EuroNeurotrophin

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

Project Coordinator

Dr Theodora Calogeropoulou,
National Hellenic Research Foundation, Greece

Project Partners

ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
National Hellenic Research Foundation

Heidelberg Institute for Theoretical Studies
HITS

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National and Kapodistrian University of Athens

TECHNISCHE UNIVERSITÄT DRESDEN

FORTH
Foundation for Research & Technology - Hellas

The University Of Sheffield.

VU VRIJE UNIVERSITEIT AMSTERDAM

Project Contact

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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.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Daniele Narducci (ESR 1)

Synthesis of dehydroepiandrosterone (DHEA) derivatives substituted by five or six membered-17-spiro substituents.

Profile

Daniele Narducci
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Host:

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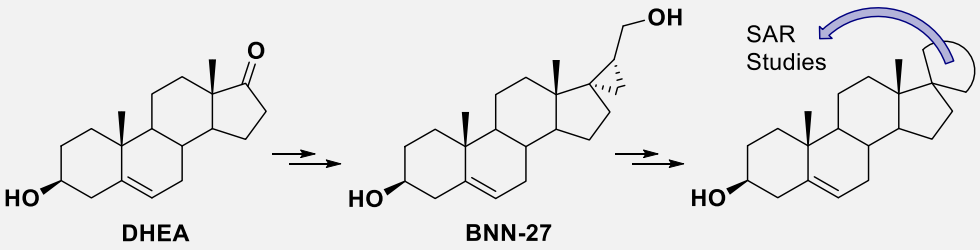
Project: EuroNeurotrophin

My Research

My research project engages in the synthesis and characterisation of complex steroidal new compounds, to obtained **S**tructure-**A**ctivity-**R**elationships of 17-spiro-DHEA derivatives agonists of neurotrophin receptors for optimum neuroprotective activity. The multistep and multicomponent synthesis will be carried out in lab-scale as well as, through a secondment to Concept Life Sciences, in larger scale of a selected compound. Furthermore, I will label active neurotrophin mimetic derivatives with fluorophores or NIR-dyes for MoA and in vivo studies and will be involved in the assessment of SNAP-PK profiles of the most potent analogue(s). Finally, I will obtain X-ray structures of my compounds with the neurotrophic receptors in a secondment at the University of Siena.



Scientific CV

- Sept 2018 – present:
  EuroNeurotrophin Early Stage Researcher,
  PhD student at the National Hellenic Research Foundation,
  enrolled at the National and Kapodistrian University of Athens (Greece).
- Oct 2011 – Jul 2017:
  Master of Science in Pharmacy, La Sapienza University of Rome (Italy)
  Thesis in Medicinal Chemistry:
  Synthesis of potentially druggable new antitumoral compounds
- Jul – Dec 2016:
  Erasmus+ for study scholarship at the Rijksuniversiteit Groningen (The Netherlands)
  Thesis in Organic Chemistry, published in RSC Adv. (2017).
  Chandgude AL, Narducci D, Kurpiewska K, Kalinowska-Tłuścik J, Dömling A. "Diastereoselective one pot five-component reaction toward 4-(tetrazole)-1,3-oxazinanes", **RSC Adv.** 2017, 7(79): 49995-49998.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Alessia Latorrata (ESR 2)

Synthesis of dehydroepiandrosterone (DHEA) derivatives substituted by three membered-17-spiro substituents

Profile

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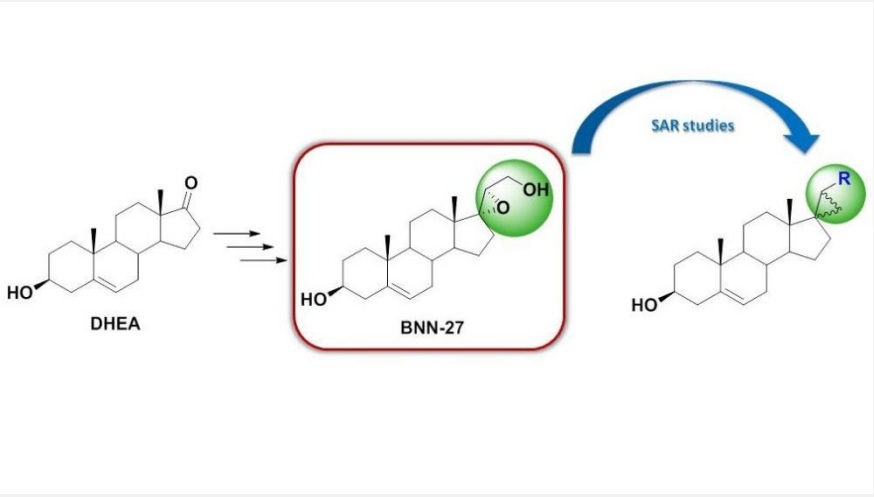
My Research

