



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

**Description of the funded research project**  
**1st Call for H.F.R.I. Research Projects to Support Faculty**  
**Members & Researchers and Procure High-Value**  
**Research Equipment**

**Title of the research project:**

**“Novel HIF-1 $\alpha$  protein interactions and their role in cancer cell adaptation to low oxygen”**

**Principal Investigator: Ilias Mylonis**

**Reader-friendly title: HIFPIN**

**Scientific Area:  
LIFE SCIENCES  
(MEDICAL & HEALTH SCIENCES)**

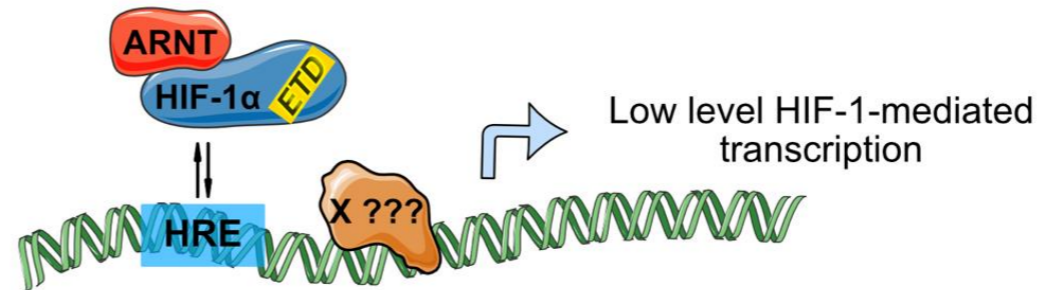
**Institution and Country:  
University of Thessaly, Greece**

**Host Institution: University of Thessaly**

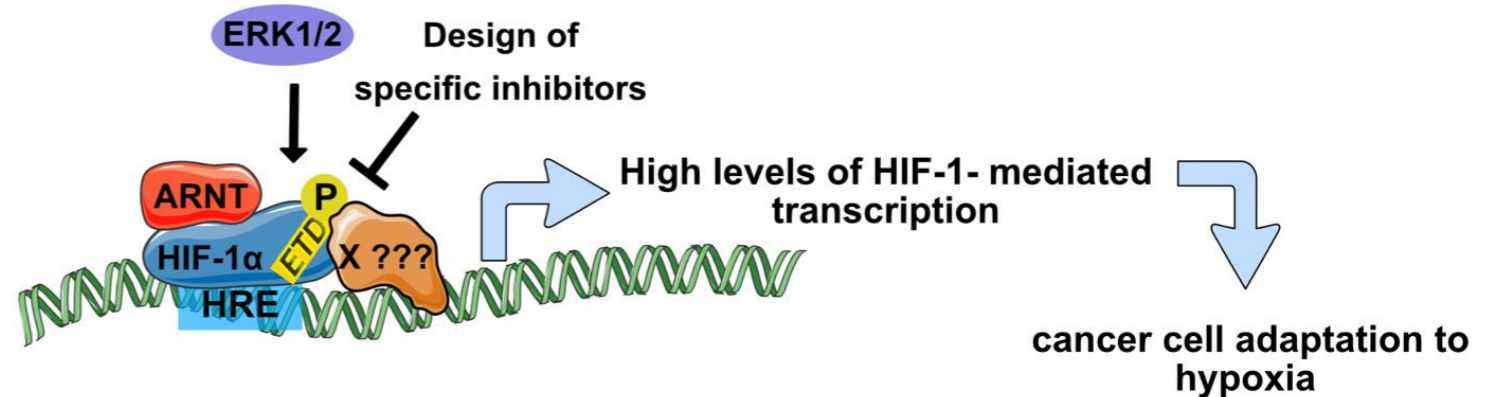
**Collaborating Institution(s): -**

**Project webpage  
(if applicable): pending**

**A**



**B**



**Principal Invest.  
Ilias Mylonis**



**Acad.Team Memb.  
George Simos**



**PhD Student  
Christina Arseni**

**Post  
Doctoral  
Researcher  
  
advertised**

**Budget: 177600 €**

**Duration: 36 months**

## Research Project Synopsis

***Oxygen deprivation (hypoxia) is a situation encountered during both physiological and pathological processes including embryogenesis, development, pulmonary dysfunction, ischemia, inflammation and cancer. A common aspect of many solid tumors is the development of hypoxic regions due to increased cell proliferation and irregular angiogenesis.***

