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

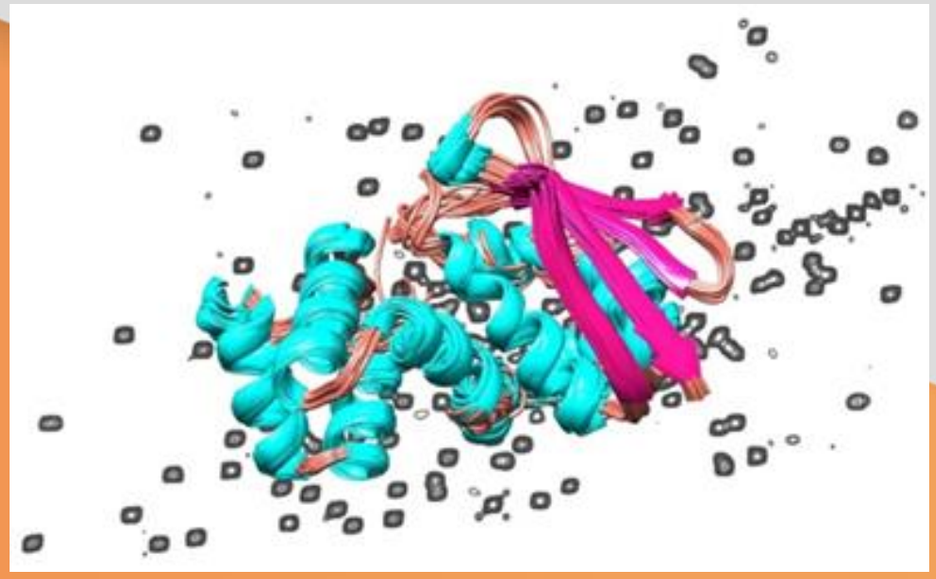
H.F.R.I.
Hellenic Foundation for
Research & Innovation

Research Project Title:

Illumination of critical structural changes of the enzyme/receptor of diatomic gases involved in cardiovascular diseases

Principal Investigator:

Aikaterini A. Zompra



Popular Title:

Illumination of critical structural changes of the enzyme/receptor of diatomic gases involved in cardiovascular diseases

Scientific Field:

Natural Sciences

Host Institution:

University of Patras

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This proposal aims at the enlightening of H-NOX domain of soluble guanylate cyclase (sGC), the NO (nitric oxide) sensor that is responsible for vasodilation and neurotransmission in mammals. The NO principal receptor (sGC) is an enzyme of enormous interest and has been an attractive target for drug discovery since sGC has been implicated in an expanding number of physiological processes and diseases. sGC is composed of two homologous subunits, α and β and the architecture of each consists of four domains. The H-NOX domain of β1 subunit has the ability to bind a single heme. The binding of NO to heme leads to the formation of Fe–NO complex and this initiates a largely uncharacterized conformational change to this domain that stimulates cyclase activity. How this structural change is translated to increased catalytic activity is poorly understood.

The main objective of this proposal is, therefore, to perform an in depth functional and structural study of the HNOX domains and to explore the structural changes of H-NOX domain towards diatomic gases (NO, CO and O2) and how they are differentiated among various organisms. The discrimination and selectivity towards diatomic gases by different H-NOX domains will be investigated. The characterization of the conformational change is of high importance since this knowledge could provide atomic-level insights of these conformational and dynamical changes occurred in the HNOX domain (N-terminal), which are strongly coupled with the signal delivered to the other domains of the enzyme. This signaling mechanism still remains elusive and largely unexplored. Therefore, the study of the NO/CO/O2 – H-NOX complexes will shed light on the way which these molecules activate sGC in order to convert GTP to cGMP. The provided knowledge is of great therapeutic interest since it will offer the essential structural characteristics for design and synthesis of new therapeutic agents

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The sGC consists of an α subunit and a β subunit and is activated by NO (diatomic gas). NO binds to heme, resulting in a conformational change in the protein and, hence, enzyme activation. This unexplored conformational change is certainly of great scientific and social impact. The exploration of this change within the project could give significant directions to the design of therapeutic agents for pathological conditions such as cardiovascular diseases, erectile dysfunction and neurodegenerative diseases, etc., related to abnormal activation of the enzyme. Given that, the percentage of people suffering from these conditions/diseases is high, this scientific approach is expected to have a significant social impact.

To me, H.F.R.I. funding would mean...

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This funding puts me in the driving seat (PI) with a modern ship (infrastructures of the Department of Pharmacy University of Patras) and a crew of specialists (scientific team). I expect both the trip (implementation of the project) and the final destination (results of the project) will reward the expectations of all involved but most of all to achieve the goals, as much as possible, for the benefit of the scientific community. This grant gives me the opportunity to enhance my research capacities and complementary skills, enabling me to establish an independent research career in Greece.

The Principal Investigator,
Aikaterini A. Zompra

Funding

Amount: **180,000 €**

Duration: **36 months**

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

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

CONTACT

185, Syggrou Ave. & Sardeon St. 2
17 121 Nea Smyrni, Greece
info@elidek.gr
www.elidek.gr

HELLENIC REPUBLIC
MINISTRY OF DEVELOPMENT AND INVESTMENTS

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GENERAL SECRETARIAT FOR RESEARCH AND TECHNOLOGY