My research project will be focused on synthesis, purification and characterization of chiral 17-spiro DHEA derivatives bearing three-membered rings, which will be further elaborated to introduce pharmacophore groups, using asymmetric organocatalysis, biomimetic approaches and other synthetic methodologies. I will probe the stereoelectronic requirements for optimum neuroprotective activity, obtaining Structure-Activity-Relationships for 17-spiro-DHEA derivatives agonists of the neurotrophin receptors. My project also focuses to analyse SNAP PK data on lead compound(s) and to label steroidal neurotrophin mimetics with fluorophores or NIR-dyes.

I will dock my synthetic compounds on the neurotrophin receptors at HITS, I will study the fluorescently labelled compounds with live imaging techniques at TUD and I will be familiarised with neuroproteomics at VUA.



Scientific CV

- September 2018 – present: EuroNeurotrophin Early Stage Researcher PhD student at National Hellenic Research Foundation and enrolment at National and Kapodistrian University of Athens.
- March 2018: II level Master course in “Drug design and synthesis” at the University of Pavia, Italy (postgraduate specialization).
- October 2017 – March 2018: Traineeship at the University of Hamburg in Organic and Pharmaceutical synthesis. Thesis title: “Synthesis of Proline-based Hydroxamic acids as inhibitors of Zn^{2+}- dependent enzymes”.
- February 2017 – September 2017: Research fellow at the IRCCS-ASMN, Reggio Emilia, Italy.
- October 2015 - April 2016: Master’s Thesis in pharmaceutical and organic chemistry at the Northumbria University, Newcastle Upon Tyne, UK. Name of the Thesis: “Synthesis of metal chelators against neurodegenerative diseases”.
- May 2016: Master’s degree in Medicinal Chemistry at the University of Parma, Italy.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Alexandros Tsengenes (ESR 3)

Computer-aided design and optimization of neurotrophin small molecule mimetics.

Profile

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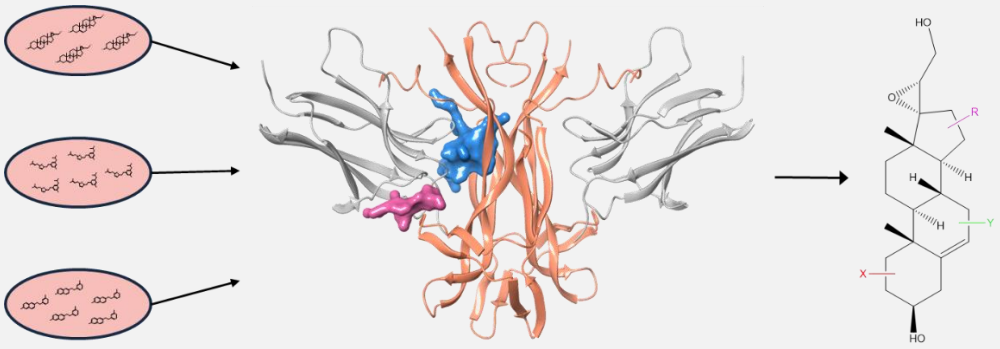
Project: EuroNeurotrophin

My Research

My research project engages in the design and optimization of small molecule mimetics and potentiators of neurotrophins, using a combination of in silico ligand-based and receptor-based drug design approaches. My project involves modelling of neurotrophins and the protein-protein complexes they form, and analysis of neurotrophin and neurotrophin-receptor binding properties. Moreover, in silico studies of known neurotrophin modulators and compounds identified in the compound library screen by the University of Caen Normandy, as well as investigations of ADMET properties are carried out. This work is performed iteratively, based on experimental feedback.



