

Description of Funded Research Projects

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

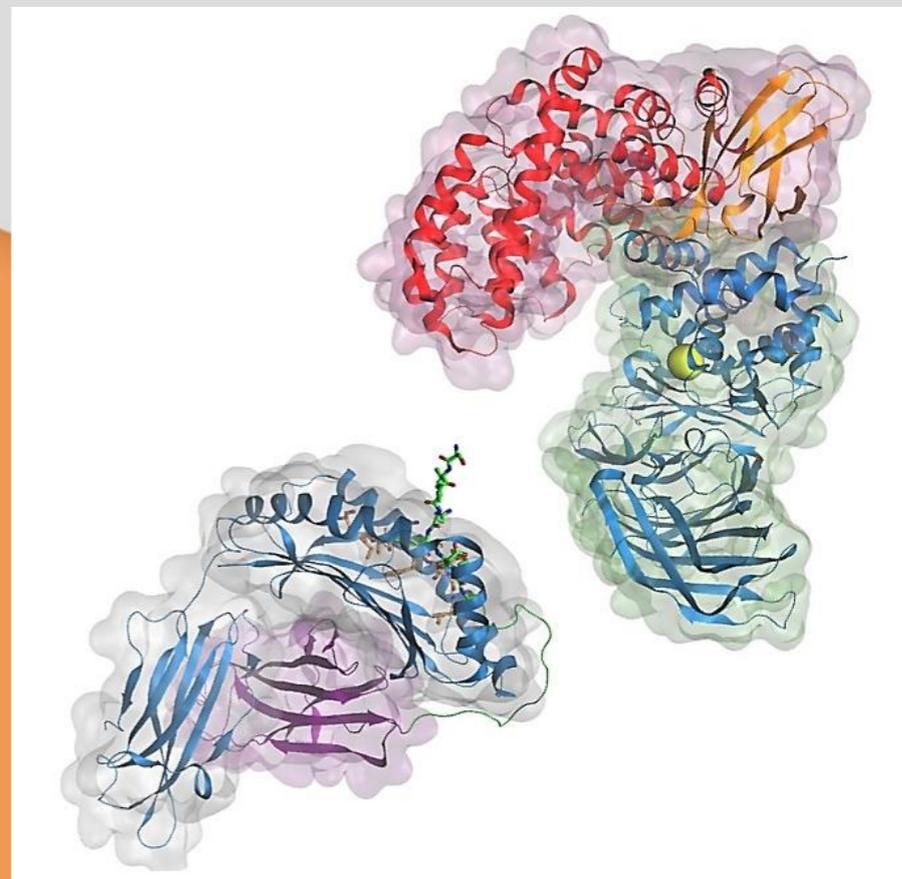


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Research Project Title:

**ARIA -
Atomic Resolution Insight into
the Antigen processing
machinery**

Principal Investigators:
Athanasios Papakyriakou
& Anastasia Mpakali



Popular Title:
Deciphering the antigen presentation machinery

Scientific Field:
Life Sciences

Host Institution:
Institute of Biosciences &
Applications, NSCR “Demokritos”



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Adaptive immune responses are driven by the recognition of molecular complexes between small antigenic peptides and Major Histocompatibility Complex Class I molecules (MHCI). These complexes are recognized by T-lymphocytes which then initiate biochemical cascades until eradication of target cells. Antigenic peptides are generated intracellularly by proteolysis, loaded onto MHCI in the endoplasmic reticulum (ER) and transported to the cell surface for presentation. ER aminopeptidase 1 (ERAP1) is an ER-resident aminopeptidase that has been shown to crucially participate in generation of antigenic peptides by trimming N-terminally extended peptide precursors to mature epitopes or by over-trimming them until destruction. Many studies have exemplified the importance of ERAP1 in regulating responses against normal and diseased cells (infected/ cancerous). Accordingly, ERAP1 inhibition has proven sufficient to generate potent anti-tumor cytotoxic responses and therefore is currently a promising pharmacological target for enhancing cancer immunotherapy. ERAP1 is polymorphic and this variability has been associated to predisposition to disease (most notably autoimmunity), which has been repeatedly validated on both genetic and functional levels. Overall, ERAP1 has been proposed to constitute a key node in the generation of the cellular immunopeptidome and establishment of immunodominance. According to recent findings, ERAP1 can trim peptides both in solution and while bound onto MHCI, implicating that MHCI molecules can influence ERAP1 activity and specificity.

Although ERAP1 was long considered as the dominant aminopeptidase in the ER, it has become increasingly clear that a second homologous trimming enzyme, ERAP2, is also very important for correct antigen processing and probably by forming a heterodimer with ERAP1, efficient trimming of diverse precursor epitopes is ensured. This research project aims to resolve two mechanistic questions of great importance in the field of immunology: a) can ERAP1 trim the antigenic peptides while bound onto MHCI molecules? b) what is the nature and significance of ERAP1/ERAP2 heterodimers?

Endoplasmatic Reticulum aminopeptidases, play an important role in the generation of the antigenic peptides that will be presented through the MHC I molecules to the immune system, and thus in its activation for the treatment of pathological diseases. Unravelling the action mechanisms of these enzymes with biochemical and structural studies under normal conditions, as well as the understanding of activity changes associated with pathological conditions (notably autoimmune diseases and various types of cancer), will reveal new data on changes concerning the immunopeptidome and the etiology of these diseases.

Rational design of small molecules that can modulate the activity of these enzymes (hyper-activation or inhibition) will open up new therapeutic strategies of treatment a number of diseases, many of which are frequently occurring in the Greek population.

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

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H.F.R.I. funding has played a key role in my decision to return to Greece from the UK. This is the first time that a Greek support program enables the postdoctoral scientist to be the Scientific Project Manager. In addition, the amount to be funded is significant to the extent of a mini-research team with the necessary consumables, micro-equipment and publicity costs.



*The Principal Investigators,
Athanasios Papakyriakou & Anastasia Mpakali*

Funding

Amount: **180,000 €**

Duration: **36 months**

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





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