Dr. Pétry - Unbiased identification of peptide ligands mimicking interacting proteins in neuroinflammation pathology
**Abstract**

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Multiple Sclerosis (MS) neuroinflammation pathology is characterized by a plethora of molecular alterations at the **blood-brain barrier** (BBB) that becomes permissive to the extravasation of blood derived immune cells and compounds. To identify peptide ligands reacting with these BBB alterations at neuroinflammatory CNS lesions entangled by non-affected CNS tissue, we have developed a double
strategy combining molecular biology and bioinformatics approaches. We performed in vivo screening of phage displayed short (12aa) peptides in CNS neuroinflammation of the experimental autoimmune encephalomyelitis (EAE) rat model of MS and healthy controls. To extract the specific peptide ligands from both generated massive phage repertoires, we developed a physical molecular DNA subtraction of both phage repertoires and thus generated a subtraction phage repertoire of EAE specific peptides that were experimentally confirmed. Next Generation Sequencing (NGS) can be used to provide a high-resolution view of the contents of selected phage displayed peptides. The comparative data analysis of the three generated phage repertoires (9.4 mio sequences) confirmed the biological data evaluation of specific peptide ligands to altered neuroinflammatory CNS. With the hypothesis that some of these peptides mimic protein domains interacting with the same targets, we developed an analysis method allowing the identification of the mimicked proteins and subsequent analysis of the encoding set of genes in three steps. Mapping of the peptides against the proteome of interest, subtraction of random noise and the matches of a control repertoire, and selection of proteins with statistically significant scores. Experimentally, among the most high score mimicked proteins, derived synthesized peptides (20aa) of mimicked domains were tested for labeling of BBB alterations in CNS sections of MS and other chronic neurodegenerative diseases. In vitro studies and in vivo monitoring by MRI, confirmed their target specificity to human endothelial cells under proinflammatory stimulation. The strategy of combining the developed molecular biology and bioinformatics approaches adapted to phage display is applicable to (m)any disease models to streamline biomarker discovery and to identify functional proteins and domains.

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