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: LncRNAs: A new class of biomarkers for therapeutic targeting of Cancer Stem Cells

Principal Investigator: Stavroula Baritaki, Msc, PhD

Reader-friendly title: CSCLncRNAs

Scientific Area: Life Sciences (Medical and Health Sciences)

Institution and Country: University of Crete, Greece

Host Institution: University of Crete Medical School

Collaborating Institution(s): Center for Systems Biomedicine, University of California, Los Angeles (UCLA), USA

Budget: 180,000 euro

Duration: 29 months

Research Project Synopsis

According to the cancer stem cell (CSC) concept which was proposed four decades ago, the tumor growth is fueled by small numbers of dedicated stem cells. Over the years, it has gradually become clear that most tumors harbor CSCs that have exclusively the capacities of plasticity, quiescence, unlimited self-renewal and tumor initiation *in vivo*. The existence of CSCs within the bulk of the tumor not only sustains tumor growth but it is also considered to be responsible for promoting metastasis and. tumor resistance to conventional chemotherapeutics. As such, CSCs are highlighted by the experts as the ideal therapeutic targets in most solid tumors, once we understand the molecular mechanisms that regulate their key biological properties. However, their identification, molecular characterization and therapeutic targeting is not quite easy due to the lack of specific and reliable CSC biomarkers. Therefore, advances in the field of CSC biomarker development are emerging.

Pancreatic adenocarcinoma (PDAC) is among the deadliest malignancies with a dismal 5% 5-year survival rate after diagnosis, while it is projected to become the second leading cause of cancer-related deaths by 2030. The existence of CSCs within the tumor is considered one of the major factors of PDAC aggressiveness and unresponsiveness to conventional treatments. Therefore, adjunctive treatment with CSC-suppressing agents could be a useful strategy to prevent recurrence and metastasis.

The short-term goal of the proposed project is the emergence of innovative molecular markers (biomarkers) of the family of long non-coding RNAs (lncRNAs) with a catalytic role not only in the viability of pancreatic CSCs (PCSCs) but also in their functional properties, including their chemoresistance. The ultimate and long-term goal of our research proposal is that these newly identified genetic signatures in PCSCs, to be therapeutically targeted by conventional or new drug formulations, which will potentially lead to PCSC eradication within the tumor and therefore improving tumor response to therapy and overall patient survival.

Project originality

Our proposal follows a Systems Biomedicine approach that makes it innovative conceptually and experimentally. Conceptually, it is based on the importance of PCSCs on tumor initiation, progression and response to chemotherapy, thus suggesting PCSCs as a new and promising therapeutic target. Although the molecular characterization of CSCs is considered to be emerging both for understanding CSC biology and identifying CSC-specific therapeutic molecular targets, the reported molecular analyses of CSCs have not exhausted the range of the total human genome transcripts. On this context, our proposal is pioneering in the type and range of molecular analysis of a newly identified PCSC subpopulation, by describing expression alterations of the lncRNAs genetic pool. Given the growing evidence about the important functions that lncRNAs exert in deregulating gene expression in cancer, it becomes clear that any lncRNA involvement in the molecular signaling of PCSC properties, deserves enormous research and therapeutic interest. In summary, our proposal is conceptually innovative as it relates to the phenotypic, molecular and functional analysis of the study subpopulation, and aims to 1) identify lncRNA biomarkers with a catalytic role in the properties of PCSCs, including chemoresistance, and 2) eliminate PCSCs by selective therapeutic targeting of identified biomarkers.

Our proposal also innovates experimentally. To strengthen the power of our findings, our experimental protocol includes a combination of technologically advanced *in vitro* and in *vivo* approaches, such as use of triple transgenic and immunocompromised mouse models. In addition, with the help our collaborative institutions abroad we can test our hypotheses in a variety of high throughput technology platforms, including ‘’omics” platforms, cell modeling platforms for real-time monitoring of cellular events, as well as advanced robotic platforms for massive screening of biologically active substances with certified pharmaceutical activity. The last increases the originality and novelty of our proposal, as it allows the fast identification of available pharmaceuticals that can selectively target our study CSC population. Overall, we strongly believe our study will reveal important functions of lncRNAs on CSC pathobiphysiology and provide a framework and resource for further large-scale studies on lncRNA therapeutic targeting in the future.

Expected results & Research Project Impact

Despite the current aggressive anti-tumor treatment remedies, PDAC represents one of the deadliest malignancies with uniform mortality in both genders. Nevertheless, it is one of the least studied type of cancers. The important role of PCSCs has been reported not only in tumor initiation and progression but also in its resistance to chemotherapy and radiotherapy. Given the heterogeneity found in most human malignancies, including PDAC, the likelihood of more than one type of RBC is high. This possibility complicates the efforts of selective therapeutic targeting of CSCs, while making the need for better and in-depth phenotypic and molecular characterization of CSC subpopulations within a tumor more emerging. Therefore, PCSCs are a modern field of research not only for the prevention and treatment of PDAC but also for eliminating the enormous cost of the unsuccessful pharmaceutical treatment currently provided to the PDAC patients.

The present study focuses on the molecular profiling of a newly-identified PDAC subpopulation that carries CSC functional characteristics, giving particular emphasis to the expression of lncRNAs. In the past few years, lncRNAs have been considered key factors in decoding the deregulated molecular signaling in various diseases, including cancer. The proposed study is the first to link the expression of lncRNAs with the PCSC properties, emphasizing on their resistance to chemotherapy. Given the increasing incidence of PDAC in the recent years and its high mortality worldwide, the identification of new regulatory pathways and biomarkers, such as lncRNAs, which may be involved in PCSC physiology, is of paramount importance at a theoretical and experimental scientific level. Finally, uncovering the mechanisms of PCSC suppression via enhancing death signals following interventional drug targeting of new biomarkers, opens up new horizons in the development of applied therapeutic strategies to manage CSCs and increase the effectiveness of conventional chemotherapy.

The importance of this funding

The return of an established scientist to Greece, after spending more than a decade in renowned Academic Institutions abroad, is definitely a difficult decision on a professional and personal level. For the scientists who have dared to take the big step, every serious national effort to support our research work in our new ‘national’ start is certainly a strong justification of our decision to return and contribute to the research and academic future of our homeland. I particularly welcome the establishment of the Hellenic Foundation for Research and Innovation (H.F.R.I) and its contribution to the research support of young and more established scientists, at a time when 'research' survival is more difficult than ever worldwide. As funding recipients, we promise that we will make the most of our potential to highlight the ability of the Greek Academic Institutions to do original and competitive research at an international level.

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

COMMUNICATION

185 Syggrou Ave. & 2 Sardeon St. 2
171 21, N. Smyrni, Greece
+30 210 64 12 410, 420
communication@elidek.gr
www.elidek.gr