Scientific CV

- September 2018 – Present: PhD studentship, Heidelberg Institute for Theoretical Studies (HITS) & Heidelberg University, Germany.
- May 2017 – July 2018: Research project, Biomedical Research Foundation of Academy of Athens (BRFAA), Greece.
- September 2011 – February 2017: Diploma in Chemical Engineering, National Technical University of Athens (NTUA), Greece.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Christina Athanasiou (ESR 4)

Modelling of mechanistic effects of neurotrophin modulators

Profile

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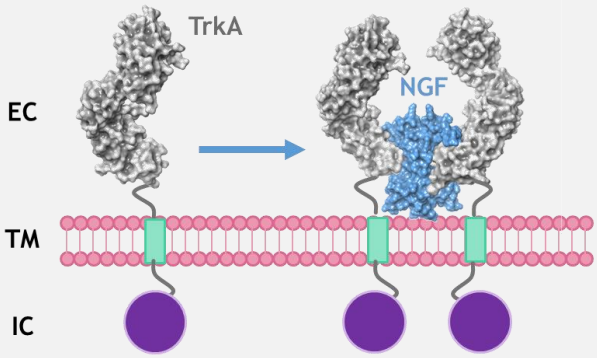
My Research

My research project is the investigation of the mechanism of action of neurotrophin small molecule mimetics and potentiators, through the use of molecular simulations and mathematical modelling techniques. My study will provide a basis for the optimisation of neurotrophin modulators and for the experimental investigation of their mechanisms. I will also study the interactions between neurotrophin mimetics and their receptors, as well as conformational changes and allosteric effects caused by the small molecules.



- Molecular simulations
- Mechanistic studies
- Conformational changes
- Allosteric effects
- Mathematical modelling

Scientific CV

- September 2018 – Present: EuroNeurotrophin Early Stage Researcher PhD student, Heidelberg Institute for Theoretical Studies (HITS) & Heidelberg University, Germany.
- February 2017 – June 2018: Research project, Biomedical Research Foundation of Academy of Athens (BRFAA), Greece.
- September 2011 – February 2017: Diploma in Chemical Engineering, National Technical University of Athens (NTUA), Greece.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Federica Carucci (ESR 5)

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

Profile

Federica Carucci
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Host:

University of Siena, Italy

Supervisor:

Prof. Stefano Mangani

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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)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Mirjana Antonijevic (ESR 6)

In silico screening and Hit to lead development of small molecules neurotrophin receptors ligands

Profile

Mirjana Antonijevic
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Host:

Université de Caen Normandie, UFR Santé - Faculté des Sciences Pharmaceutiques, Centre d'Etudes et de Recherche sur le médicament de Normandie, France

Supervisor:

Prof. Christophe Rochais
Professor of Organic Chemistry
UFR Santé - Faculté des Sciences Pharmaceutiques, Centre d'Etudes et de Recherche sur le médicament de Normandie

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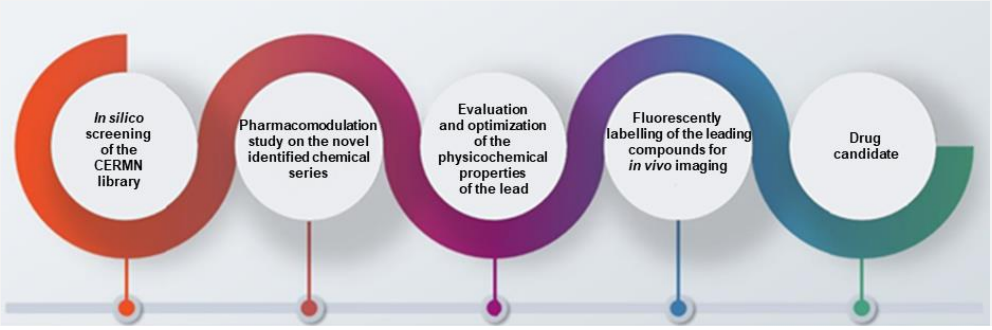
LinkedIn: Mirjana Antonijevic

Project: EuroNeurotrophin

My Research

To identify hit molecules as ligands for neurotrophin receptors, we will perform *in silico* screening of CERMN chemical library. *In silico* data will be evaluated along with high-throughput screening of the before mentioned chemical library. Selected hit molecules will be subjected to the study of the hit to lead optimization, to better understand the molecular patterns involved in target-ligand interactions. Additionally, these studies will be expanded by the physicochemical optimization of the selected hit compounds. The final lead compounds will be fluorescently labelled for *in vivo* bioimaging studies.



