EuroNeurotrophin Newsletter December 2021

Neurotrophin mimetics: recent frontiers in neurodegenerative disorders

One of the main causes of neurodegeneration relies in changes of the expression of neurotrophins (NTs) and/or their receptors. Indeed, imbalances between NTs and their receptors (TrkA, TrkB, TrkC and $p75^{NTR}$) or changes in their activity, lead to neuronal damage resulting in neurological and neurodegenerative conditions. The therapeutic role of neurotrophins attracted the attention of many scientists during the years but their poor pharmacokinetic properties, such as reduced bioavailability, inability to penetrate the BBB and short half-life make the large neurotrophin proteins not suitable as drugs (Josephy-Hernandez et al. 2017).

For this reason, several efforts are ongoing for the development of neurotrophins mimetics (small molecules and peptidomimetics) that can modulate the action of Trks and/or $p75^{NTR}$ receptors with improved pharmacodynamic and pharmacokinetic properties. Specifically, the neurotrophin mimetics can be classified in TrkA and TrkB receptor agonists and, on the other hand, in $p75^{NTR}$ antagonists, as summarized in Figure 1 (Josephy-Hernandez et al. 2017; Longo et al. 2013).

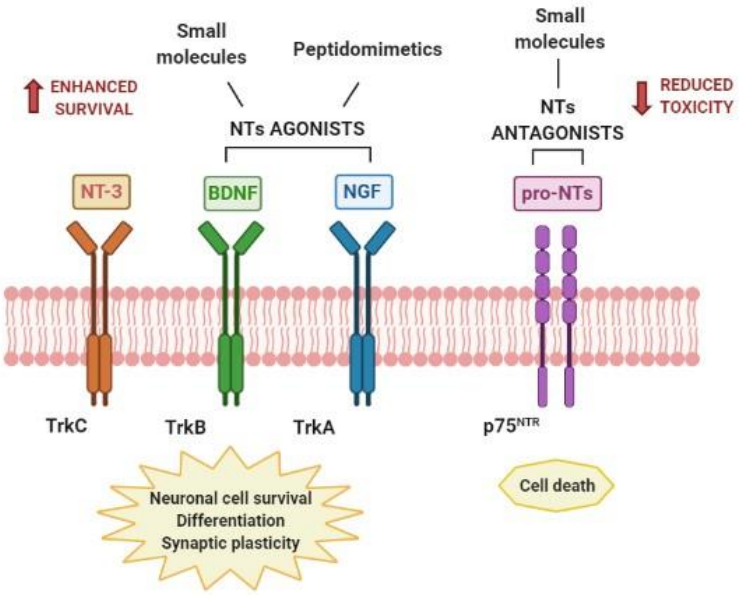

Figure 1. *Potential therapeutic strategies of neurotrophin mimetics depending on the receptors and their functions.*

Project Coordinator

Dr Theodora Calogeropoulou, National Hellenic Research Foundation, Greece

Project Partners

ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
National Hellenic Research Foundation

HITS
Heidelberg Institute for Theoretical Studies

UNIVERSITÀ DI SIENA
1240

UNIVERSITÉ CAEN NORMANDIE

HELLENIC REPUBLIC
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

info@euroneurotrophin.eu
www.euroneurotrophin.eu

Social

Twitter: @eneurotrophin
Group: EuroNeurotrophin
Project: EuroNeurotrophin

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TrkA AGONISTS

Among the TrkA agonists, the small molecule gambogic amide exerts a potent neurotrophic activity decreasing apoptosis in primary hippocampal neurons (Jang et al. 2007); the non-peptidic agonist of TrkA, MT2, protects neurons from Aβ amyloid-mediated death in NGF-deficient neurons (Scarpi et al. 2012) and Talaumidin and its derivatives show neuroprotective effects, promoting neurite outgrowth in PC12 cells, selective for TrkA receptor (Harada et al. 2020). More impressive is the peptidomimetic Cerebrolysin, known for its protective role in Alzheimer's disease (AD) (Alvarez et al. 2006). Indeed, in a double-blind trial, it was able to improve the daily activities and psychiatric symptoms in patients with mild to severe AD, after intravenous administration (Alvarez et al. 2011). In addition, the cyclic peptide Tavilermide (MIM-D3), acting as a selective TrkA agonist, showed a relevant improvement of cognitive capacities of treated aged rats, leading to selective survival of the cholinergic neurons (Bruno et al. 2004). Currently, it is in Phase 3 clinical trials for treating the signs and symptoms of dry eye (NCT03925727).

