NeuroproMiSe WP H1

- **Neuropathology Reference Center**
  - Determination of neuropathological phenotype of experimental models, created in the consortium
  - Expression of new target molecules in brain tissue
  - Genotype / pathology phenotype correlation in multiple sclerosis
  - DNA collection from MS autopsy tissue and MS biopsy patients

NeuroproMiSe WP H1

- **Determination of neuropathological phenotype of experimental models, created in the consortium**
  - Conventional neuropathology
  - Immunocytochemistry, confocal laser microscopy, immune electron microscopy
  - In situ hybridization
  - Morphometry
  - Established interaction (P3,6,8,12,14)

NeuroproMiSe WP H1

- **Expression of new target molecules in brain tissue**
  - Archival experimental material
    - Normal brain, EAE models (transfer, active, CD4 or CD8 mediated), brain trauma, ischemia, excitotoxicity, neurodegeneration;
  - Archival human material
    - Normal, multiple sclerosis, other encephalitis, vasculitis, leukoencephalopathies, ischemia, neurodegeneration (AD, others)

NeuroproMiSe WP H1

Partner 5 (MUW)

MS Material	Göttingen	Vienna	Rochester	Total
Biopsies	**170**	**29**	**620**	**819**
Early Autopsies	**12**	**31**	**33**	**76**
Chronic Autopsies	**114**	**40**	**78**	**232**

NeuroproMiSe WP H1

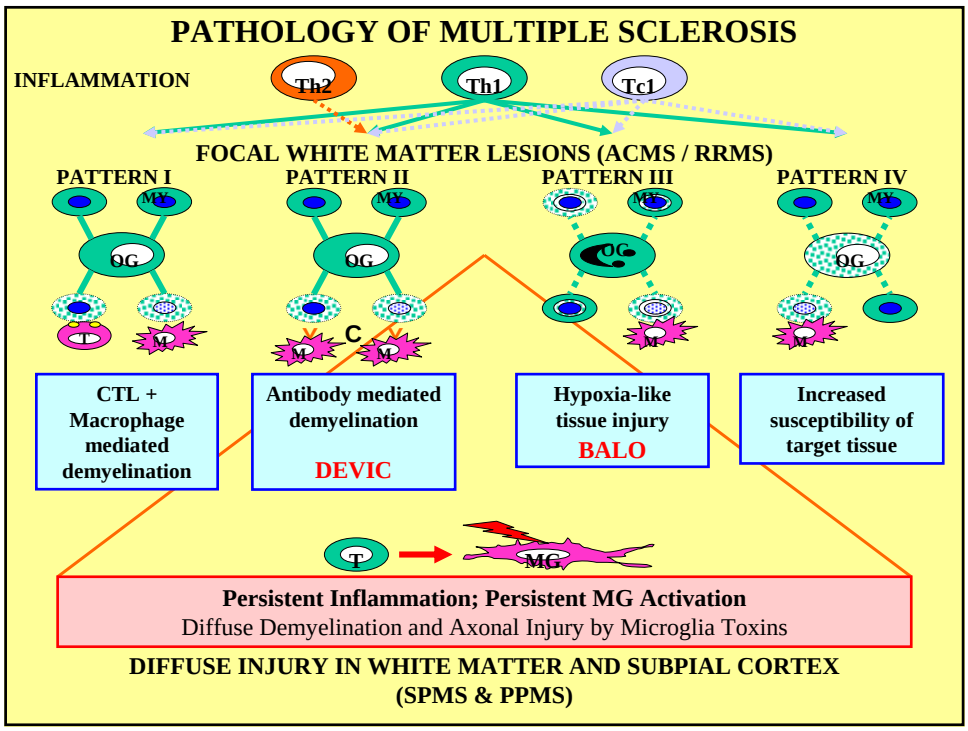
- **Genotype / pathological phenotype corelation**
  - Quantitative determination of pathological phenotype
    - Inflammation, patterns of demyelination, extent of remyelination, extent of axonal injury
  - Genotyping
    - PCR based
    - SNP screening (biopsies; P2b)

NeuroproMiSe WP H1

- **Methods of genotyping:**
  - Biopsies:
    - Identification of biopsied patients
    - Genotyping from blood samples (SNP)
    - Genotyping of paraffin material
  - Autopsies:
    - Genotyping of paraffin material

