**MARIE SKŁODOWSKA-CURIE POSTDOCTORAL FELLOWSHIPS 2021**

**EXPRESSION OF INTEREST FOR HOSTING MARIE CURIE FELLOWS**

## HOST INSTITUTION

NOVA University Lisbon | NOVA Medical School

## RESEARCH GROUP AND URL

DNA Breaks
http://cedoc.unl.pt/dna-breaks/

## SUPERVISOR (NAME AND E-MAIL)

Vasco M. Barreto
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## SHORT CV OF THE SUPERVISOR

Vasco M. Barreto (VMB) is a Group Leader at CEDOC, where he heads the DNA Breaks lab/gene editing service of CEDOC, currently composed of 4 postdocs, 1 PhD student, 1 MSc student and 1 technician. He has independently secured 8 external competitive grants and several fellowships for my team, totaling ~1.2 M, and authored a total of 53 publications, including 30 international publications, with peer-reviewed articles (average citation/paper=81 from Google Scholar) in some of the very top journals in the life sciences (eg Nature Commun, Mol Cell, JEM, Nature Immunol, PLoS Pathog, PNAS, Cell), 12 of which as first or corresponding author. One recent working paper and one invited review have been submitted; 1 additional invited review and 5 original research articles are currently in preparation. His research articles have been highlighted in Nature Immunol, Faculty of 1000 and JEM. VMB graduated in Biology at the Univ. of Lisbon (1994) and conducted his doctoral studies at the Inst. Pasteur in Paris, obtaining a PhD degree in Immunology from the UPMC in 2001. He then moved to The Rockefeller Univ. in New York, first as a Postdoc and then as a Research Associate, where he worked in M. Nussensweig's lab on the molecular mechanisms of antibody formation. He returned to Portugal in 2008 to launch his group at the Inst. Gulbenkian de Ciencia and address two hallmarks of B cells: 1) the interplay between the mechanisms that promote genetic diversity in somatic cells and DNA repair; 2) the epigenetics of mono-allelic expression. He was awarded a Ciencia 2008 contract to initiate his independent career at the IGC and then an Associate Researcher position (IF 2015), after which he moved to CEDOC, where since 2016 he has been developing research work supported by 3 FCT grants. This has allowed him to make key contributions to the understanding of both the regulation of Activation-Induced Deaminase (AID), the editor of immunoglobulin genes, and the process of V(D)J recombination. VMB published as senior author in journals such as Nature Commun, filed a patent, and supervised 6 postdocs, 4 PhD students (3 graduated) and 3 MSc students (3 graduated). He reviewed for the FCT and major journals (eg Cell, J Exp Med, Nat Methods, Infect Genet and Evol, Nucleic Acids Res), was external examiner of 7 national and international theses, delivered invited talks at national meetings/institutions as well as abroad (Spain, Sweden, Israel) and (co-)organized modules of 4 international PhD programs as well as 2 national and 1 international scientific meetings. VMB collaborate(d) with world experts in his field (eg G Victora, The Rockefeller University, USA; A Gimelbrant, Harvard Medical School, USA; A Ramiro, CNIC, Spain), served in 5 thesis committees and was appointed to the Selection Committee of the International Plants for Life PhD Program (2016) and the Editorial Board of SpringerPlus (2015).

## 5 SELECTED PUBLICATIONS

- Kubasova N, Alves-Pereira CF, Gupta S, Vinogradova S, Gimelbrant A*, **Barreto VM*** (2021) Single-cell reconstitution reveals persistence of clonal heterogeneity in the murine hematopoietic system. BioRiv (pre-print) * *Co-corresponding authors*

- Thiago S. Guzella TS; **Barreto* VM**; J Carneiro J*. (2020) Partitioning stable and unstable expression level variation in cell populations: A theoretical framework and its application to the T cell receptor. PLOS Computational Biology 16 8: e1007910-e1007910. https://doi.org/10.1371/journal.pcbi.1007910. **Co-corresponding authors*

- Pereira CF, Freitas R., Lopes T., Gardner R., Marta F., Vieira P., **Barreto VM** (2014) Independent recruitment of Igh alleles in V(D)J recombination. Nature Communications 5: 5623 DOI:10.1038/ncomms6623

- **Barreto VM**, Pan-Hammarstrom Q, Zhao Y, Hammarstrom L, Misulovin Z, Nussenzweig (2005) AID from bony fish catalyzes class switch recombination. Journal of Experimental Medicine 202(6):733-8 DOI: 10.1084/jem.20051378

- **Barreto, V**, Reina-San-Martin, B, Ramiro, AR, McBride KM, and Nussenzweig MC (2003). C-terminal deletion of AID uncouples class switch recombination from somatic hypermutation and gene conversion. Molecular Cell 12, 501-508.


## PROJECT TITLE AND SHORT DESCRIPTION

***Natural gene editing in B cells: new approaches to lingering and emerging problems***

B cells are remarkable for their ability to assemble and edit the immunoglobulin (Ig) genes. This goal is achieved by a fine-tuned interplay of the enzymes – the RAG1/RAG2 endonuclease and Activation-Induced Deaminase – that modify the Ig genes with the DNA repair pathways and epigenetic machinery that protect the genome. Such interplay has been difficult to elucidate and manipulate. To fully apprehend it, we need comprehensive studies at the organismal level able to capture the key cellular and molecular interactions that target the changes to the Ig genes (the spatial component), as well as the long-term impact on the cells of the genetic and epigenetic modifications associated to the genotoxic and other stresses shaping the B lineage (the temporal component), of which the most extreme manifestations are the B cell lymphomas. Three interrelated problems stand out: the interplay between the generation of somatic diversity and the dynamics of cellular selection; the lingering enigma which is the targeting of the editing machinery to the immunoglobulin genes; and the impact of cellular stresses on B cells, namely the cell-intrinsic genotoxic effects associated with gene editing and the recurrent hypoxia associated to the changing environments to which B cells are exposed in the GCs. Our international team aims at solving these questions by developing original, ambitious and timely approaches using state of the art technology that will generate critical data and new tools for cross-pollination of other fields (namely, T cell biology, Oncobiology and Development). Of note we introduce the first quantitative gene tracer reporters and we propose the first thorough genetic manipulation of the editing machinery of B cells, which could have a major impact in antibody production, including antibodies with clinical relevance and value for biomedical research.

*This Project was short-listed in of the "la Caixa" Banking Foundation call Health Research Proposal calls.*

## SCIENTIFIC AREA WHERE THE PROJECT FITS BEST*

Life Sciences (LIF)