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Description of the funded research project

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

Title of the research project: **DNA Damage & Metabolism in Progeria and Natural Aging**

Principal Investigator: **Evi Goulielmaki**

Reader-friendly title: **DNA Damage & Metabolism**

Scientific Area: **Life Sciences**

Institution and Country: **IMBB-FORTH, Greece**

Host Institution: **IMBB-FORTH, Greece**

Budget: **180.000**

Duration: **36 months**

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The almost exclusive link between inborn defects in DNA metabolism and an extending class of syndromes with phenotypes resembling accelerated ageing in many, but not all, organs and tissues points to genomic damage as a major culprit in the ageing process. For helix-distorting damage, cells employ the nucleotide excision repair (NER) pathway that recognizes and removes helical distortions throughout the genome or selectively from the actively transcribed strand of genes. Defects in NER lead to enhanced cancer predisposition or to a heterogeneous group of progeroid syndromes. So far, it has been challenging to unravel the molecular basis of the DNA damage driven degenerative processes with advancing age. To tackle this, we propose to use a unique series of NER progeroid animals coupled with numerous validation approaches to dissect not only the functional relevance of DNA damage to the premature onset of metabolic abnormalities in vivo but also the impact of DNA damage-driven metabolic reprogramming in age-related diseases, including cancer. Our research strategy has the potential to achieve a major breakthrough with an impact beyond the research domain of NER; it will allow us to explore the functional links between DNA repair mechanisms, the rapid onset of innate immune activation mechanisms and the wide range of metabolic complications associated with ageing. Understanding these connections will provide us with insights into how genome maintenance is connected to disease mechanisms.

DNA damage-driven metabolic abnormalities are thought to underlie a wide range of chronic diseases, including the metabolic syndrome, chronic inflammation and cancer. The mechanisms driving changes of cell metabolism due to accumulation of DNA damage in the same cell have attracted keen scientific interest. DNage goal will be to unravel the mechanism by which genomic instability in innate immune cells can drive metabolic changes in other cell populations/tissues, thus rewiring glucose metabolism of the whole organism. The impact of these metabolic alterations on chronic inflammation and related pathologies will be the subsequent question DNage will attempt to approach.

Our research strategy will allow us to explore the functional links between DNA repair mechanisms, the rapid onset of innate immune activation mechanisms and the wide range of metabolic complications associated with ageing. Understanding these connections will provide us with insights into how genome maintenance is connected to disease mechanisms and possibly suggest new therapeutic approaches beyond the research domain of NER. The impetus for DNage is based on the magnitude of the DNA damage-driven pathologies in Western societies: cancer and aging. This is clearly justified by the increasing cancer incidence problem of the elderly and the continuously expanding European aging population. Intensive research is, therefore, greatly needed across the scientific spectrum of genome maintenance and DDR mechanisms.

<<DNage>> funding by the Hellenic Foundation for Research and Technology facilitated my presence in the research field for the next years. Moreover, it will help me evolve not only scientifically, since the project requires new multidisciplinary functional approaches, but also professionally, since the proposed work will reinforce my supervision skills, by taking over the direct supervision of a PhD student. Moreover, the fellowship will provide the opportunity to expose myself to fundamental management skills. Eventually, these qualities can help enormously all the applicants to acquire the necessary competences to embark an independent career path and line of work, attract further funding and apply for academic positions in the foreseeable future.

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