

Description of Funded Research Projects

1st Call for H.F.R.I. Research Projects
to support Post-Doctoral Researchers

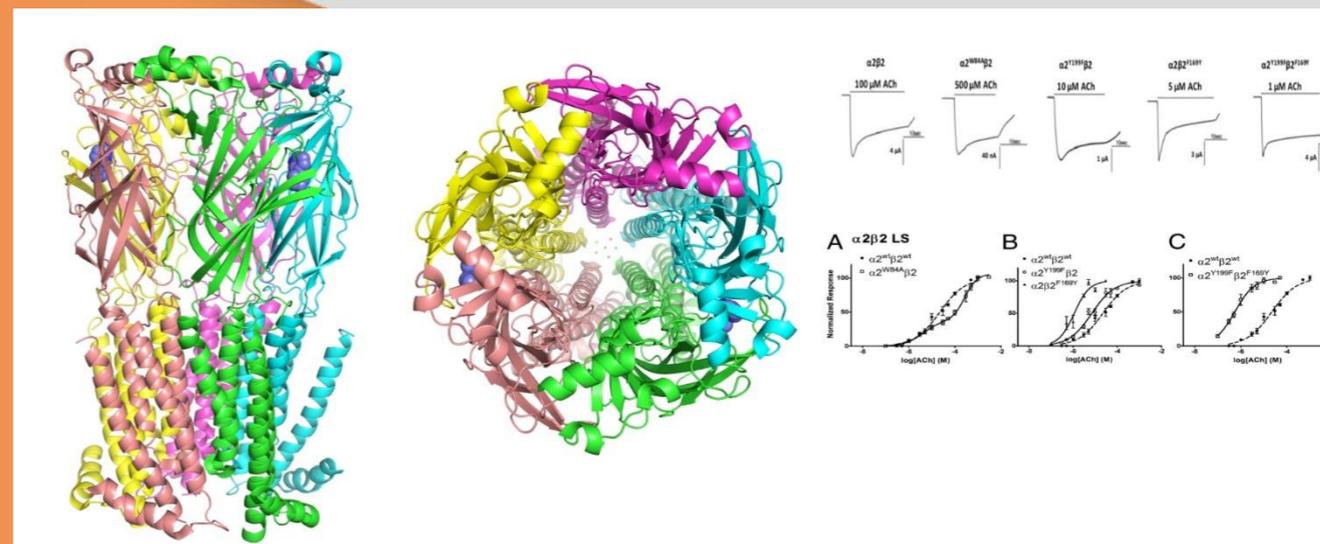


H.F.R.I.
Hellenic Foundation for
Research & Innovation

Research Project Title:

**Structural and Functional
Studies of Nicotinic
Acetylcholine Receptors**

Principal Investigator:
Petros Giastas



Popular Title:
Studies of membrane receptors

Scientific Field:
**Life Sciences, Structural Biology and
Biochemistry**
Host Institution:
Hellenic Pasteur Institute



H.F.R.I.
Hellenic Foundation for
Research & Innovation

Nicotinic acetylcholine receptors (nAChRs) belong to the family of pentameric ligand gated ion channels (LGIC) and are key molecules in mediating fast neurotransmission and in regulating neurotransmitter release. nAChRs are protein molecules embedded to the cell membrane, which upon acetylcholine binding at their extracellular domain, transmit allosterically the signal across the plasma membrane. It is then when nAChRs undergo complex conformational changes that lead to transient opening of the ion channel, depolarizing the cell membrane and initiating a cascade of events. Apart from nAChRs, the pentameric LGIC family comprises receptors activated by glycine, GABA and serotonin. Due to their involvement in a series of neurodegenerative diseases and disorders, LGICs are the main targets of a series of psychotropic drugs with therapeutic or alleviating properties (including nicotine, varenicline, benzodiazepines, alcohol, antiemetics, general anaesthetics etc).

The recent advancements in methodologies pertinent in structural studies, involving higher eukaryotic expression systems, stoichiometry manipulation of the pentameric assemblies, protein crystallization and data collection, and the further development of the electron cryo-microscopy technique, have led to an increasing number of the available structures of LGICs over the last three years. However, given the large variety of LGIC subtypes, expressed in various areas of the central or peripheral nervous system, our structural knowledge is acutely poor and requires further additions in order to reveal the specific mechanistic features of the various subtypes at the atomic level, their distinct pharmacology and ultimately to allow for the design of selective and potent drugs. The aim of StruNic is to elucidate the structures of domains or near-intact pentameric LGICs, to study at the molecular level their gating mechanisms and their distinct pharmacology and to correlate genetic abnormalities with structural and functional features.

The neurological diseases associated with dysfunction of neuronal nAChRs are numerous, affecting several millions of people worldwide, whereas nAChR-mediated addiction to nicotine and alcohol affects billions. To date, mainly due to the lack of high-resolution structures, only one drug towards nAChRs has been approved for clinical use, the $\alpha 4\beta 2$ nAChR partial agonist varenicline for smoking cessation, which while significantly effective has some psychiatric side-effects. The elucidation of the high-resolution structures of the neuronal nAChRs will, among others, reveal the 3D structure of their orthosteric and allosteric ligand-binding sites (known and novel to be identified in this project).

These findings are expected to pave the way for the design of more effective and highly selective drugs, targeting distinct nAChR subtypes related to specific diseases. Moreover, the studies of StruNic will contribute to the development of novel diagnostic tools through the association of genetic polymorphisms found in specific receptors with functional phenotypes.



During the last years, the severe economic crisis in Greece has led to large cuttings in research funds and education. Moreover, due to the prolonged pause in faculty position openings in Greek academic institutions and universities many researchers either quit research or migrated to other countries, leading to the so-called “brain-drain” phenomenon. As being one of the researchers that faced that dilemma, I can emphatically stress that funding by HFRI will allow me to continue advancing my research, by implementing cutting edge techniques and by developing strong collaborations with prominent researchers.

This grant will also advance other than my experimental-scientific skills, by emphasizing on the development of my communication, organization and mentoring skills. Hopefully, this individual funding will establish my profile in the scientific community of the field and could probably allow me prepare successful interdisciplinary proposals by becoming directly involved in co-authoring funding applications.

*The Principal Investigator,
Petros Giastas*

Funding

Amount: **180,000 €**

Duration: **36 months**

Foundation: **H.F.R.I.**





H.F.R.I.
Hellenic Foundation for
Research & Innovation

CONTACT

127, Vasilissis Sofias Avenue
115 21 Athens, Greece
info@elidek.gr
www.elidek.gr



HELLENIC REPUBLIC
MINISTRY OF
DEVELOPMENT AND INVESTMENTS



GENERAL SECRETARIAT FOR
RESEARCH AND TECHNOLOGY