Scientific CV

- 2018-present: **PhD in Chemoinformatics and Medicinal Chemistry,** University of Caen, Caen "*In silico* screening and Hit to lead development of small molecules neurotrophin receptors ligands". ***ESR at EuroNeurotrophin project***
- 2017-2018: **Professional Associate,** Department of Pharmaceutical chemistry, Faculty of Pharmacy, University of Belgrade, Belgrade
- 2012-2017: **Master of Pharmacy**, Faculty of Pharmacy, University of Belgrade, Belgrade *Master thesis*: "3D-QSAR study, design of serotonin 5-HT_{2A} receptor antagonists and *in vitro* testing of the blood-brain barrier permeation of selected antipsychotics", supervised by Prof. Katarina Nikolic.

Publication:

- **Antonijević, M.**, Nikolić, K., Vučićević, J., Oljačić, S. and Agbaba, D. (2017). 3D- QSAR modeling and pharmacophore study of serotonin 5-HT_{2A} receptors antagonists. Arh.farm. 2017;67: 233 – 247.

Poster presentations:

- 2018 *Combined ligand and structure- based approach in search of 5-HT_{2A} receptor agonists and antagonists* K. Nikolic, **M. Antonijevic**, M. Radan, D. Agbaba, T. Djikic. 11th FENS Forum of Neuroscience, Berlin, 7-11 July, 2018.
- 2019 *In silico screening and Hit to lead development of small molecules neurotrophin receptors ligands* **M. Antonijevic**, R. Bureau, P. Dallemagne, C. Rochais. 26th Young Research Fellow Meeting, Paris, 20-22 February, 2019.
- 2019 *In silico screening and development of small molecules neurotrophin receptors ligands* **M. Antonijevic**, R. Bureau, P. Dallemagne, C. Rochais. 27th Annual GP2A Medicinal Chemistry Conference, Nottingham, 21-23 August 2019 – best poster award.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Paolo Giaccio (ESR 7)

Isolation of new natural neurotrophin mimetics from marine microorganisms

Profile

Paolo Giaccio
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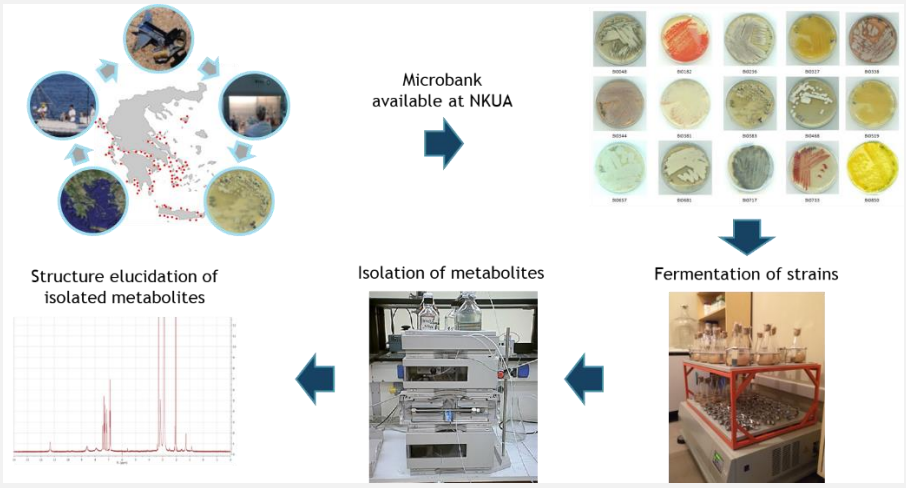
Project:EuroNeurotrophin

My Research

The aim of my research is the isolation of natural products from marine bacteria and/or fungi from the East Mediterranean basin that act as mimetics of neurotrophins using a bioassay-guided isolation protocol.