TrkB AGONISTS

A large number of TrkB agonists mimetics have been studied for neurodegeneration. Among these, some deserve more consideration; deoxygedunin, with a selective TrkB activity, is able to promote axon regeneration in topical treatments (English et al. 2013) and it is proven to be efficient in two Parkinson's disease (PD) animal models, leading to the protection of locomotor function and the reduction of neuronal death in dopaminergic neurons (Nie et al. 2015). A number of studies corroborated that the flavonoid 7,8-dyhydroxyflavone (7,8-DHF) shows neuroprotection in PD and Huntington's disease (HD) models (Jang et al. 2010) (Jiang et al. 2013) together with antioxidant activity (Chen et al. 2011) and enhances motor neuron survival, motor function and spine density in an amyotrophic lateral sclerosis (ALS) model (Korkmaz et al. 2014). The benzothiazole riluzole has neuroprotective effect and it has been approved in the United States in 1995 for the treatment of ALS, increasing BDNF and GDNF levels with improvement of motor neuron survival (Dennys et al. 2015). It is also under several clinical trials in combination with other drugs. Brimonidine exerts neuroprotective effect in retinal ganglion cells (RGCs) through up-regulation of the expression of BDNF in these cells (Gao et al. 2002). Brimonidine is used in the treatment of glaucoma as eye drops to reduce intraocular pressure (IOP) under the brand name Lumify®. Different drugs, used against PD such as Rotigotine, Selegiline, Rasagiline, Memantine and Levodopa interact with TrkB and increase BDNF expression. Furthermore, of particular note, Massa et al. discovered small molecules neurotrophic mimetics with specificity for TrkB at nM concentration (Massa et al. 2010). One of these, LM22A-4, prevents neuronal death in in vitro models of AD, HD and PD (Longo et al. 2013).

p75^{NTR} ANTAGONISTS

In this class it is worthwhile to highlight the small non peptide LM11A-31 developed by Massa et al (Simmons et al. 2014). Oral administration in AD mice models reduces degeneration of cholinergic neurites (Simmons et al. 2014). Furthermore, with a direct activation of p75^{NTR} signalling and inhibition of the apoptotic pathway improves motor function in spinal cord injury (SCI) mouse model and leads to an antiapoptotic effect in mice after traumatic brain injury (TBI) (Tep et al. 2013) (Shi et al. 2013).

Neurosteroids as potent neurotrophin mimetics

Neurosteroids affect survival, development and function of neurons and it has been found that their levels in the brain reduce in neurodegenerative conditions. Recent studies have shown that the neurosteroid dehydroepiandrosterone (DHEA) acts as a neurotrophic factor in the brain and prevents neuronal apoptosis by interacting with the neurotrophin receptors TrkA and p75^{NTR} (Lazaridis et al. 2011). In addition, DHEA regulates microglia inflammation via TrkA dependent signalling and reduces the inflammation, downregulating the expression of the pro-inflammatory cytokines (Alexaki et al. 2018). Nevertheless, DHEA is metabolized in humans into estrogens and androgens, thus, its long-term administration increases the risk for hormone-dependent cancer. Therefore, DHEA analogues with modifications at position C17 of the steroid skeleton were synthesized aiming to improve the antiapoptotic activity and neuroprotection of the parent molecule, without the undesired hormonal side effects. The C17-spiroepoxy DHEA analogues BNN27 and BNN20 are remarkable. These steroid derivatives, synthesized by Calogeropoulou et al. (Calogeropoulou et al. 2009) are able to cross the BBB without the undesired hormonal side effects of DHEA and they are selective for TrKA and TrkB, respectively. Specifically, BNN27 activates TrkA, exerting antiapoptotic effect in PC12 cells and it increases survival of mouse motor neurons co-cultured with human astrocytes from SOD1 ALS patients. *In vivo* studies showed an antiapoptotic effect and reduction of the toxic effect of cuprizone in oligodendrocytes restoring the myelin loss (Pediaditakis et al. 2016) (Bonetto etal. 2017) (Glajch et al. 2016). In addition, BNN27 interacts with p75^{NTR} inhibiting apoptosis in primary cultures of cerebellar granule neurons (CGNs), specific for p75^{NTR} (Pediaditakis et al. BNN27, 2016).

