

Description of Funded Research Projects

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

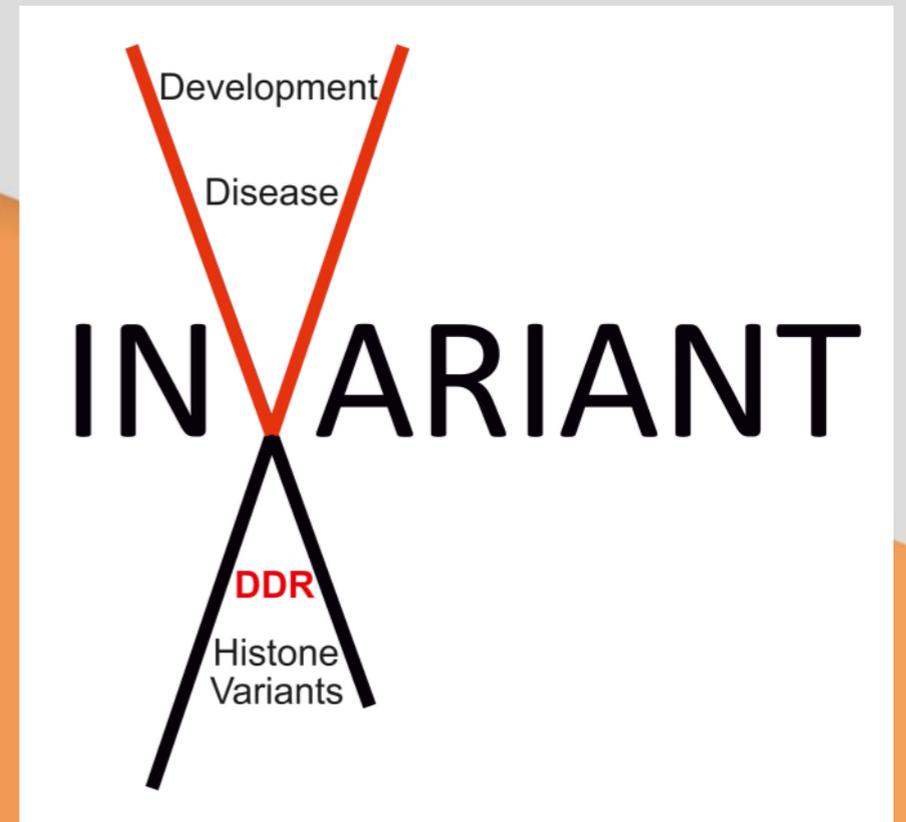


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Research Project Title:

**DNA damage & histone variants
in development & disease**

Principal Investigator:
Georgia Chatzinikolaou



Popular Title:
The impact of DNA organization and genetic damage in development and disease

Scientific Field:
Life Sciences

Host Institution:
IMBB-FORTH, Greece



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Research Project Summary

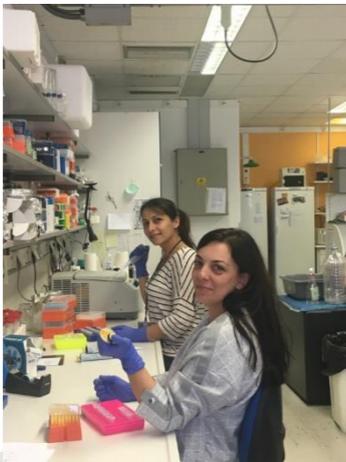
Mammalian cells rely on genome maintenance, chromatin architecture and transcription to organize, maintain and utilize their genomes. In turn, such complex biological processes depend on the timely, orchestrated action of ATP-dependent nucleosome remodeling and basal transcription factors, the myriad of histone post-translational modifications and the exchange of canonical histones for histone variants. Together, these multifaceted events are known to dynamically modulate chromatin accessibility for the fine-tuning of gene expression programs during development or with disease onset. In accordance, the cell's DNA damage signaling and repair machineries also operate on a chromatinized substrate to detect, repair and restore damaged DNA, maintaining genome stability. For bulky helix-distorting DNA lesions, such as the main ultraviolet (UV)-induced photoproducts and numerous bulky chemical adducts, the major repair mechanism is the evolutionarily conserved nucleotide excision repair (NER) pathway. Defects in NER lead, in addition to cancer and aging, to developmental abnormalities whose clinical heterogeneity and varying severity cannot be fully explained by the DNA-repair deficiencies. Recent evidence has revealed that NER factors play a fundamental role, in addition to DNA repair, in chromatin looping, the process of RNA synthesis and the three-dimensional organization of our genome during mammalian development. Although emerging evidence supports that histone variants facilitate efficient repair of DNA damage in the chromatin environment, the functional interplay between NER machinery and chromatin organizers is still incomplete.

Thus, we propose a highly multidisciplinary approach, to dissect the functional role of histone variants in the repair of intrinsic DNA damage in vivo. We anticipate that the mechanistic understanding of such responses will reveal new knowledge and novel insights into how histone variants, the fundamental chromatin building blocks in mammals, are causally involved in the execution of developmental gene expression programs and/or the premature onset of DNA damage-driven pathologies

The impetus for this project (“INVARIANT”) is based on the magnitude of the DNA damage-related pathologies (e.g. cancer and aging) in Western societies. 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 DNA damage response mechanisms.

The proposed interdisciplinary research strategy has the potential to achieve a major breakthrough with an impact beyond the research domain of DNA repair; it will allow us to explore the functional links between DNA repair mechanisms and the chromatin architecture. Understanding these connections will provide us with insights into how genome maintenance is connected to developmental defects and disease mechanisms, thus opening new roads towards novel targets for personalized therapy.

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Applying and securing research funding from H.F.R.I. improves career prospects of young scientists, establishes a long-lasting research and training program, promotes academic collaborations, generates novel scientific information and strengthens Greek human potential in research. The H.F.R.I. research program has the great potential to form the basis for early-career scientists who have produced excellent supervised work, to retain their competitive edge, to maximize the visibility of their own research achievements and to establish productive collaborations with research groups with highly relevant scientific activities. H.F.R.I. funds will be decisive towards establishing the first steps of talented early-career young researchers towards independence.

*The Principal Investigator,
Georgia Chatzinikolaou*

Funding

Amount: **180,000 €**

Duration: **36 months**

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





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