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**Presenter's name:** Konstantinos Karakostis, PhD

**Brief biography of the presenter**

Dr. Konstantinos Karakostis studied Chemistry (BSc) and Protein Biotechnology (MSc) at the University of Crete (Greece) and the Institute of Molecular Biology and Biotechnology of the Foundation for Research and Technology Hellas (IMBB-FORTH). His PhD on Molecular Biology and Biochemistry at the CNR (Italy); the CNRS (France) and the University of Stuttgart (Germany) was funded by the EU Marie Skłodowska-Curie Actions (ITN).

His Post-Doctoral research at the group of Therapeutic targets at the French National Institute of Health and Medical Research (INSERM, Paris) was on cell signaling pathways and molecular interactions regulating Development, Evolution and Oncogenesis (cancer). He has been working in tight collaboration with Prof. Dr. Robin **Fahraeus** (INSERM, Paris, FR) and Director RNDr. Bořivoj **Vojtěšek** (Masaryk Memorial Cancer Institute, Brno, CZ) who also share a long history of research activities with Dr. Vassilis **Zoumpourlis** (NHRF, Athens, GR).

He has authored several *peer-reviewed* scientific articles as first, last or corresponding author; reviewed/edited in several journals and has initiated several international collaborations with highly ranked Bioscientists. He has been also actively participating in international conferences of scientific interest in the areas of Molecular and Cellular Biology, Biochemistry, Immunology, Genetics, Proteomics, Structural Biology, Molecular Evolution and Translational Research (Personalized Healthcare, Precision Medicine). On 2018, he joint Qualia Pharma (iDNA Genomics) for the development and implementation of **pioneer molecular clinical diagnostic tools** in the areas of Pharmacogenomics and Nutrigenomics (as Scientific R&D Director); and for the dissemination and scientific training of *state-of-the-art* healthcare services. Under the supervision of Dr. Vassilis Zoumpourlis, he is currently **supervising** the preparation of research and review articles by three MSc students (NHRF and University of Athens).

He was awarded with the **Seal of Excellence of the Marie Skłodowska-Curie** Individual Fellowships (Submitted on 2020; host: NHRF) and he has recently submitted two more candidacies for research grands: an international **ERC Starting Grand 2021** (Host: NHRF) and a national **ELIDEK 2021** grand for post-doctoral researchers (Host: NHRF).

**Presentation's Abstract**

Molecular evolution of synonymous mutations and their implications to the activation of the TP53 tumour suppressor.

Gene variations are currently identified by genomic screening of cancer patients determining the personalized mutational profiles, significantly aiding the prognosis or/and the selection of targeted therapies; with an unforeseen success rate. Yet, the efficiency of genetic diagnostic tests (Dx) relies on genomic statistical studies and clinical trials, while several mechanistic aspects of underlying cellular regulatory elements and processes, especially involving synonymous mutations (SMs), remain poorly understood. The implications of key SMs in the regulation of genotoxic stress response pathways, has recently started to unravel. Pioneer findings indicate prominent roles of SMs on the activation of the p53 tumour suppressor following DNA damage. Addressing the underlying mechanisms of cancer aetiology & progression, will dramatically enhance the clinical potential of Dx testing.

TP53 is a transcription factor that involves intrinsically disordered regions (IDRs) of high mutation rates, thus acting as a carcinogenic driver mutation gene that constitutes a target for therapies [1-4]. It is employed as a superior model, having essential roles in development, ageing, cancer and cellular stress responses [5]. Under normal conditions, p53 is negatively regulated by the E3 ubiquitin ligase activity of MDM2 that targets it for degradation via the 26S ribosomal pathway [6-9]. However, during DDR, the ATM kinase phosphorylates MDM2 on S395 inducing a conformational change that promotes it binding on the *p53* mRNA, which leads to p53 stabilization and activation [10-12]. The conserved *p53* mRNA sequence that binds the C-term of MDM2 to stimulate p53 synthesis, encodes the peptidic domain that binds the N-term of MDM2 to control p53 stability. As shown in a model of high conceptual impact that unified the **co-evolutionary** significance of both *p53* RNA and protein structures in binding MDM2 [13-15], the MDM2-p53, protein-protein interaction (PPI) is not present in the pre-vertebrate *Ciona intestinalis* (Ci); while the MDM2-*p53,* protein-mRNA interaction (PRI) is conserved and regulated by the *p53* mRNA secondary structure [13, 16]. In addition, the current *state of the art*, highlights the crucial role of ***single* SMs changing the *p53* mRNA folding.** A single cancer-derived SM in codon 22 (p53(L22L), CUA to CUG) averts the MDM2-*p53* PRI and prevents the phosphorylation of the nascent p53-Ser-15 (DDR activation), by altering the secondary mRNA structure, which determines the formation of the *p53* mRNA-MDM2-RPL complex, facilitating the recruitment of ATM to the p53 polysome where it phosphorylates the nascent p53 peptide [17]. However, it remains unclear whether additional SMs altering the *p53* mRNA structure, similarly impair the p53 activation, thus forming **a whole new mechanism** and type of clinical targets. This mechanism [16, 17], has addressed a minimal set of factors required for the SM-dependant activation of the nascent p53.

In this presentation, recent findings on the role of p53 SMs in p53 activation will be discussed along with perspective molecular, genetic, structural, evolutionary and clinical aspects that were awarded with the Seal of Excellence of the Marie Skłodowska-Curie Individual Fellowships (2020) and remain to be elucidated in the frame of two recently submitted grant proposals' candidacies (ERC STG and ELIDEK).

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