

neuro TRANSMITTER



**Neural Plasticity
and Repair**

National Center of Competence in Research

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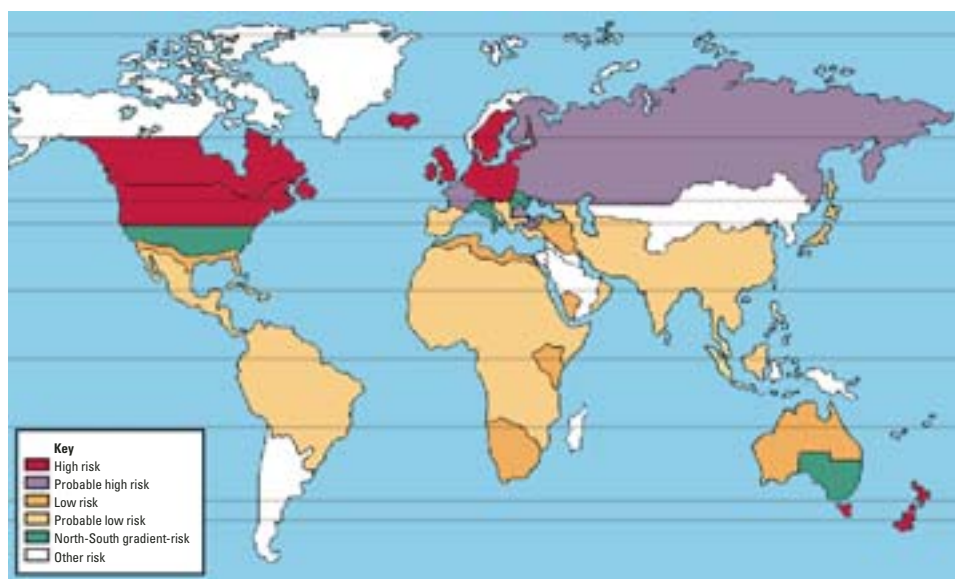
COVER STORY

Multiple Sclerosis: when the immune system declares war on the brain

Multiple Sclerosis (MS) is the most common inflammatory disorder of the central nervous system (CNS). In Europe and North America, approximately one in 1'000 inhabitants is affected by MS. In Switzerland alone, more than 10'000 patients suffer from the disease. Clinical and histopathological evidence suggests that there are different subtypes of MS: whereas the relapsing/remitting course of MS more frequently affects young women, the

primary chronic progressive course is more common in middle aged men. Although a genetic predisposition is implied by epidemiological and experimental data, migration studies strongly indicate additional external factors such as infections. Since any part of the CNS can be affected, disease symptoms are manifold and range from sensory disturbances, vision impairment, ataxia or paralysis to fatigue and cognitive deficiencies.

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World distribution of Multiple Sclerosis.

www.nccr-neuro.unizh.ch

A new initiative for Multiple Sclerosis



It is a pleasure to acknowledge the success of an unusual initiative on behalf of clinical and experimental research in Multiple Sclerosis (MS). Coming from the clinical side of neurology, I regularly see large numbers of MS patients in the clinic. I have always felt the urge to promote research in MS with the hope of better understanding the disease

mechanism and with the goal of finally finding a cure or being able to prevent the disease.

Following the foundation of the Neuroscience Center Zurich, a window of opportunity arose to make my dream of a center for MS research come true. After an international MS meeting organised on behalf of WHO in Geneva I presented the project to the board of directors at the pharmaceutical company Serono in Geneva. Although the directors were very positive, I also needed the support of Ernesto Bertarelli, famous not only as a sailor on Alinghi but also as head of Serono. After initial hesitations and intense discussions he finally considered the project to be of interest to the company. Martin Schwab, Wolfgang Knecht and Adriano Fontana helped to quickly advance the initiative. The contract between Serono and the Neuroscience Center Zurich provided the generous support for two assistant professorships. Importantly, there was no constraint whatsoever on the academic freedom of research.

