



Federica Carucci (ESR 5)

X-Ray crystal structure determination of Neurotrophin Receptors in complex with small molecules to drive receptor-based drug design

Profile

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My Research

Neurotrophins are a family of secreted proteins that control a variety of functions in both central and peripheral nervous system. Their pleiotropic effects, such as development, differentiation and survival of neurons are mediated by Neurotrophin Receptors (NTRs). Aim of the project is to develop neurotrophin mimetics, ligands of the NTRs, that can be used to prevent and/or slow the progression of neurodegenerative diseases. To clarify structural determinants for ligand binding to Neurotrophin receptors, I will develop a purification protocol for the NTRs and obtain pure crystals of target proteins in complex with both neurotrophins and potential ligands. Crystal structures of the complexes will be determined by X-ray crystallography, allowing optimization of neurotrophin mimetics.

Moreover, during my secondments at the Foundation for Research and Technology Hellas (FORTH) in Crete and at the University of Sheffield, I will be trained on testing and screening the effects of the neurotrophin mimetics *in vitro* cultures and *in vivo* models of neurodegenerative diseases, such as Alzheimer's disease and amyotrophic lateral sclerosis.

Scientific CV

- 2018: EuroNeurotrophin Early Stage Researcher PhD student, University of Siena (Italy)
- 2017: Master of Science in Biochemistry – Protein Chemistry, Copenhagen University (Denmark) Purification and NMR structure of Intrinsically Disordered Protein
- 2014: Bachelor in Biotechnology, "La Sapienza" University of Rome (Italy)





EuroNeurotrophin

A European training network for the discovery of neurotrophins small molecule mimetics as candidate therapeutic agents for neurodegeneration and neuroinflammation

Project Coordinator

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Project Partners



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Introduction

Neurodegenerative diseases like Alzheimer's disease or Parkinson's disease are on the rise in developed societies worldwide affecting millions of people. Neurodegenerative diseases primarily affect neurons in the human brain and currently there exists no cure for any of them since most of the available drugs fail to tackle the pathogenesis of neurodegenerative diseases.

Preclinical studies point to the therapeutic potential of neurotrophins, which have been shown to control a number of aspects of survival, development and function of neurons. However, the poor pharmacokinetic properties of neurotrophins render their use as drugs prohibitive.

Objectives

EuroNeurotrophin will address the major limitations of neurotrophins by developing novel small molecule, neurotrophin mimetics with favourable profiles of stability, tissue penetration and targeted biological actions. In the long term, the project will contribute to the further development of small molecule therapeutics for the treatment of neurodegenerative diseases and neuroinflammation, revealing new concepts of neurotrophin receptors signalling and to create a pan-European Neurotrophin Network.

Furthermore, EuroNeurotrophin aims at creating a new generation of young scientists with a broad understanding and skill set in chemical biology with emphasis on the neuroscience field and to educate 14 young researchers regarding the knowledge underpinning the neurotrophin related field as well as on drug and natural products research for neurodegenerative diseases.

Impact

Neurotrophins offer one of the most compelling opportunities to significantly improve the treatment of serious age-related, neurological diseases such as Alzheimer's, Parkinson's, MND/ALS. A major therapeutic advantage of neurotrophic factors is that they tackle both the symptoms of a disease (improving clinical status) as well as its pathogenesis (delaying disease progression) without any prerequisite deep insight into the aetiology or specific pathogenic variables driving the disease process.

We will study neurotrophin small molecule mimetics (synthetic or natural) in depth, and will use them as molecular probes to interrogate the role of neurotrophins and their receptors. It will contribute important new knowledge to the next frontier in biomedical sciences.

