

Myelin structure and its role in autoimmunity (MARIE)

an ESF Scientific Network

This Network is galvanising European research into the role of myelin and its structure in a range of autoimmune degenerative diseases such as multiple sclerosis (MS). Myelin is the multi-layered membrane sheath rich in lipids (fats) providing the electrical insulation for axons, whose deterioration causes disease by disrupting the conduction of nerve impulses. Myelin structural research over the past 30 years is being rekindled by recent progress in a variety of key fields, notably biophysics, electron and scanning probe microscopy, x-ray crystallography, and bioinformatics. However, Europe's research effort in the field is fragmented and dominated by traditional specialists in neuroimmunology and cell biology. It is now recognised that collaboration between both traditional and newer fields in the biophysical and computational domains is necessary to make substantial progress, and this Network is conducting the task. There is great hope of success following a highly promising exploratory workshop in Potenza, Italy in June 2002, which brought together researchers from all the component fields, including 54 from Europe and 16 from North America, and also existing practitioners of MS therapies. This workshop concluded that the overwhelming priority was to decipher how myelin is made in order to unravel how the mechanisms of assembly and function go wrong in the event of disease.

Building upon historical research, an important need exists to further develop our understanding of the structural biology, intermolecular interactions and role of myelin proteins. Such knowledge is required to elucidate the pathogenic mechanisms of demyelinating diseases, and in particular the effects of soluble myelinotoxic factors such as cytokines, antibodies, free oxygen radicals and matrix metalloproteinases.

This Network is founded largely on the premise that the time is now ripe for substantial progress following a reinvigoration of research. The ability to delve more deeply into the structures of constituent proteins has become possible through improved crystallisation techniques and progress with imaging via scanning probe microscopy and x-ray diffraction. These techniques will also complement more general approaches employed for the analysis of molecular complexes (e.g., by confocal microscopy). At the same time, a breakthrough in genetic and protein sequence analysis through microarray techniques, allied to data retrieval, analysis and 3D native protein modelling provides the potential to determine the overall structure of myelin and its constituent proteins far more accurately than before. Furthermore, immunological studies have demonstrated the degenerate recognition of antigens by T cells and highlighted the need to understand the structure of the peptides involved in MHC-T cell receptor interplay.

These various breakthroughs have come in several previously distinct fields, and so to exploit them for myelin research requires collaboration between the respective researchers that has not taken place much before. This has proved a sticking

point so far, for it is acknowledged that biophysicists and neuroimmunologists have at times had difficulty understanding each other's presentations, without which collaboration cannot even begin. This Network therefore has three important strategic objectives:

- 1) To promote the interest of biophysicists in structural studies of myelin proteins and of the peptides involved in the antigen presentation, as well as to have neurologists and neuro-immunologists participate more directly in structural studies.
- 2) To develop a common language to facilitate interaction between experts in the different fields.
- 3) To promote the training of young scientists in different fields and develop their ability to organize research projects and carry out experiments with various approaches and techniques.

The ability to form the kind of strong and fruitful interaction between disciplines was demonstrated in the 2002 Exploratory Workshop "Myelin Structure and its Role in Autoimmunity", providing a sound basis for this Network to achieve the following scientific objectives:

- 1) Research on multiple sclerosis and other demyelinating diseases by workers from all fields, including biophysics and bioinformatics, that have so far been under-represented, in addition to those in more established areas involving cell and molecular biology.
- 2) To facilitate interaction among structural biologists interested in the architecture of myelin proteins, in relation to the high-resolution structure of myelin.
- 3) To encourage the synthesis of different kinds of expertise in the fields of biophysics, biochemistry, molecular biology, neurology, neuroimmunology and bioinformatics.
- 4) To exploit knowledge of myelin structure to study its breakdown in demyelinating diseases, and to elucidate how myelinotoxic factors can both attack the myelin sheath and also disrupt the membrane.
- 5) To understand the role of myelin proteins in autoimmunity and the contribution made to this by molecular mimicry, which is a typical structural problem.
- 6) To identify and describe selected techniques in biophysics, biochemistry, and bioinformatics that would be of general interest to all participants in the network, but particularly to young scientists.
- 7) To define multiple sclerosis and autoimmunity and the possible role of myelin proteins in pathology.

All of these objectives require collaboration between specialists in different disciplines and measures to help the various researchers communicate better.

This Network was approved by the ESF Network Group in November 2003 for a three-year period



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