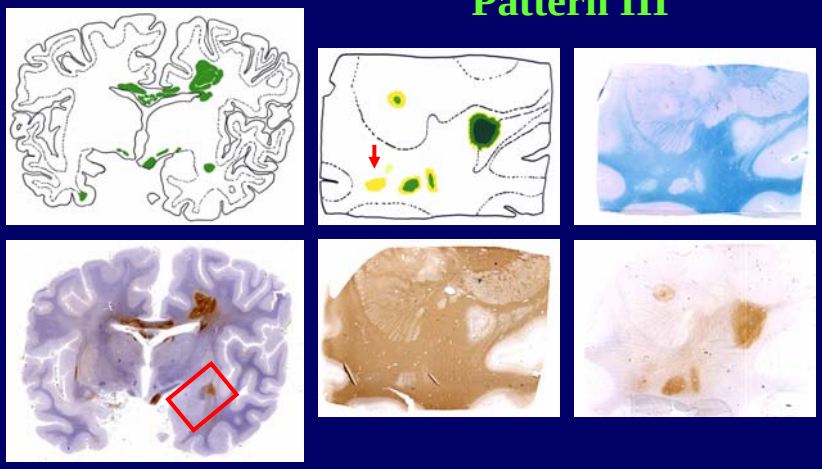
NeuroproMiSe WP H1

- Pathological Phenotype of MS
  - What is the initial lesion in acute and early MS
  - What are the mechanisms behind different patterns of demyelination in MS
  - Do the patterns of inflammation and tissue damage differ between early (RR) and late (progressive) MS
  - Interindividual differences in the extent of tissue damage (demyelination, oligodendrocyte damage, remyelination

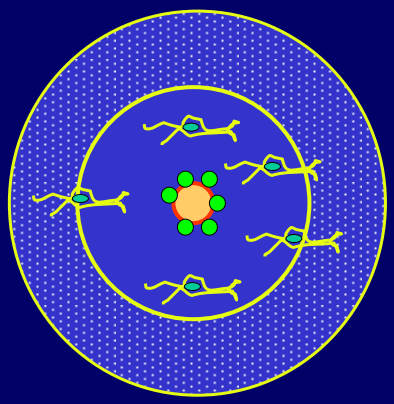


The Initial MS Lesion

Pattern III



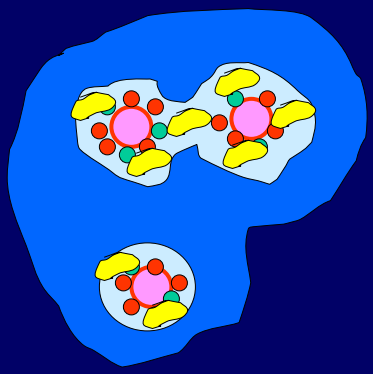
THE INITIAL MS LESION: Pattern III



- **Mild BBB Damage**
- **Edema**
- **Acute Axonal Injury**
- **DNA Fragmentation in Oligodendrocytes**
- **Intact Myelin**