On the other hand, BNN20 binds with high affinity to TrkB, showing antiapoptotic activity *in vitro*. Its neuroprotective activity was analysed in Weaver mouse genetic model of PD where long term administration of BNN20 protects dopaminergic neurons by mimiking BDNF and induces antiapoptotic, antioxidant and anti-inflammatory effects (Botsakis et al. 2017).

Conclusion

All these results point out that several small molecules possess promising activity against neurodegenerative disorders and lay the foundation for the future development of new neurotrophin mimetics with BBB-permeability and selective neuroprotective and neurogenic activities with potential application in neurodegenerative diseases.

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Biomolecular simulations to investigate neurotrophin receptor mechanisms and interactions with neurotrophin mimetics

Neurotrophins (NTs) are proteins with critical roles in neuronal survival, axonal and dendritic network maintenance, and synaptic plasticity (Gómez et al. 2013; Huang et al. 2001; Majdan et al. 2001). Because of their important functions, NTs and their receptors are pharmaceutical targets for neurodegenerative diseases (Meldolesi et al. 2017). In humans there are four NTs; nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), which bind to four NT receptors; tropomyosin receptor kinases A, B, C (TrkA, TrkB, TrkC), which are receptor tyrosine kinases, and p75 neurotrophin receptor ($p75^{NTR}$), which is a tumor necrosis factor receptor (Chao et al. 2003). The NT receptors are transmembrane receptors that exert their activity intracellularly upon NT binding. Understanding the mechanism of receptor activation can aid the development of successful pharmaceuticals. Biomolecular simulations have been proven in the past to provide valuable insights into the structural and dynamical aspects of several transmembrane receptors by calculating the evolution of biomolecular systems with time (Arkhipov et al. 2017; Lelimousin et al. 2016; Prakaash et al. 2021). Since the compounds designed in the EuroNeurotrophin consortium act on NT receptors, simulations are employed to assist drug design. This article provides a short review of molecular simulations performed on NT receptors from the extracellular to the intracellular domains (Figure 2), as well as work done by the consortium members at Heidelberg Institute for Theoretical Studies (HITS).

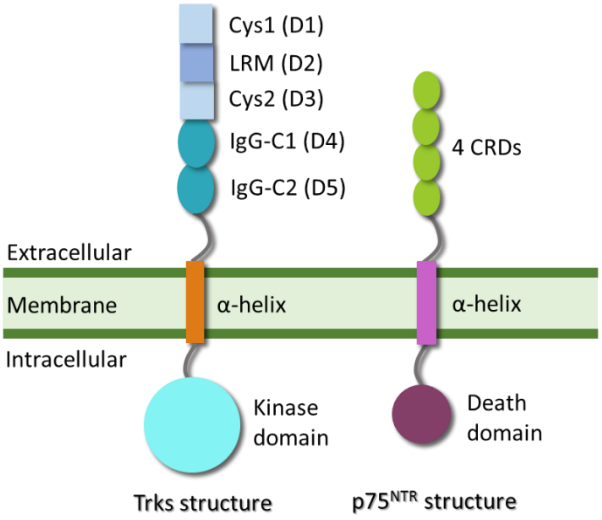

***Figure** 2: Structures of Trk and $p75^{NTR}$ receptors. The extracellular part of each Trk has 5 domains; two cysteine-rich domains (Cys1:D1, Cys2:D3), one leucine-rich motif (LRM:D2) and two immunoglobulin-like domains (Ig-C1:D4, Ig-C2:D5), while $p75^{NTR}$ has four cysteine-rich domains (CRDs) in the extracellular segment. Both types of receptors have a helical transmembrane domain and, intracellularly, a kinase or a death domain in the Trk and $p75^{NTR}$, respectively. The structures of all the domains have been solved by X-ray crystallography or NMR except for the linkers between the transmembrane domain and the other domains.*