The procedure includes:

i. small-scale fermentation of existing strains from the MicroBank available at NKUA and preparation of extracts that will be tested for neuroprotective activity using HTS facilities at USFD,
ii. large-scale fermentation of strains exhibiting positive hits and fractionation of extracts thereof to crude fractions according to polarity, which will be subjected to another round of HTS facilities at USFD,
iii. chromatographic separations of fractions exhibiting positive hits using normal and reversed phase liquid chromatography so as to obtain secondary metabolites in pure form to be evaluated for their bioactivity as neurotrophin mimetics,
iv. comprehensive spectroscopic (1D and 2D NMR, UV, IR) and spectrometric (HR-MS and MS^n) analyses for the structure elucidation of the isolated metabolites.



Scientific CV

- 2018: EuroNeurotrophin Early Stage Researcher, PhD student at the Section of Pharmacognosy and Chemistry of Natural Products, Department of Pharmacy, National and Kapodistrian University of Athens, Greece.
- 2018: Postgraduate fellowship in Natural Products and their derivatizations at the Italian National Research Council (CNR), Italy.
- 2017: M.Sc. in Pharmaceutical Chemistry, University of Naples "Federico II", Italy. Thesis in Organic Chemistry: Design, synthesis and biological evaluation of novel FXR ligands.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Canelif Yılmaz (ESR 8)

Evaluation of small molecule neurotrophin mimetics in models of neurodegeneration and neuroinflammation

Profile

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Host:

Faculty of Medicine Carl Gustav Carus, TU Dresden

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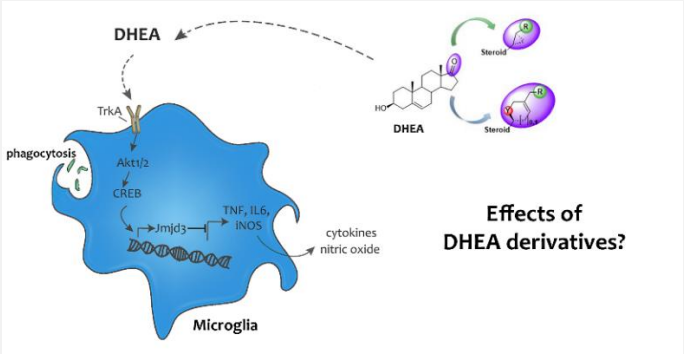
Project: EuroNeurotrophin

My Research

My research project focuses on investigating the anti-inflammatory effects of novel DHEA mimetics, which will be synthesized by fellow ESR's in the consortium. Inflammatory responses of microglia, the innate immune cells of the brain, have previously been shown to be regulated by NGF, the native ligand of TrkA, and also DHEA via TrkA dependent signalling[1,2].



Building on that knowledge, I will be testing whether our novel DHEA mimetics will also have a similar effect on regulating neuroinflammation. For this purpose I will use primary microglia, and study the effects of the compounds on the inflammatory responses of microglia, such as cytokine expression and phagocytosis. Furthermore, I will study the brain uptake of labelled DHEA mimetics in spinning disk microscopy. Finally, I will evaluate the efficacy of the DHEA mimetics on Cuprizone model of Multiple Sclerosis, and evaluate if the DHEA mimetics can improve disease pathophysiology.

During my PhD I will also visit our partner AvantiCell Science to receive training in 3D cell culture and bioprinting technologies, FORTH to assess the efficacy of compounds in neuronal cells, and finally UniCaen to assess the druggability of effective compounds.

CV

- 2018-Present, EuroNeurotrophin Early Stage Researcher, PhD student
  Faculty of Medicine Carl Gustav Carus, TU Dresden, Germany
- 2015-2017, M.Sc. in Neuroscience
  Bilkent University, Ankara, Turkey
- 2009-2015, B.Sc. in Molecular Biology, with a minor degree in Chemistry,
  Koç University, İstanbul, Turkey

Publications

- Erol O, Uyan I, Hatip M, Yilmaz C, Tekinay AB, Guler MO. Recent Advances in Bioactive 1D and 2D Carbon Nanomaterials for Biomedical Applications, *Nanomedicine* (2017)
- Okur Z, Senturk OI, Yilmaz C, Gulseren G, Mammadov B, Guler MO, Tekinay AB. Promotion of neurite outgrowth by rationally designed NGF-β binding peptide nanofibers, *Biomater Sci* (2018)
- Yilmaz C, Karali K, Fodelianaki G, Gravanis A, Chavakis T, Charalampopoulos I, Alexaki VI. Neurosteroids as regulators of neuroinflammation, *Front Neuroendocrinol (2019)*