***Cells respond to hypoxia by changing the expression pattern of genes in order to adapt and survive. Essential to this response is the hypoxia-inducible factor HIF-1 that regulates the transcription of most hypoxia-target genes, such as those involved in angiogenesis, metabolism, cell survival/apoptosis and other tissue specific functions. According to our recent research and preliminary data, HIF-1 $\alpha$  phosphorylation status influences a balance between genomic and non-genomic HIF-1 $\alpha$  functions and, thus, cell response to hypoxia. These HIF-1 $\alpha$  functions are related not only to the long-term adaptation of cells to hypoxia conferred by its function as transcriptional regulator but, importantly, to adaptive changes at the onset of hypoxia by non-genomic functions based on protein-protein interactions.***

***This project aims:***

- To explore unknown aspects of HIF-1 $\alpha$  regulation mediated by ERK-controlled HIF-1 $\alpha$  protein-protein interactions.***
- Investigate HIF-1 $\alpha$  genomic or non-genomic functions that depend on its phosphorylation by ERK1/2.***
- As HIF-1 $\alpha$  is an established target of anticancer research, to develop new tools in order to investigate cancer cell response to hypoxia and specifically target HIF-1 $\alpha$  function as means of treatment.***

## Project originality

***Investigation of HIF-1 control is essential in order to understand the molecular mechanisms that govern cellular homeostasis and maladaptive involvement of HIF-1 $\alpha$  in the pathogenesis of cancer and other serious diseases. The importance of HIF-1 $\alpha$  oxygen-dependent regulation is unquestionable and the pioneers of this research were recently awarded with the Nobel price in Physiology and Medicine. However, HIF-1 $\alpha$  oxygen-independent regulation remains relatively unexplored. The proposed research aims to fill parts of this knowledge gap by investigating for novel HIF-1 $\alpha$  interactions and for their importance to HIF-1 function and to cancer cell adaptation to hypoxia.***

***So, this research will provide novel insight in the following aspects of hypoxia biology:***

- ***Discover and investigate new HIF-1 $\alpha$  protein-protein interactions that depend on HIF-1 $\alpha$  phosphorylation by ERKs.***
- ***Provide new knowledge in previously unknown non-genomic HIF-1 $\alpha$  functions.***
- ***Provide new evidence on isoform-specific and ERK phosphorylation-regulated HIF-1 transcriptional activity.***
- ***Develop new tools that will assist to investigate and specifically target cancer cell adaptation to hypoxia.***

## Expected results & Research Project Impact

HIF-1 is heavily implicated to cancer pathogenesis and is a prominent and valid target of anticancer research. Recent research and preliminary data support that important HIF-1 $\alpha$  genomic and non-genomic functions are controlled by its phosphorylation status. These HIF-1 $\alpha$  functions are related not only to the long-term adaptation of cells to hypoxia conferred by its function as transcriptional regulator but, importantly, to adaptive changes at the onset of hypoxia by non-genomic functions based on protein-protein interactions.

Thus, it is expected to:

- develop transformed cell lines as new tools of cancer research by applying innovative and powerful techniques such as CRISPR/Cas9 gene editing.
- delineate the mechanism by which HIF-1 $\alpha$  chooses its binding sites depending on its phosphorylation by combining proteomic and transcriptomic analysis.
- provide essential data (e.g. libraries of gene and protein expression patterns) to better understand hypoxia and carcinogenesis.
- reveal novel HIF-1 $\alpha$  mechanisms of action (e.g. potential feedback loop mechanisms).
- develop new strategies such as agents that target specific HIF-1 $\alpha$  functions that will pave the way for effective management of hypoxia-related diseases.

## The importance of this funding

- *One young postdoctoral researcher and one young PhD candidate will have the opportunity to be trained and to perform modern and innovative research in a Greek institution and, thus, give them the prospect of a carrier in science.*
- *The Principal Investigator will be able to boost the potential of his research as two new members will join his team and have a funding source for consumables and equipment.*
- *It is very important that the grant covers, apart from consumables, costs for small equipment that will greatly improve everyday research in the laboratory.*
- *Finally, this grant will allow to broaden our research activities and potentially increase the opportunities for scientific collaborations with scientists in Greek or International Institutions.*



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