The extracellular domain (Figure 1) of the NT receptors has been shown to be the binding site of NTs, (Gong et al. 2008; Wehram et al. 2007) as well as small-molecule receptor agonists such amitriptyline and BNN27 (Shoemark et al. 2015; Pediaditakis et al. 2016; Pediaditakis et al. *Neuropharmacology*, 2016). Saturation transfer difference nuclear magnetic resonance (STD-NMR) experiments have indicated the interface between NGF and the extracellular regions of TrkA as the binding region of BNN27 TrkA agonist, while docking and molecular dynamics (MD) simulations showed that the compound can be stabilized at the interface of the two proteins (Pediaditakis et al, *Neuropharmacology*, 2016). Additionally, MD simulations have shown that BNN27 binds favorably at the interface of $p75^{NTR}$ and NGF (Pediaditakis et al, *Front. Pharmacol.* 2016). Accordingly, BNN27 analogues developed in the EuroNeurotrophin consortium are examined for their ability to bind stably to the interface of NT and receptors, using docking and MD simulations.

The complex of the extracellular domain of TrkA dimer bound to NGF has been investigated through MD simulations for its stability and possible conformations. Previous MD simulations have indicated that the complex forms water-mediated hydrogen-bond interactions at its interface, (Settanni et al. 2003) while another study highlighted the importance of the N-terminal peptide of NGF for the binding to TrkA (Berrera et al. 2006). Advanced simulations have also been used to compute the free energy of different conformations of the full extracellular TrkA domain in complex with NGF (Pietropaolo et al. 2018). An important feature of the extracellular domain of the Trk receptors and $p75^{NTR}$ is its glycosylation state, which is necessary for membrane localization and ligand-dependent activation (Watson et al. 1999). In this regard, simulations that examine the conformational effects of glycosylation in the extracellular segments of the receptors have been employed within the consortium (Figure 3).

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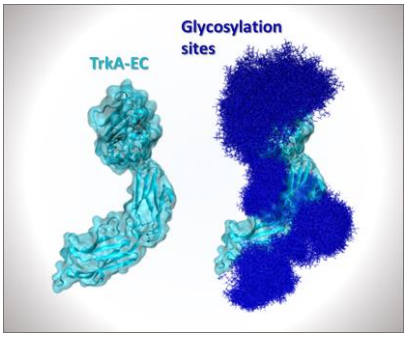

***Figure 3**: Extracellular (EC) domain of TrkA from crystral structure PDB ID: 2IFG (Wehram et al. 2007). The protein is shown with (right) and without (left) glycans at the glycosylation sites. Various glycan conformations observed in MD simulation are superimposed and shown in dark blue with the protein surface in cyan. (Athanasiou et al, unpublished data).*

NT binding to the extracellular domain leads to a conformational change to the intracellular domain that is mediated by the transmembrane domain. Understanding the dynamics of this domain is pivotal for elucidating the mechanism of receptor activation. Additionally, the transmembrane domain of TrkB has been shown to be a target of antidepressant drugs (Casarotto et al. 2021). MD simulations revealed that drug binding to the transmembrane domain of TrkB can stabilize the helical dimer in an arrangement that is independent of cholesterol concentration in the membrane (Casarotto et al. 2021). The interaction between the transmembrane domains of TrkA and $p75^{NTR}$ has also been studied recently, with simulations indicating that $p75^{NTR}$ interacts with TrkA in a way that leaves the active interface of TrkA accessible for another TrkA monomer, thus facilitating TrkA activation (Franco et al. 2021). Based on the aforementioned data, multiscale simulations are performed within the EuroNeurotrophin consortium to understand the dynamical behavior of the transmembrane homodimers of NT receptors (Figure 4), as well as their interactions with small molecules.

