MARIE CURIE ACTIONS – INTERNATIONAL RE-INTEGRATION GRANTS

Project Title:
"DIRECTED EVOLUTION OF SMALL-MOLECULE CANCER THERAPEUTICS"

Project Acronym: DEVOCAT

Summary description of project context and objectives. Cancer imposes a tremendous socioeconomic burden in modern societies, causing ~1.7 million deaths in the EU annually. 15-20% of these cases occur due to mutations in the oncosuppressor gene p53, which destabilize the protein and inactivate its ability to mediate apoptosis under physiological conditions. Today, no drugs exist which can restore the function of mutant p53 and treat cancer. The present project deals with the discovery of potential cancer therapeutics of this type. The topic of the proposed research is the directed evolution of small molecules which can bind to and restore the folding and function of destabilized oncogenic variants of p53 (p53*). These compounds are being selected from libraries of small molecules which are biosynthesized in microbial cells. Biosynthesis is carried out using an approach that allows the facile preparation of a very large number of test compounds, exhibiting high levels of chemical and structural diversity. Using this strategy, close to 10^7 different compounds have already been biosynthesized. In order to screen these small-molecule libraries, we have constructed a high-throughput genetic system, which has been used to identify the compounds with the ability to bind to and improve the folding of p53*. A number of potential hits have been identified and the effect of the identified compounds on the stability of p53* is currently being evaluated in vitro by using biochemical and biophysical methods of protein analysis. Subsequently, the ability of these compounds to revitalize the pro-apoptotic activity of p53* will be tested in selected human cancer cell lines. The compounds which will be found capable of restoring the stability and apoptosis-mediating function of p53* will become drug candidates against a broad panel of cancers and the potential for a high socioeconomic impact.

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Beneficiary – Participant:
Institute of Biology, Medicinal Chemistry and Biotechnology,
National Hellenic Research Foundation, Athens, Greece

Researchers:
Co-ordinator: Dr. Soterios Kyrtopoulos, Research Director
Marie Curie Fellow: Dr. Georgios Skretas, Research Assistant Professor
Research Associate: Mrs. Dafni Delivoria, PhD Candidate