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Ana Aragón (ESR 9)

Development of Human Cell-Based Models for study of Blood Brain Barrier Molecular Permeability

Profile

Ana Aragón González
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Host

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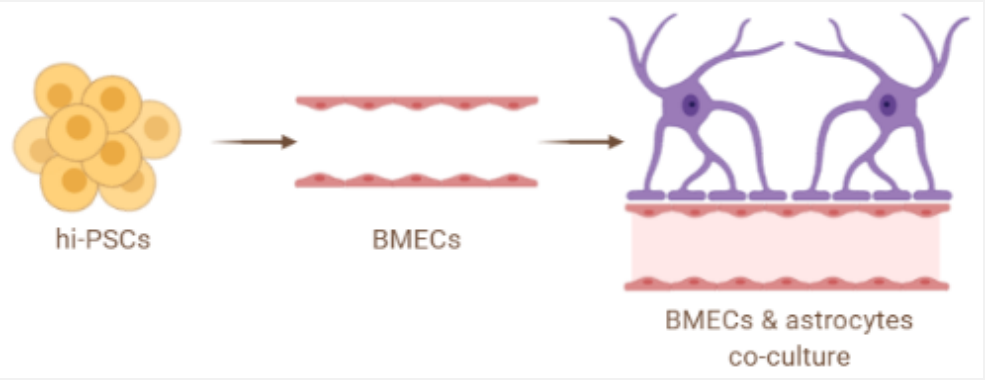
Project: EuroNeurotrophin

My Research

The aim of my project is the development of Human Cell-Based Models for the study of Blood Brain Barrier Molecular (BBB) permeability. The main goal is to reproduce the human BBB by the controlled differentiation of hi-PSCs into microvascular cells. To check the BBB integrity and filtration properties, primary astrocytes and hi-PSCs-derived microvascular cell co-culture will be developed. With these models, we shall then evaluate neurotrophic agonists and antagonists. As such, the permeability properties of small molecules having neurotrophic mimetic properties identified during the EuroNeurotrophin project will be tested.



Scientific CV

- 2019-present: **EuroNeurotrophin Early Stage Researcher**, University of Sheffield, Sheffield Institute for Translational Neuroscience.
- 2018-2019: **Master of Neuroscience** in University of Barcelona, Spain and practices in Vall d'Hebron Research Institute. Master thesis: 'Astrocyte's role in neuroinflammation: a key cell in neurodegenerative diseases'
- 2017-2018: **Erasmus+ fellowship** in the University of Wroclaw, Poland and practices in Cytobiochemistry Department. Bachelor thesis: 'Molecular bases study of two anemia hemolytic disease cases with an heterozigotic mutation in NT5C3A gene'
- 2013-2017: **Degree of Biochemistry** in the University of Cordoba, Spain

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Débora Pita Illobre (ESR 10)

Cell-Based Models for Neurotrophic Therapeutic Testing

Profile

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Vrije Universiteit Amsterdam,
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Project: EuroNeurotrophin

My Research

The overall goal of my project is to provide a cell-based model of human neuronal function, being a representation of cells with human neuronal characteristics and functionality produced by the controlled differentiation of neuronal stem cells (NSCs) for neurotrophic therapeutic testing. Specific aims are:

1. Differentiation of the NSCs into different types of neurons (cortical neurons, dopaminergic neurons, among many other types of neurons) and glial cells in 2D cultures.
2. Differentiation of the NSCs into different types of neurons and glial cells in 3D cultures.
3. Validation of the cell-based model using synthetic and natural compounds produced in the EuroNeurotrophin network.