Now, the two new assistant professors, Burkhard Becher and Norbert Goebels, have been appointed and are reporting on their work in this issue of the Neurotransmitter. An experimental research program (Becher) is complemented with a clinical unit including consultancy of patients (Goebels). It is never without difficulties that a new endeavour finds its place in an old University establishment. But we all should feel satisfied and honored that this ambitious and promising MS research project is now flourishing for the future benefit of the patients.

Prof. Jürg Kesselring

Head of the Department of Neurorehabilitation, Klinik Valens

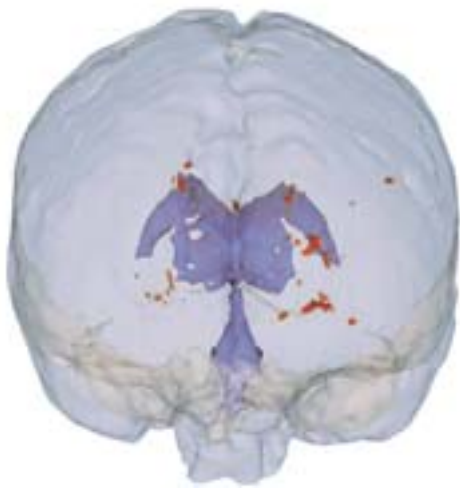
A major problem for patients and their physicians is the unpredictable course of MS. While most patients suffer initial relapses and in later stages of the disease may develop a gradual increase of disability, about 10-20% experience a mild, benign form of MS with minimal impairment. However, some patients may also develop a severe form with rapidly increasing neurological deficit. There is currently no "cure" for MS. High dose corticosteroids can often limit the symptoms of an acute attack, while immunomodulators such as β -interferon can reduce the frequency of new relapses by about one third. Rehabilitation and symptom-oriented therapies can also improve the patient's condition. A number of novel immuno-therapies are currently being tested in clinical trials offering a glimpse of hope on the horizon. However, recent failures of initially promising compounds make us cautious about potentially dangerous side-effects. What is needed is a better understanding of the pathophysiology of this disease in order to design more specific therapeutic strategies which target only the "pathogenic" immune response and which, due to limited side effects, are thus suitable for long-term disease management.

What are the causes of MS and what is autoimmunity?

This is the 10 million franc question. The short answer is: we don't know, but we have some pretty good ideas. We know for certain that MS is an inflammatory disease, which means that the immune system invades the CNS. The immune system is an armada of white blood cells, so called leukocytes. The most specialized and adapted cells of these leukocytes are the lymphocytes. Their presence reveals an organized specific immune attack. This inflammatory attack is thought to destroy the myelin insulation of the nerve fibers, which ultimately can result in the loss of neurons.

All of us, no matter how healthy we are or feel, have detectable numbers of auto-aggressive lymphocytes that can be isolated from our blood. This means that these lymphocytes carry an antigen-receptor specific for a "brain molecule" such as a myelin component. Why do these lymphocytes usually not attack the brain? It's because the immune system has developed complex control mechanisms to prevent auto-

MS: when the immune system declares war on the brain



The dark blue area represents the brain ventricles. The various red areas represent Multiple Sclerosis lesions.

immunity. While auto-aggressive T cells are potentially harmful, they usually lie dormant and do not cause damage to the CNS. This process is called tolerance and is maintained via both active and passive mechanisms. Tolerance to "self" seems to be disturbed in MS patients and their immune system no longer tolerates the CNS tissue, subsequently launching an attack. There are numerous ways in which tolerance can be broken and autoimmunity can be initiated: 1) A pathogen, which hides from the immune system by molecular mimicry, i.e. it pretends to be a natural part of us, might be detected by the immune system, which subsequently turns itself against the CNS. 2) A neurotrophic microbe attacks the brain and antiviral immunity causes the release of CNS antigens into the systemic compartment. When these antigens are recognized by dormant autoaggressive cells, tolerance is broken. 3) There is now good evidence that the tolerance mechanisms in MS patients do not function properly. Hence, naturally occurring

auto-reactive lymphocytes may become activated and escape from the control of tolerance.

