



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

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PhD student - Early Stage Researcher (ESR1) Synthesis of dehydroepiandrosterone (DHEA) derivatives substituted by five or six membered-17-spiro substituents

EuroNeurotrophin Overview

EuroNeurotrophin will be the first European consortium to study small molecule neurotrophin mimetics (synthetic or natural) in depth, use them as molecular probes to interrogate neurotrophins, and emphasise their clinical translation.

Neurodegenerative diseases (ND), like Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and motor neuron disease, are on the rise worldwide. Preclinical studies point to the therapeutic potential of neurotrophins in preventing or slowing the progression of ND. The key idea behind this project is to address the major limitations of neurotrophins by developing novel **small molecule, neurotrophin mimetics** with favourable profiles of stability, tissue penetration and targeted biological actions.

EuroNeurotrophin meets the emerging need for training young researchers in drug discovery and development with a focus on the design, synthesis and isolation of new neuroprotective small molecule neurotrophin mimetics and their assessment using multimodal approaches, as well as their use towards market applications.

Host Institution

The [National Hellenic Research Foundation](#) (NHRF), one of the largest Research Centers in Greece, was founded in 1958. It is a non-profit Research Foundation supervised by the General Secretariat for Research and Technology (GSRT) of the Ministry of Culture, Education and Religious Affairs in Greece.

The [Institute of Biology, Medicinal Chemistry and Biotechnology](#) (IBMCB) was established in March 2012, with the objective to act as a focal point of Excellence, through an interdisciplinary approach in Chemical Biology, with the aim of providing solutions for state-of-the-art issues in the areas of health, drug research, and biotechnology. Dr Theodora Calogeropoulou (<http://www.eie.gr/nhrf/institutes/iopc/cvs/cv-calogeropoulou-gr.pdf>), is a Research Director of IBMCB with >22 years of experience in medicinal chemistry and development of synthetic methodologies. She has been involved in a number of Marie-Curie Actions as coordinator or participant. Author of 65 publications and 11 international patents, two on steroidal neurotrophin mimetics.

Description of tasks for the position

a) To probe the stereoelectronic requirements for optimum neuroprotective activity of 17-spiro-DHEA derivatives. **b)** To obtain Structure-Activity-Relationships for 17-spiro-DHEA derivatives agonists of the neurotrophin receptors. **c)** To obtain SNAP PK data on selected active derivatives. **d)** To label steroidal neurotrophin mimetics with fluorophores or NIR-dyes.

The synthesis of the new compounds will be based on methodologies developed by our group and taking advantage of the tremendous potential arising from the availability of novel synthetic methodologies and technologies. The state-of-the-art infrastructure of IBMCB/NHRF (NMR, MS) will be instrumental for the characterisation and determination of the stereochemistry of the complex steroidal new compounds. To this end the key step in the synthesis will be the ring closing and enyne metathesis of appropriately 17-disubstituted precursors, which will generate oxygen or nitrogen substituted unsaturated cyclic derivatives which can further participate in cycloaddition reactions (i.e. Diels-Alder) for the generation of more decorated analogues. Furthermore, densely functionalized scaffold diversity can be obtained through multicomponent reactions (MCRs i.e Ugi 3 component reaction) which represent a useful tool for the never-ending hunt for biologically active compounds. **STD-NMR approaches** will be used to identify compounds which interact with purified TrkA, TrkB, TrkC and p75^{NTR} receptors which can be further evaluated in the *in vitro* and *in vivo* assays within the network. Active analogues will be labeled with fluorescent or NIR dyes for *in vivo* imaging studies. Quantification of a small number of lead compounds (1-2) to determine SNAP curves and PK parameters using LC-MS will be performed prior to *in vivo* activity studies.

Requirements

- Applicants must hold a MSc or equivalent in the field of chemistry or pharmaceutical sciences.
- Applicants can be of any nationality.
- Applicants must have a very good knowledge (written and oral) of the English language.
- **H2020 MSCA Mobility Rule:** researchers must not have resided or carried out their main activity (work, studies, etc.) in the country of the host organisation for more than 12 months in the 3 years immediately before the recruitment date. Compulsory national service, short stays such as holidays, and time spent as part of a procedure for obtaining refugee status are not taken into account.
- **H2020 MSCA eligibility criteria:** Early Stage Researchers (ESRs) must, at the date of recruitment by the host organisation, be in the first four years (full-time equivalent research experience) of their research careers and have not been awarded a doctoral degree. Full-Time Equivalent Research Experience is measured from the date when the researcher obtained the degree entitling him/her to embark on a doctorate (either in the country in which the degree was obtained or in the country in which the researcher is recruited, even if a doctorate was never started or envisaged).

Benefits

- ✓ The position is full-time with a 12 month duration renewable to 36 months.
- ✓ A very attractive salary plus allowances package according to the allowance amounts defined in the rules for Early Stage Researchers (ESRs) EU Marie Skłodowska-Curie Actions Innovative Training Networks (ITN) (http://ec.europa.eu/research/participants/data/ref/h2020/wp/2016_2017/main/h2020-wp1617-msca_en.pdf)
- ✓ Network-wide specialised training and training in transferable/technical skills.
- ✓ Local specialist training provided by the host institution.
- ✓ Intersectoral and interdisciplinary secondments within the EuroNeurotrophin network.
- ✓ International exposure through participation in scientific conferences.

Application

The application form can be downloaded from our website (www.euroneurotrophin.eu). Interested candidates for the position should submit the completed application form along with their cv, motivation letter, copies of publications and/or thesis (if available) and scans of transcripts to the

following emails:

tcalog@eie.gr and info@euroneurotrophin.eu

IMPORTANT: Please also arrange for two recommendation letters to be submitted directly to tcalog@eie.gr and to info@euroneurotrophin.eu

Additional Information

For additional information about the research project and this individual position, please contact:
Dr Theodora Calogeropoulou. Email: tcalog@eie.gr