Scientific CV

- November 2019 – present: EuroNeurotrophin Early Stage Researcher PhD student at Vrije Universiteit Amsterdam, The Netherlands.
- July 2017: Exposition of the Master's Thesis at "XIII days for young researches in Neuroscience", Santiago de Compostela, Spain.
- January 2017 – July 2017: Master's Thesis. Department of Morphological Sciences, University of Santiago de Compostela, Spain. Name of Thesis: "Angiotensin (1-7)/Mas Receptor in dopaminergic neurons".
- 2016-2017: Master Program in Neuroscience – Specialty in Cellular and Molecular Neurobiology, University of A Coruña, Santiago de Compostela and Vigo (Spain).
- February 2016 – May 2016: Bachelor's Thesis. Department of Hematology, Santa Creu and Sant Pau's Hospital, Barcelona, Spain. Name of Thesis: "Diagnosis of inherited thrombocytopenia using the MLPA".
- July 2015 – September 2015: Intership Erasmus + scholarship, Department of Molecular and Cell Biology – University of Leicester (UK).
- 2012-2016: Biotechnology Degree, University of Vic – Central University of Catalunya (Spain).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Thanasis Rogdakis (ESR 11)

Evaluation of microneurotrophins activity on neurotrophin receptors and their role in signalling in *in vitro* and *in vivo* neurodegenerative conditions, such as Alzheimer's Disease

Profile

Thanasis Rogdakis
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Host:

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INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY

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Project: EuroNeurotrophin

My Research

My research project is engaging in the screening and biological assessment of novel steroidal and natural compounds for their ability to bind to and activate neurotrophin receptors, such as TrkA, as well as to prevent cell death. Compounds that are active and present favourable pharmacokinetic profiles will be selected to be further tested in *in vitro* and *in vivo* models of Alzheimer's Disease. I will evaluate their capacity to promote neuronal survival against Aβ in primary neuronal cultures and animal models of the disease. Lastly, the impact on synapse number and function, as well as the behavioural phenotype will also be examined.

Scientific CV

- October 2018 - Present: **EuroNeurotrophin Early Stage Researcher** PhD candidate, Foundation for Research and Technology – Hellas, Institute of Molecular Biology and Biotechnology & Medical School, University of Crete
- February 2018 – September 2018: **Research Technician**, Neural Computation lab, Wolfson Institute for Biomedical Research, University College London. Supervisor: Professor Michael Hausser
- February 2016 – January 2018: **Research Technician**, Cell and Developmental Biology Department, University College London. Supervisor: Professor Patricia Salinas
- September 2015: **Msc in Neuroscience**, Institute of Psychiatry, Psychology and Neuroscience, King's College London
- July 2013: **Bsc in Biology**, Faculty of Biology, University of Athens, Greece

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Despoina Charou (ESR12)

In vitro and in vivo effects of new synthetic and natural compounds on neural stem cells and adult neurogenesis in Alzheimer's Disease

Profile

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Project: EuroNeurotrophin

My Research

Neurotrophins are growth factors that promote neuronal survival and neurogenesis, while abnormal expression of neurotrophins and their receptors has been associated with neurodegeneration. While these molecules have been shown to slow or prevent neurodegenerative symptoms, limitations like reduced bioavailability, poor ability to penetrate the blood-brain-barrier and short half-life do not allow their therapeutic use. Recent studies have demonstrated that small molecule mimetics that have similar effects and efficacy to neurotrophins, are not constrained by the same limitations, making them better therapeutic candidates.

The overall goal of this project is to test synthetic and natural neurotrophin mimetics on specific neurotrophin-dependent, mainly TrkB expressing, cellular populations and assess the molecular mechanisms and functions leading to increased neuronal survival, synaptogenesis and adult neurogenesis affected in AD. The main focus is be put on the neurorestorative and neurogenic effect of the new compounds, a role that up to now is highly associated with the endogenous neurotrophin, BDNF.

Scientific CV

- 2018- current: Euroneurotrophin Early Stage Researcher, PhD student
  Institute of Molecular Biology and Biotechnology (IMBB), Foundation for Research and Technology Hellas (FORTH) & Department of Pharmacology, Medical School, University of Crete
- 2015-2018: Research Assistant, University of Oxford (Clinical Neurosciences)
- 2013-2014: MSc by Research in Biomedical Sciences, University of Edinburgh
- 2007-2013: Biology D., National and Kapodistrian University of Athens

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 765704

Evangelia Thanou (ESR 13)

Investigation of the potency of small molecule mimetics of neurotrophins to rescue the reduction in synapse number and the aberrant synapse proteome in mouse models of Alzheimer's Disease