The first indication that MS is an autoimmune disease was accidentally discovered by Louis Pasteur. While he was experimenting with vaccination against pathogens, he attempted to immunize patients against the rabies virus. He used rabies-infected rabbit spinal cord tissue as a source for his vaccine. Upon vaccination some of his patients developed an acute disseminated encephalomyelitis (ADEM). Clinically as well as histopathologically, this disease is strikingly similar to MS. Pasteur concluded that the attenuated virus had caused the disease. Only later was it discovered that the autoimmunity was initiated by vaccinating with rabbit spinal cord tissue, or more precisely, with its myelin content.

Once the CNS is infiltrated by immune cells, CNS resident cells, in particular microglia, become activated and support the immune attack against myelinating cells and indirectly against nerve cell axons as well. The pathogenesis can thus be divided into three phases: 1) initiation of an autoimmune response and breakdown of tolerance, 2) migration of leukocytes into the CNS and inflammatory damage and 3) axonal degeneration and brain atrophy.

What are we doing to learn more about MS and autoimmunity?

There are a number of open questions that desperately need answers if we are to design novel and specific therapies: 1) Why does the immune system attack the CNS and what makes lymphocytes pathogenic?, 2) Which molecular structures are primarily attacked by the immune system?, 3) How do lymphocytes recognize their

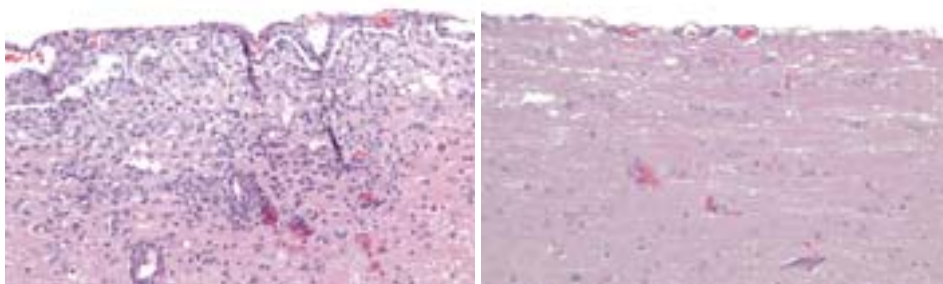
Research Project on Multiple Sclerosis

Burkhard Becher	Department of Neurology, University Hospital Zurich
Norbert Goebels	Department of Neurology, University Hospital Zurich
John DeLamarter	Serono International S.A., Geneva
Youssef Fezoui	Serono International S.A., Geneva

The experimental and clinical research on Multiple Sclerosis is part of Project 6 "Infection and Immunity in the Central Nervous System".

antigens in the nervous system?, 4) How can the damage be repaired?

The MS-Center of the Department of Neurology of the University Hospital Zurich is embedded in the NCCR Neuro and the Neuroscience Center Zurich (ZNZ). Our two research groups combine experimentally oriented basic neuroimmunology (B. Becher) and clinically oriented neuroimmunology (N. Goebels). To tackle the questions outlined above we study the complex interactions of the immune system with the CNS, especially the role of local antigen presenting cells in a number of different in vitro and in vivo models (group of B. Becher). In the human system we analyze single lymphocytes derived from the cerebrospinal fluid (CSF) or from micro-dissected human MS lesion tissue. This is done by single cell PCR, reconstruction of their antigen receptor by recombinant methods and by identifying the target antigens they recognize (group of N. Goebels).



The spinal cord section of an affected mouse (left) shows invading leukocytes (blue), which are absent in the spinal cord tissue of a healthy mouse (right).



