EXECUTIVE SUMMARY

NEUROPRO is a consortium of 8 academic groups and 3 SMEs. This project aimed 1) to validate prolyl oligopeptidases (PREPs) as drug targets, 2) to improve the pharmacological properties of its inhibitors and 3) to use modern techniques to make a substantial progress in the understanding of the physiology of PREPs and their role in disease. In a great scientific effort from all participants, intense research was conducted to discover the actual biological relevance of PREPs in health and disease.

Intracellular, PREP intervenes in the signalling to control axonal transport, secretion and the processing of prohormones and proneuropeptides. Extracellular, it is involved in the activation of immunoactive cells and the control of neural plasticity and migration. Importantly, all these processes are compromised in neurodegeneration and one of the main conclusions derives from the role of PREP in neuroinflammation. The interactions of PREP with alpha-synuclein, GAP43 and structural cytoskeletal proteins have been established, which are respectively related to Parkinson's disease (PD), nerve outgrowth and vesicle traffic. Structural analysis of inhibitor bound PREP has provided information on the relations with activity structure and protein-protein interactive features. This information leads to a next generation of drugable compounds targeted to specific functions of PREP.

Of medical impact, we have obtained remarkable results which link PREP directly with plaque deposition in neurodegeneration. In cellular models, it was found that PREP is important for the processing of amyloid precursor protein (APP). Disruption of the APP metabolism and/or clearance is one major feature in Alzheimer's disease (AD). In fact, it was discovered that PREP co-localizes with beta-amyloid plaques in human AD brains, but also that its interaction with tau protein was disturbed compared with healthy brains. Furthermore, PREP interacts with alpha-synuclein, modifying its patterns of aggregation. In animal and cellular models of Parkinson's disease (PD), striking results showed that alpha-synuclein plaque density is decreased upon administration of PREP inhibitors. To support these findings, it was observed that there is indeed co-localization of PREP and alpha-synuclein in actual PD brains.

In the biotechnological and drug development arenas, this project has made significant contributions. A peptide chip technology has been validated for use in diagnostic and clinical research applications. New specific targets for inflammatory disease have been found during the off-target hunting of PREP inhibitors and the underlying mechanism was unravelled. Due to the changes of PREP expression in human serum found in neuroinflammatory conditions, PREP is proposed as a new and reliable marker at least for multiple sclerosis and hepatic encephalopathy. Perhaps the most striking application is based on the discovery that PREP activity inhibition is an adjuvant for plaque clearance in PD and the possibility to extend the same principle for other plaque forming diseases.

The consequences of PREPL deficiency were known based on a small group of patients with the hypotonia-cystinuria syndrome. This metabolic syndrome is characterized by weak muscle tone and dwarfism, but the molecular mechanism(s) causing this phenotype were still unknown at the beginning of NEUROPRO. The research performed within the consortium has unveiled that PREPL is involved in the regulation of membrane trafficking. These insights, combined with observations made during the treatment of patients have now resulted in the rational design of a therapeutic regimen, which will be tested in a small clinical trial.

From an academic point of view, this project has resulted in several dozens of scientific articles and this high productivity will continue in the aftermaths beyond the end of the funding period. Due to the scientific production of this project, the impact on the scientific community has grown significantly and this growth is now geometrical, counting the number of citations of our work, from an average of 300 citations at the beginning of the project to almost 1000 citations in 2011, a number that will very possibly be surpassed in 2012.

In summary, this project has accomplished all milestones and deliverables. We have considerably advanced the state-of-the-art in PREP and PREPL, opening new and promising research lines. Proof-of-concept on drug targets, compound scaffolds and therapeutic and diagnostic applications for commercial purposes have also been outlined.