● **CD8 T-cells** **I-NOS+ MG** Fibrin deposition

THE INITIAL MS LESION:
Pattern II



Edema, profound serum protein (fibrin) leakage

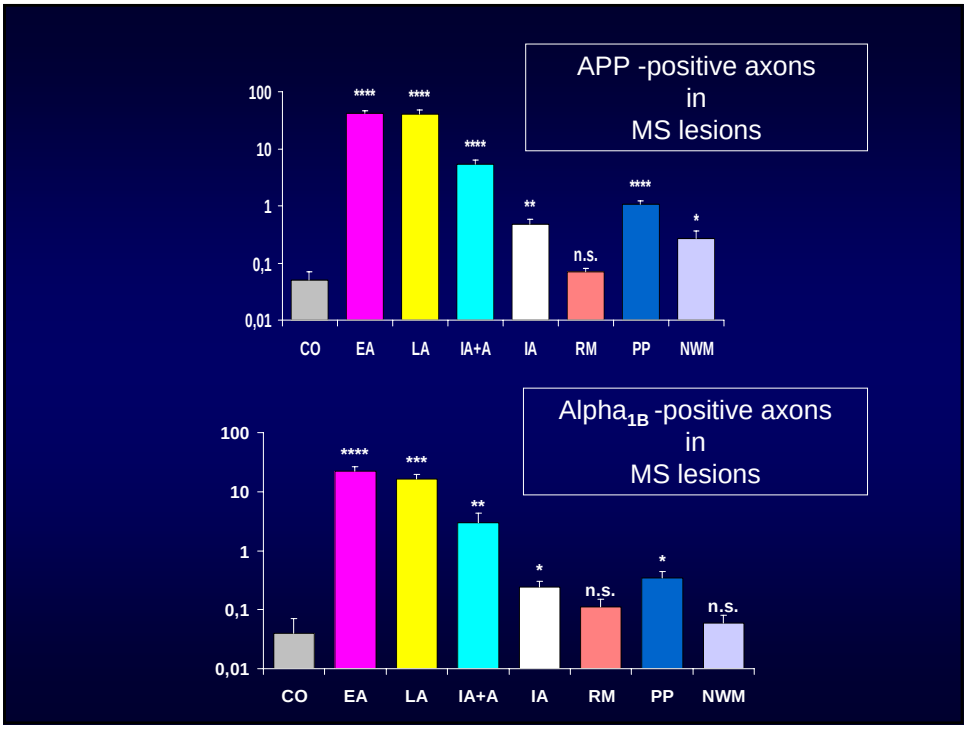
Massive BBB Damage

Perivenous confluent demyelination

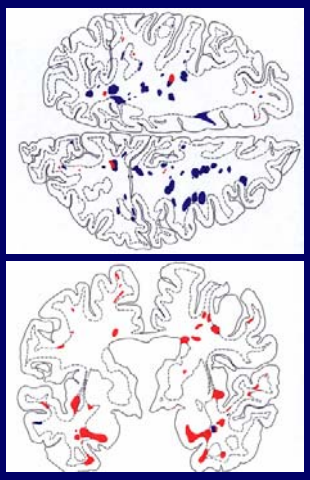
Axonal Injury

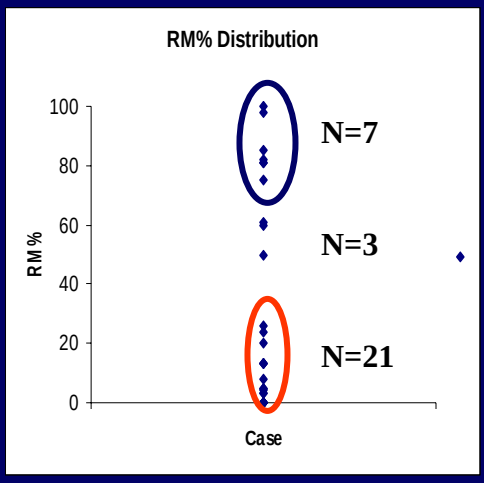
- **CD8 & CD4 T-cells**

Act. MG: CD68, MHCII>> i-NOS

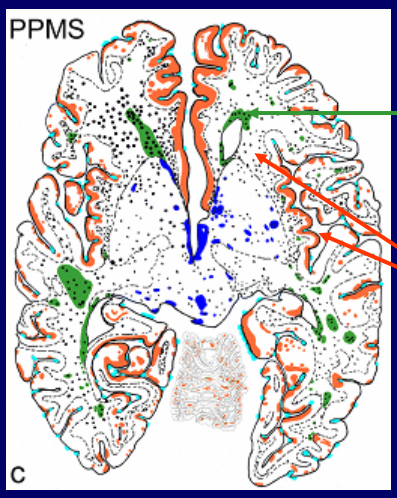


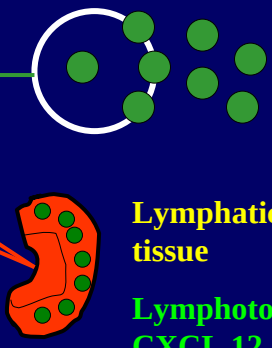
REMYELINATION IN MULTIPLE SCLEROSIS





Focal vs. Compartmentalized Inflammation in MS





Lymphatic like tissue

Lymphotoxin, CXCL 12, CXCL 13, CCL 19, BAFF

NeuroproMiSe WP H1

- **Workplan 18 Months:**
  - **Experimental:**
    - see WPs Identification, Validation
  - **Human studies**
    - Quantitative phenotypic characterization of MS lesions
    - Identify mechanisms of inflammation and tissue injury in situ
    - Validate methods of genotyping in archival material
    - Identification and clincal characterization of MS biopsy patients (Aim: inclusion of 100 MS biopsy patients)

Hellenic Pasteur Institute, Partner 14
Subproject Horizontal Integration WPH2

Pre-existing knowledge

•Differentially expressed genes staged during development of experimental MS (EAE, Tg6074), stroke (pMCAO) and Alzheimer disease (TgAPP23)

Neuropromise Workplan (5 year)

Generation & validation of algorithm

- Functional categorisation of differentially expressed genes for each disease.
- Identification of disease-unique and disease-common genes and pathways.
- Modification of algorithm sensitivity using blind data sets.

"Humanisation" of algorithm (collaboration with P5)

- Testing of relevance for corresponding human disease by expression analysis of selected disease-relevant genes/pathways in appropriate human samples

Effectiveness for evaluation of therapeutic regimens (collaboration within consortium)

- Testing of effectiveness for evaluation of experimental therapies