Profile

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Host:

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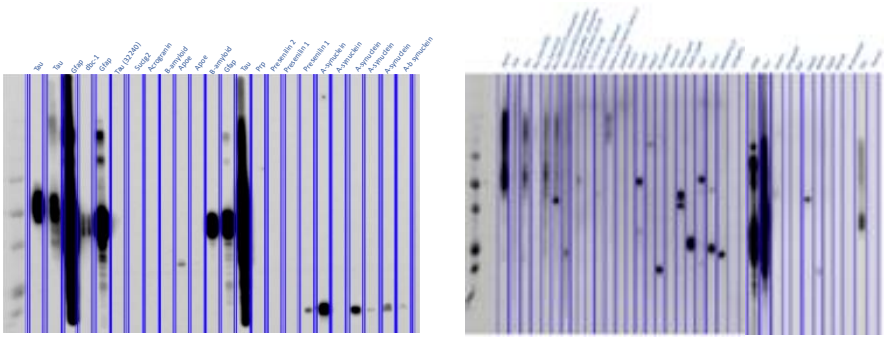
My Research

The main focus of my project is the examination of the temporal effects of neurotrophin mimetics on the brain tissue and on synaptic proteomes in mouse models of neurodegeneration (APPswe/PS1dE9 and 5xFAD transgenic mice for AD; cuprizone mouse model of MS). Firstly, it is expected that the large-scale proteomics data will be hypothesis generating that will guide the subsequent functional studies to explain the mechanistic aspects of the disorders and their rescues by the neurotrophin mimetics. Secondly, our data will provide hints on the neurotrophin mimetics' efficacy on the rescues, which should assist in the design of the future optimal mimetic for the eventual clinical treatment of the disorders. I will use (1) quantitative proteomics to reveal the global changes of proteins in the brain. Around 3000 proteins per sample will be quantified. As current quantitative proteomics are not effective in distinguishing protein isoforms and posttranslational modifications, we use (2) quantitative western blotting to examine these changes. In addition, I will obtain secondments studying signalling pathways in cell culture (FoRTH), compound tracking and brain imaging (TUD) and clinical trial design (Novartis, Athens).



Antibodies against protein isoforms implicated in AD (hippocampus brain region).

Scientific CV

- 2018-recent: EuroNeurotrophin Early Stage Researcher PhD student, Vrije Universiteit Amsterdam, The Netherlands.
- 2016-2018: Master student in Molecular Biomedicine at the Medicine School of National and Kapodistrian University of Athens in collaboration with Alexander Fleming Institute, The role of LRRK2 signaling in resident and infiltrating immune cells in different models of familial and sporadic Parkinson's disease
- 2012-2016: Biology Department School of Sciences and Engineering, University of Crete, Greece.

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Marco Destro (ESR 14)

Evaluation and discovery of new Neurotrophin mimics using high-through put screening in amyotrophic lateral sclerosis (ALS) patient-derived *in vitro* models, and taking forward hit compounds into *in vivo* models

Profile

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My Research

In order to assess the potential neuroprotective effects of new neurotrophin mimics, I am currently performing high-throughput screening of 169 synthetic compounds and 100 marine microbial extracts on *in vitro* co-cultures of ALS patient and control-derived astrocytes and motor neurones. Functional screening of top hits will be performed in order to ascertain their mechanism of action. Most promising molecules will then be tested on *in vivo* zebrafish models of ALS, and then taken forward for *in vivo* testing in mouse models of ALS.

Scientific CV

- 2018: EuroNeurotrophin Early Stage Researcher PhD student, University of Sheffield, Sheffield Institute for Translational Neuroscience.
- 2016-2018: MSc in Molecular Biology and Genetics from the University of Pavia (Italy). High-Mobility Group Box 1 protein (HMGB1) signaling modulates neuroprotective responses and/or pro-inflammatory responses in non-pathological and ALS mouse astrocytes.
- 2013-2016: BSc in Biomolecular Sciences and Technologies from the University of Trento (Italy). Interaction between Cyclin-Dependent Kinase 1 (CDK1) and Androgen Receptor (AR) in the context of Spinal and Bulbar Muscular Atrophy (SBMA), and development of *C. elegans* lines stably expressing elongated PolyQ Androgen Receptor.

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