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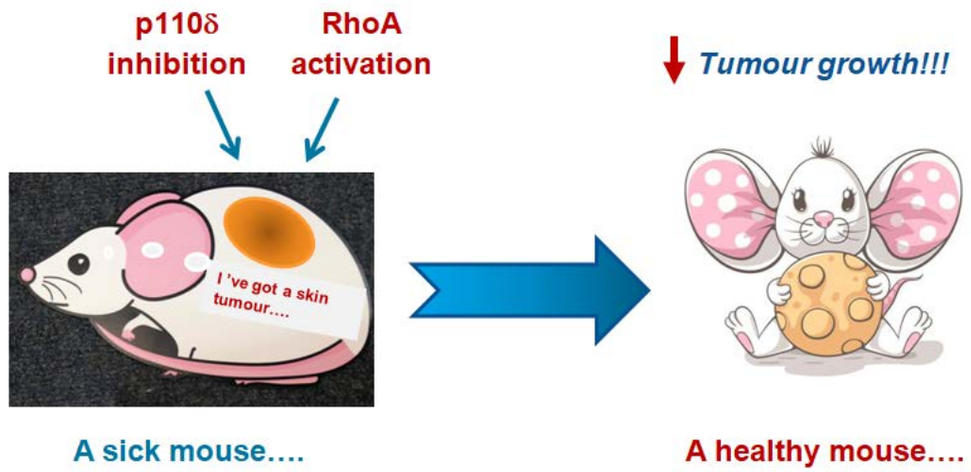
Description of the funded research project

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:

Investigating a combined opposite targeting of RhoA and p110δ PI3K as a novel approach to treat skin cancer



Principal Investigator: Evangelia Papakostanti

Reader-friendly title: CROPMEN

Scientific Area: Life Sciences (Medical & Health Science)

Institution and Country: University of Crete, Greece

Host Institution: University of Crete

Budget: 180,000 €

Duration: 24 months

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Research Project Synopsis

Besides cancer cells that accounts for skin cancer development to advanced stages, tumor-associated macrophages (TAMs) are the major immune-constituent of cancer stroma in skin cancers, drive tumor progression and correlate with poor prognosis by promoting cancer cells proliferation, angiogenesis, immunosuppression, invasiveness and metastasis. Therefore, a wealth of evidence suggests that combination approaches targeted against cancer cells and TAMs may improve cancer therapy and that targeting of TAMs can be clinically beneficial however, remain a challenge.
We recently documented that pharmacological inhibition of the p110δ PI3K almost completely blocked the formation of breast tumors and metastasis and discovered that the targeted inactivation of p110δ in macrophages significantly reduces the positioning of macrophages to tumour sites and that was sufficient to confer tumor growth regression and to prevent metastasis. We have also previously found that the PTEN tumor suppressor protein is regulated by the GTPase RhoA at least in those cancer cells that PTEN remains wild type.
In the current proposal we step forward to determine the impact of the combined targeted increase of RhoA activity (which will results in increased PTEN activity) into tumors with the inactivation of p110δ in macrophages on melanoma and non-melanoma skin cancers in mice models using integrated and multidisciplinary approaches.

The overall scientific aims of the present project are:

1. to investigate and validate a functional role of RhoA and p110δ in mechanisms underlie melanoma and non-melanoma cancer progression in mice models
2. to emerge the increased activity of RhoA as a novel approach that might offer therapeutic potential in carcinomas that express low p110δ
3. to increase the understanding of the fundamental mechanisms underlie skin cancer and metastasis

The expected results of the current proposal are anticipated to pave the way for the use of novel and effective therapeutic approaches in skin cancer treatment.

Project originality

Skin cancer is a complex disease and the understanding of deregulated signalling pathways in melanoma and non-melanoma skin tumors growth is crucial. The role also of macrophages in skin cancer progression is known however the mechanism that regulates their recruitment to tumour sites remains largely unclear. **To date, there has been no investigation studying the role of a combined targeting, which will bridge the two major therapeutic targets named cancer cells and macrophages, in skin cancer development and metastasis.**

In the current proposal we will investigate whether a novel therapeutic approach, the targeted activation of RhoA into tumors and the concurrent inactivation of p110δ PI3K in macrophages prevents skin cancer development and metastasis. **The existence of this mechanism *in vivo* is anticipated to revolutionize the current knowledge in the complex field of skin cancer and metastasis, to open new avenues for therapeutic intervention and to lead the way for development of promising drugs targeting specific molecules and cells functions which will prolong the life of patients with cancer.**

Expected results & Research Project Impact

Melanoma, a malignant neoplasm of melanocytes, is recognized as one of the most aggressive cancers with relatively high propensity for metastasis. The incidence of melanoma continues to increase despite public health initiatives that have promoted sun protection. Unfortunately, strategies devoted solely to protecting against UV radiation have, at best, had only a modest effect on the development of melanoma and standard systemic therapies for melanoma remain unsatisfactory. The increasing incidence of melanoma and its poor prognosis in advanced stages mandate the development of novel approaches for its prevention.

The current project is likely to provide important information for better understanding of the mechanisms underlie skin cancer and metastasis and drug development. Facilitating drug development in these areas by working at the interface of fundamental and applied research is anticipated to contribute significantly to an improvement of the quality of life. This project proposal is thus underpinning science of strategic and industrial relevance. This work aims to exploit breakthroughs in skin cancer research field for the benefit of public health and to increase the competitiveness of Biotech Industry. It also aims to bring basic knowledge through the application stage to enable real progress in medicine.

The importance of this funding

My ELIDEK funded research grant has given me the opportunity to enhance my research. I have been able to hire research assistants, undertake crucial research with a substantial support, participate in conferences, which will give the opportunity to my team members to get to know other researchers in the field of PI3-kinase signalling and cancer, and moreover to be significantly productive. All of these, combined with the fact that the current project is really exciting should provide me with the chance to publish in first class international journals paving the way for a more successful career of myself and moreover of my team members.

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