fixed antigen-presenting cells back into the patient, coaxing their immune systems to develop a tolerance to them. This involved an innovative manufacturing process: "Taking a leukapheresis (similar to a blood donation, but the patients get their red blood cells back), we are able to isolate a large number of white blood cells. Next, we add myelin peptides and a coupling agent, incubate everything for one hour and perform several washing steps to remove free peptides and coupling agent. After performing several quality control and safety checks, we reinfuse the myelin peptide-coupled cells to the patient," Martin details. Once injected, the coupled cells die by apoptosis. This process causes the myelin antigens to be presented to autoreactive T cells in a tolerogenic way and to silence them.

Existing treatments for MS suppress the entire immune system, thereby increasing susceptibility to infection and even cancer. However, the treatment employed in ETIMS halts only those autoimmune responses that are already activated, without compromising the function of the rest of the immune system. Results showed immune reactivity to myelin was reduced by up to 75 per cent, with a direct correlation between the dose of T cells and the reduction in myelin reactivity. The trial is thus promising to successfully reset the immune systems of MS patients.

Moreover, the treatment caused no serious adverse effects and did not affect immunity to genuine pathogens. This first-in-human study demonstrated the safety and feasibility of the approach, but the road ahead is long: "We still need to show clinical efficacy," Martin comments. "We know that the procedure is safe, and mechanistic data indicate that it induces tolerance, but further data are needed."

A NEW TREATMENT PARADIGM?

ETIMS paves the way for a phase II trial to investigate whether the treatment can actually prevent the progression of the disease in humans, something that has already been demonstrated in mice. In the future, Martin suggests this treatment paradigm could be used for other diseases, simply by attaching different antigens to the white blood cells: "Our studies could have broad implications for many other autoimmune diseases, including Type 1 diabetes and rheumatoid arthritis," he enthuses. "Furthermore, the approach is showing promise for severe allergies and the prevention of organ transplant rejection according to animal data from the Miller laboratory."

In the past 25 years, Martin has made significant contributions to his field. He has provided fresh insight into MS; but with knowledge comes complexity – it is now clear that the pathogenesis of MS is more intricate than ever imagined. By considering both the immune and nervous systems, and their interactions, this complexity is slowly unravelling. Studies from the Martin laboratory have helped to elucidate how T cells recognise myelin antigens, the nature of cross-reactivity and how these mechanisms become manifested as disease. Using this knowledge, his group has pioneered a new treatment strategy with the potential to transform the treatment options for autoimmune disease.

INTELLIGENCE

SEARCH FOR CANDIDATE AUTOANTIGENS AND FOREIGN (VIRAL/BACTERIAL) TRIGGERS IN MULTIPLE SCLEROSIS

OBJECTIVES

- To investigate the cellular immune mechanisms and target antigens in multiple sclerosis (MS) as well as understand the disease heterogeneity
- To develop new treatments, mainly in areas of unmet medical need of MS, from the idea to early clinical application

KEY COLLABORATORS

Clemencia Pinilla, PhD, Torrey Pines Institute for Molecular Studies, USA • **Yingdong Zhao, PhD**; **Richard Simon, PhD**, National Cancer Institute, USA • **Hans-Georg Rammensee, PhD**; **Stefan Stevanovic, PhD**, University of Tuebingen, Germany • **Roy Mariuzza, PhD**, University of Maryland, USA • **Wolfgang Brück, MD**; **Imke Metz, MD**, University of Goettingen, Germany • **Riccardo Saccardi, MD**, Careggi University Hospital, Italy • **Paolo Muraro, MD, PhD**, Imperial College London, UK • **Pablo Villoslada, MD**, IDIBAPS, Hospital Clinic Barcelona, Spain • **Carmen Espejo, PhD**, Autonomous University of Barcelona, Spain

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