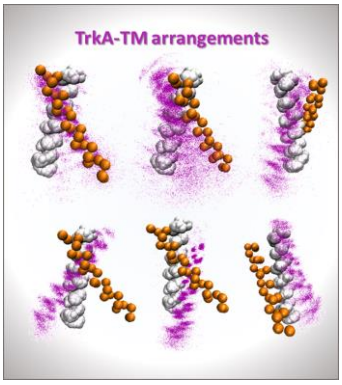

***Figure 4**: Different arrangements of the transmembrane (TM) helical TrkA homodimer obtained by coarse-grained simulations. The helical dimers have been aligned to the first helix shown in white. The second helix from the available NMR structure (Franco et al. 2020) is shown in orange and the one from different simulation snapshots in purple. (Athanasiou et al, unpublished data).*

In the intracellular region of the receptors there are the juxtamembrane linker and globular domains. The latter is a kinase for the Trks and a death domain for the $p75^{NTR}$. The juxtamembrane domains of the epidermal growth factor receptor (EGFR) and the fibroblast growth factor receptor 3 (FGFR3) play an important role in receptor activation (Tamagaki et al. 2014; Red Brewer et al. 2009). The juxtamembrane domain of TrkA has been probed with MD simulations for its interaction with the membrane (Wang et al. 2019). The simulations showed interactions of the basic protein residues with anionic membrane lipids and a three-residue insertion into the membrane (Wang et al. 2019). In order to investigate the relative orientation and interactions with lipids found in neuronal membranes, simulations of the transmembrane and intracellular domains of NT receptors (Figure 5) are being performed in the EuroNeurotrophin consortium, which have revealed specific interaction patterns, potentially important for receptor function.

Each of the aforementioned simulations provides a piece of the puzzle of understanding how these receptors function. Together with simulations of the complete receptors, they will offer valuable insight into the recognition and activation processes, which will aid the design of neuroactive compounds that will target these receptors to treat neurodegeneration.

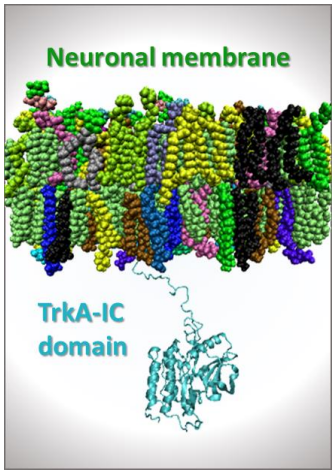

***Figure 5**: System of the transmembrane TrkA domain embedded in a neuronal membrane and the intracellular (IC) domain (cyan) in the aqueous solvent region. (Athanasiou et al, unpublished data).*

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All for one and one for all; The story about multi-target directed ligands

What are the "multi-target directed ligands" (MTDLs)? That is the question that we always get when we start the story about them. For answering it we need to go from the beginning and explain first the basic terms in the world of medicinal chemistry. Active molecules are interacting in a specific way with their targets, and the part of the molecular structure that is in charge for establishing the interaction and having the activity is called the pharmacophore. The majority of known drugs are single-target ones, meaning their pharmacophore is specific for only one target. However, from the aspect of neurodegenerative diseases, single-target molecules have not been that effective (the drug does not reach the target *in vivo*; the drug-target interaction is not sufficient in order to reduce the signs and symptoms of the disease, etc.) (Wenzel et al. 2018).

On the other side, the MTDLs have been obtained by combining (at least two) different pharmacophores into one molecule (Figure 6). These different pharmacophores are either overlapping each other, or are being separate by a linker, in one molecule. They are also known as multi-modal therapies, fragment-based pharmacology, poly-pharmacology, multi-target designed drugs, and hybrid compounds (Wenzel et al. 2018).

