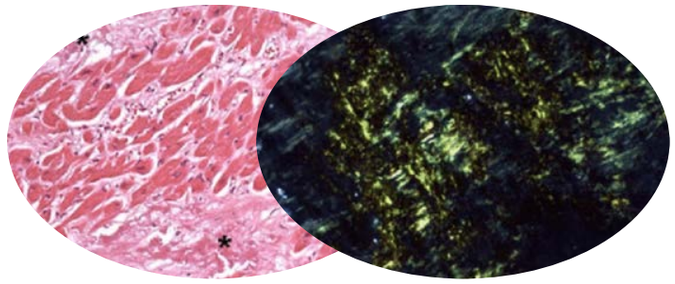
H.F.R.I.
Hellenic Foundation for Research & Innovation

Description of the funded research project

2nd Call for H.F.R.I. Research Projects to Support Post-Doctoral Researchers

ITHACa



Title of the research project: *Immunoglobulin Light Chains and amyloid fibrils induced cardiotoxicity. Amenability of the cardiac proteasome activity.*

Principal Investigator: *Panagiotis Efentakis*

Reader-friendly title: *Proteasome as a novel target for MGUS, multiple myeloma and amyloidosis related cardiomyopathies*

Scientific Area: *Basic Research in Cardiology – Cardio-oncology*

Institution and Country: *National and Kapodistrian University of Athens , Greece*

Host Institution: *National and Kapodistrian University of Athens*

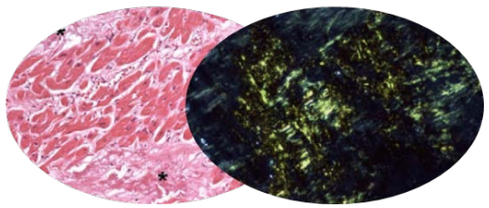
Collaborating Institution(s): -

Project webpage (if applicable):

Budget: *180.000€*

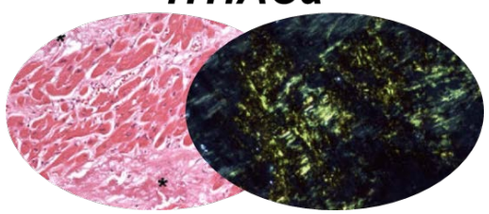
Duration: *36 months*

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



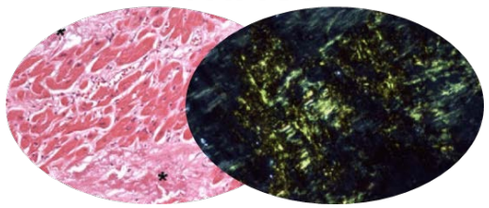
Research Project Synopsis

The correlation of blood dyscrasias, such as multiple myeloma (MM) and the manifestation of cardiac events is well described and evident in the clinical praxis. Cardiac AL-amyloidosis, stands as the most life-threatening outcome of blood malignancies and still remains a rare but non-treatable cardiovascular morbidity, rendering a poor prognosis in the affected individuals. Aside cardiac AL-amyloidosis, gammopathies are also emerging risk factors for cardiac-related diseases, leading to progressive damage on the myocardium. Pre-clinical studies have presented that circulating immunoglobulin light chains (LCs) can disrupt cardiomyocytes' homeostasis, through mitochondrial and autophagosomal dysregulation, whilst the effect of amyloids on the cardiomyocytes remains poorly investigated. Since both LC- and amyloid- cardiotoxicity stand as proteotoxic moieties, the scope of the current proposal is i. to investigate the mechanism of LC-induced and ii. the mechanism of amyloid-induced toxicity on isolated cardiomyocytes, in terms of molecular signaling and extra- or intracellular localization. Both in vitro approaches will emphasize on the ubiquitin-proteasome system, as it is still merely studied in the mediated cardiotoxicity. The contribution of the reversible and irreversible proteasome inhibition on the LC- and amyloid-treated cardiomyocytes phenotype, will be studied using clinically applicable proteasome inhibitors (PIs). Finally we will seek to iii. establish a novel model of gammopathies as the first in vivo model that can recapitulate the clinically observed onset and progression of gammopathies and iv. based on the in vitro results, we will confirm the aforementioned mechanisms of cardiotoxicity and furtherly study the effect of reversible and irreversible proteasome inhibition on the cardiac phenotype of the transgenic mice.



Project originality

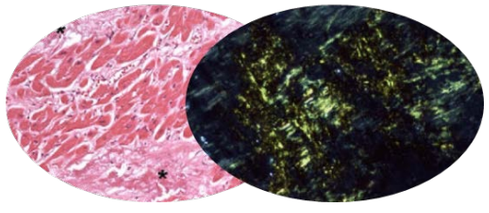
Current research concerning the effects of gammopathies and MM as well as AL-amyloidosis on the myocardium is still on the beginning, with the aforementioned pathogenicities gaining increasing scientific interest (~500% increase of published peer reviewed articles on cardiac AL-amyloidosis over the last 10 years, Pubmed data). On the other hand, publications on LCs and amyloid fibril derived cardiotoxicity are scarce. It is striking that, to the best of our knowledge, there are currently no publications on the involvement of proteasome in LCs or amyloid fibril cardiotoxicity. Therefore, the current proposal provides a state-of-art and innovative insight in the cardiomyocytes response to the circulating immunoglobulin light chains and amyloid aggregates. Moreover, basic research is lacking of satisfactory in vivo models to mimick the pathogenic moieties found in the clinical praxis. The current proposal s targeted to establish the transgenic model of LysM-Cre IL-$6^{OE/+}$, a murine model of IL-6 overexpression in the myelomonocytic cells, as a novel reliable mouse model of polyclonal gammopathy. In conclusion, the present study aims to investigate the mechanism of toxicity of LCs and amyloids in the heart, with emphasis on proteasome activity, seeking to discover new targets for the treatment of patients with MGUS-induced cardiovascular events or AL-amyloidosis.



Expected results & Research Project Impact

The scopes of the current proposal are: to investigate the mechanism of

- LC-induced toxicity and Amyloid-induced toxicity on isolated cardiomyocytes, in terms of molecular signaling and protein trafficking and extra-or intracellular localization. Both in vitro approaches will emphasize on the ubiquitin-proteasome system, as it is still merely studied in the mediated cardiotoxicity. Additionally, the contribution of the reversible and irreversible proteasome inhibition on the LC-and amyloid-treated cardiomyocytes phenotype, will be studied using clinically applicable proteasome inhibitors (PIs).
- Establish a novel model of gammopathies, that of LysM-Cre IL-6OE/+transgenic mice, as the first in vivo model that can recapitulate the clinically observed onset and progression of gammopathies and
- Based on the in vitro results, we will confirm the aforementioned mechanisms of cardiotoxicity and furtherly study the effect of reversible and irreversible proteasome inhibition on the cardiac phenotype of the transgenic mice.



The importance of this funding

This proposal will elucidate in depth the contribution of proteasome in the LCs-and amyloid fibrils-mediated cardiotoxicity in vivo and vitro and set it as a key mediator of all the up-to-now known induced signaling cascades. Subsequently, proteasome activity can be used in clinical praxis as a diagnostic marker for the susceptibility of patients ailing from MGUS, MM and/or AL-cardiac amyloidosis to cardiac injury and can be a reliable marker before the initiation of PIs treatment. This proposal will also provide the basis for discovering new targets that can be exploited for the discovery of new drugs for the treatment of AL-amyloidosis.

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