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Calendar of events

Der gespiegelte Mensch Exhibition

9 July 2004–2 January 2005
Landesmuseum, Zürich

Swiss Society for Neuroscience Joint Meeting of the USGEB-SSN-SSBP Annual Meeting

17–19 February 2005
ETH-Hönggerberg, Zurich

NCCR Neuro Symposium 4–5 March 2005

Kartause Ittingen, Warth, Kanton Thurgau

Day of Clinical Research 17–18 March 2005

University Hospital of Zurich

American Academy of Neurology 57th Annual Meeting

9–16 April 2005
Miami Beach, Florida, USA

Festival Science & Cité / BrainFair 2005

19–24 May 2005
Various locations in Zurich and 14 other
Swiss cities
www.festival05.ch

ZNZ Symposium 2005 21 October 2005

ETH Zürich

American Society for Neuroscience Neuroscience Meeting 2005

12–16 November 2005
Washington, DC, USA

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Awards



Adriano Aguzzi

The Marcel Benoist Prize, one of Switzerland's oldest and most prestigious awards, was presented to Adriano Aguzzi in recognition of his exceptional achievements in the understanding of prion protein-related diseases such as Creutzfeldt-Jakob Disease (CJD) a fatal brain disorder. Adriano Aguzzi is director of the Institute of Neuropathology at the University Hospital Zurich and of the Swiss National Reference Center for Prion Diseases. He is a member of the NCCR Project on Infection and

Immunity in the Central Nervous System. The award was presented by Bundesrat Pascal Couchepin, Swiss minister of the Interior, at a ceremony at the University of Zurich on 11 November 2004.

Isabelle Mansuy

Isabelle Mansuy's outstanding work on the neuronal mechanisms of learning and memory was acknowledged by awards from both the Federation of European Neuroscience Societies (Boehringer Ingelheim Award) and the Federation of European Biochemical Societies (FEBS Anniversary Award). Young European scientists are honored by these awards.

Burkhard Becher

Burkhard Becher received the Sobek Research Junior Faculty award for Neuroimmunology on 26 November 2004 in Stuttgart for his research achievement in the field of Multiple Sclerosis.

Gery Colombo

The Entrepreneur of the Year Award, presented by Ernst&Young of Switzerland, recognizes outstanding businessmen and women. The Award in the Start-Up category 2004 went to Gery Colombo for the development of the Lokomat in his Volketswil-based company, Hocoma AG. The Lokomat has greatly advanced neurological rehabilitation for patients with spinal cord injury. Gery Colombo is the NCCR delegate for technology transfer.

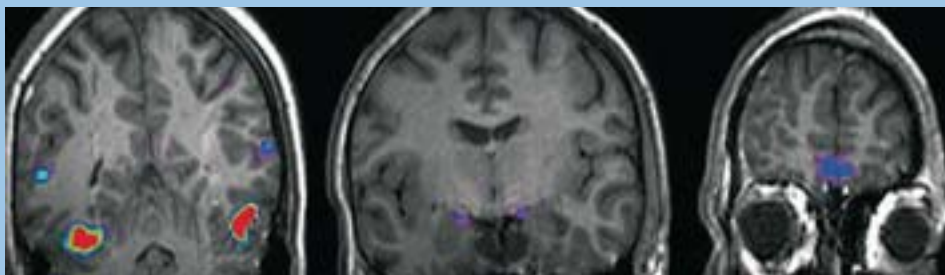
Project News

Faces, emotion and the brain

Face recognition is the most developed visual skill in humans. When we look at faces, brain activation is found in a network of regions that include the visual cortex, limbic system and prefrontal cortex, where information about facial identity and expression is processed. Interestingly, we respond faster and better to emotional (fearful, surprised, or happy) faces, as compared with neutral ones, presumably due to their importance in social communication. Our group uses functional brain imaging techniques, namely fMRI and MEG, to investigate the neural mechanisms that mediate such behavioral advantages. Recently we have found that emotional faces evoke

greater cortical activation than neutral faces, thus providing neural evidence for their privileged status. Our paradigm can be extended to investigate the response to emotional stimuli in psychiatric patients with mood and anxiety disorders. We predict, for example, that individuals with increased levels of anxiety would show patterns of brain activation that are correlated with their behavioral manifestations.

Alumit Ishai
Department of Neuroradiology, University Hospital Zurich



Activation in the visual system (left), amygdala (middle) and orbitofrontal cortex (right) in response to emotional faces.