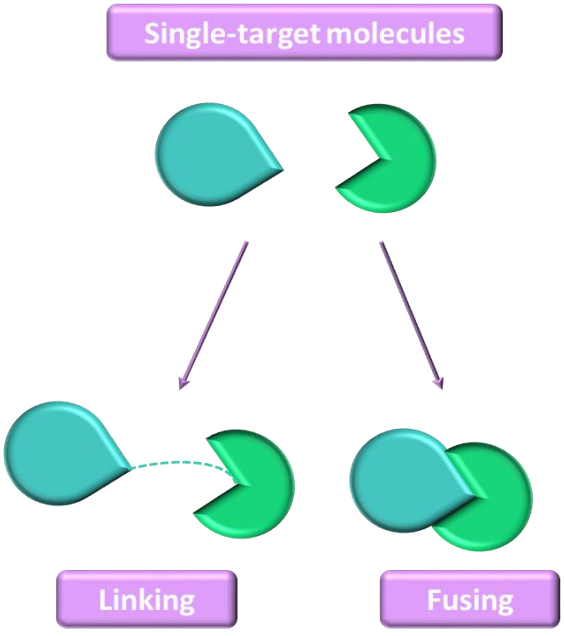

***Figure 6**: Representation of the process of designing MTDLs*

These molecules could represent a promising strategy in the combat against neurodegenerative disorders (ND), since they represent multi-factorial diseases. For example in Alzheimer's disease besides production of the toxic amyloid-β peptide, the cholinergic neurotransmision is also altered (Forner et al. 2017; Congdon et al. 2018; Weller et al. 2018). One of the MTDLs with promising results in the preclinical stage of research is the donecopride (Lecoutey et al. 2014; Rochais et al. 2020), molecule that is targeting both serotonin subtype 4 receptor (as RS67333) and acetylcholinesterase (as donepezil) (Figure 7).
MTDLs may also provide a more effective treatment, than the combinations of the single-target drugs, can have less complexed dosing and better patient compliance (Wenzel et al. 2018).

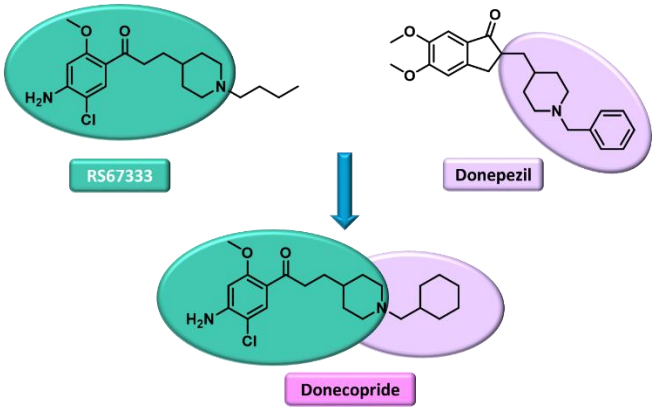

***Figure 7**: Representation of the process of designing the donecopride (Lecoutey et al. 2014; Rochais et al. 2020)*

Nevertheless, development of these types of molecules represents quite a challenge. Still when we take in consideration their benefits, and the fact that the single-target approach seems to fail when it comes to the ND, maybe now is the time for the medicinal chemist to turn their work towards the development of the MTDLs?

In the EuroNeurotrophin project one of our objectives was to develop the first multi-target ligands which target will be, beside the TrkB receptor, also a serotonin 5-HT_4 receptor. By targeting these two receptors we will be able to prevent the death of neurons and also induce the regeneration of already damaged ones, which could lead to development of the future therapies for the ND.

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EuroNeurotrophin Conference "Neurotrophic Factors and Neurodegenerative Disorders; Current Advances and Future Perspectives"

The EuroNeurotrophin Conference entitled "Neurotrophic Factors and Neurodegenerative Disorders; Current Advances and Future Perspectives" was organised in the context of the "EuroNeurotrophin" Project and took place at the Foundation for Research and Technology Hellas, in Crete, Greece from 27th-29th August 2021.

