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

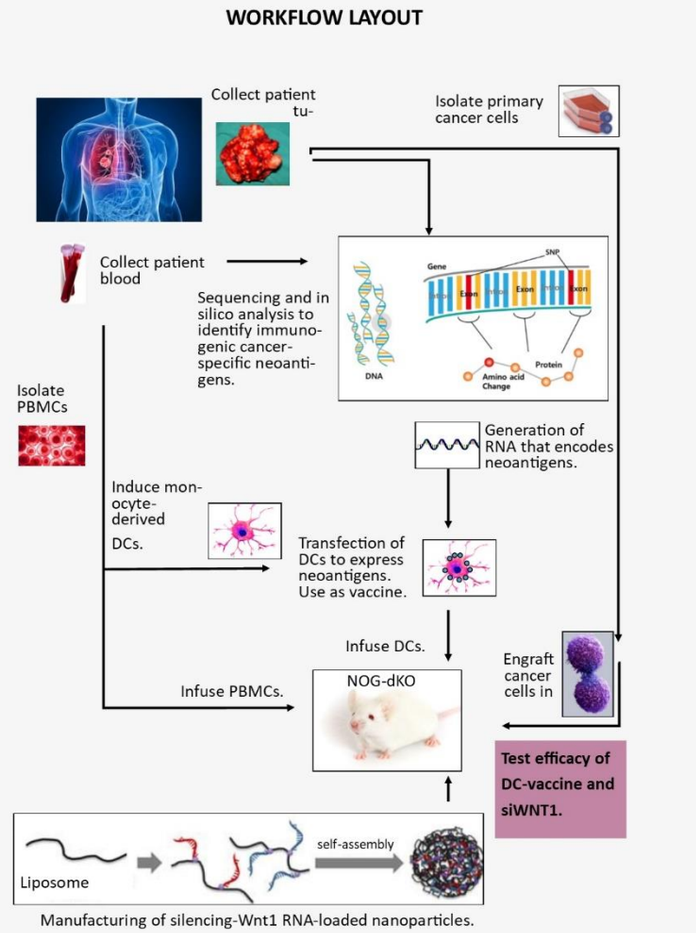
H.F.R.I.
Hellenic Foundation for
Research & Innovation

Research Project Title:

Targeting human Wnt1 via siRNA nanoparticles to boost dendritic cell vaccination against lung cancer neoantigens

Principal Investigator:

Maria Tsoumakidou



Manufacturing of silencing-Wnt1 RNA-loaded nanoparticles.

Popular Title:

Targeting human Wnt1 with nanoparticles to boost dendritic cell vaccination against lung cancer

Scientific Field:

Life Sciences

Host Institution:

B.S.R.C. "Alexander Fleming"

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Lung cancer is the world's leading cause of cancer death. Lung cancers have a particularly high number of somatic mutations. Peptides containing these mutations could be immunogenic (neoantigens). A crucial need has arisen to create vaccines that effectively mobilize neoantigen-specific immunity. Dendritic cells (DCs) are the natural agents for antigen delivery upon vaccination trials. Vaccination-based therapies show limited success, largely because tumors employ strategies to suppress DCs. This indicates that most cancer patients are unlikely to respond to vaccination monotherapy approaches and suggests that combination strategies with agents that specifically target the immunosuppressive tumor microenvironment should be adopted. We recently set up in vivo models of transplantable lung tumors, coupled with analysis of primary human tumors, which show that Wnt-1 expressed by lung cancer cells acts paracrine on intratumoral DCs to promote T cell tolerance against cancer-associated antigens. The hypothesis of NEOVAC is that integrating Wnt1-targeting to DC-based vaccination against patient-specific neoantigens can induce effective antitumor immunity and consecutively increase survival in lung cancer.

We will first apply deep-sequencing technologies to analyze tumor-normal pairs and identify the mutations present within the protein-encoding part of the genome of an individual tumor. Then, we will use RNA-sequencing to select for the highly expressed variants and proceed to additional filtering via software algorithms that predict the MHC/HLA binding affinity of the mutated peptides. To generate neoantigen-expressing DCs for vaccination trial, for each amino acid substring with high predicted MHC affinity a "minigene" construct will be made and multiple minigenes will be genetically fused to tandem minigene constructs. These will be in vitro transcribed to RNA and introduced to autologous monocyte-derived DCs. For the pre-clinical testing of the therapeutic efficacy of combining Wnt1 blocking with DC-based vaccination against neoantigens, humanized mouse xenograft models will be used. Tumor growth and immunological responses will be analyzed.

NEOVAC aims to develop a new combinatorial strategy to target the individual mutanome of lung cancer patients, based on the administration of Wnt1-silencing nanoparticles coupled to genetically engineered neoantigen-expressing DCs. It is further designed to provide proof of principle that human Wnt1 is a major novel immunotherapeutic target in NSCLC and acts in synergy with DC-based vaccination to unleash DCs from tumor-induced suppression. Since Wnt1 is overexpressed by various tumors, such as colon, breast and ovarian, the targeted breakthrough of NEOVAC is expected to have vast therapeutic implications for other types of cancer.

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

During the development of this proposal I will gain new knowledge in neoantigen-targeted immunotherapies and dendritic cell-based vaccination and experience working with humanized mice, which will broaden my future options of developing new lines of research in my laboratory. Currently, only a few research groups are focused on neoantigen vaccination approaches in Europe and none in Greece. On the other hand, I will bring international collaborations to my lab: Dr. George Coukos (Director of Ludwig Institute For Cancer Research, Switzerland), a renowned expert in dendritic cell vaccines. By the time NEOVAC is complete, I envisage to have accomplished the following: a) At least two last author publications in high impact journals in the field; b) Increase in my current international scientific network; c) Scientific maturity and consolidation of independence through additional funding.

The Principal Investigator,
Maria Tsoumakidou

Funding

Amount: **180,000 €**

Duration: **24 months**

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

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