The conference was organised as part of the EuroNeurotrophin training network for the discovery of neurotrophins small molecule mimetics as potential therapeutic agents for neurodegeneration and neuroinflammation. The conference hosted by Prof. Ioannis Charalampopoulos (FORTH) and the project coordinator Dr. Theodora Calogeropoulou (NHRF), has been organised in the fourth year of the project as a major activity to bring together different stakeholders and ensure sharing key results and knowledge from the project results. The conference was organised in a hybrid format due to the COVID-19 restrictions. The EuroNeurotrophin consortium members participated in person while, the speakers and participants remotely. The event attracted 240 participants worldwide.

The 3-day conference covered 7 session topics with presentations from high-level renown speakers of the field of neurotrophins and neurodegenerative diseases from Europe, USA, Canada and China (10 keynote speakers, 1 invited lecture) (Figure 8) and from our 14 Early Stage Researchers.

Keynote Speakers
Prof. Dame Pamela J. Shaw, *University of Sheffield & Sheffield Institute for Translational Neuroscience (SITraN), UK*
Prof. Ilpo Vattulainen, *University of Helsinki, Finland*
Prof. Didier Rognan, *Université de Strasbourg, France*
Prof. Frank Longo, *Stanford University, USA*
Prof. Eero Castren, *University of Helsinki, Finland*
Prof. Carlos F. Ibáñez, *IDG/McGovern at Peking University & Chinese Institute for Brain Research, China & Karolinska Institute, Sweden*
Dr Evgenia Saltas, *Netherlands Institute for Neuroscience, Netherlands*
Prof. Clive Svendsen, *Cedars Sinai Medical Center, USA*
Prof. Uri Saragovi, *McGill University, Canada*
Dr. Ioannis Sotiropoulos, *NCSR "Demokritos", Greece*
Invited Speaker
Dr Iosif Pediaditakis *Emulate, USA*

***Figure 8**. Keynote and invited speakers at the EuroNeurotrophin conference*

Overall, the aim of the conference was to provide a multidisciplinary platform for discussing the latest high-level science in the field of neurotrophic factors and new agonists/mimetis while, at the same time to showcase the EuroNeurotrophin project results to the international community and to the neurotrophin experts. Furthermore, the 14 ESRs, benefited through the interaction with prominent scientists involved in the neurotrophic factors field paving the way for potential collaborations and for enhancing their career prospects.

We would like to thank all speakers, organisers and attendees for their active contributions.

***Figure 9**. The EuroNeurotrophin Consortium*

***Figure 10**. The EuroNeurotrophin ESRs*

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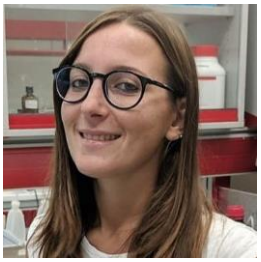
About the Authors

The EuroNeurotrophin November 2021 Newsletter was written by three of the Early Stage Researchers (ESRs) working on individual projects as part of the EuroNeurotrophin project.



ESR 2: Alessia Latorrata

Alessia joined the EuroNeurotrophin network as ESR2 at the National Hellenic Research Foundation, Athens, Greece. Her work involves the synthesis of chiral 17-spiro DHEA derivatives, which will be further elaborated to introduce pharmacophore groups, using asymmetric organocatalysis, biomimetic approaches and other synthetic methodologies. Her project also focuses to analyse SNAP PK data on lead compounds and to label steroidal neurotrophin mimetics with fluorophores or NIR-dyes.

ESR4: Christina Athanasiou

Christina joined the EuroNeurotrophin network as a PhD student at the Heidelberg Institute for Theoretical Studies (HITS). She investigates the mechanism of action of neurotrophin small molecule mimetics and potentiators, through the use of molecular simulations and mathematical modelling techniques. She also studies the interactions between neurotrophin mimetics and their receptors, as well as conformational changes and allosteric effects caused by the small molecules.

ESR 6: Mirjana Antonijević

Mirjana is hosted at the Université de Caen Normandie, France and the aim of her research is the *in silico* screening of UNICAEN chemical library in order to identify hit molecules as ligands for neurotrophin receptors. Additionally, these studies have been expanded by the physicochemical optimization of the selected hit compounds. The final lead compounds will be fluorescently labeled for *in vivo* bioimaging studies.

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