ANNOUNCEMENT FOR THE OPENING OF AN INTERNATIONAL CALL FOR THE SELECTION A PhD HOLDER JUNIOR RESEARCHER UNDER DECREE-LAW NO. 57/2016

Internal code: Researcher/FCT_Proj2021/i3S/2305/2023

A call is opened for the position of a PhD holder, for an unfixed term work contract to carry out research duties within the project "Molecular Control of Foxn1 Expression in Thymic Epithelial Cells: Advances in Thymus Regenerative Therapies", with reference PTDC/MED-IMU/0888/2021, funded by Fundação para a Ciência e Tecnologia IP.

Scientific Area: LIFE AND HEALTH SCIENCES

1. Project summary and work plan

T cells are key components of the immune response to pathogens and tumour cells. Yet, they can also be detrimental in autoimmune disorders. Given the present interest in the development of new T cell-driven immunotherapy, it is crucial to understand the principles that control T cell responses. As the generative organ of functionally diverse and self- tolerant T cells, the thymus plays a central role in the establishment of immunity and tolerance induction. Aberrant T cell development can lead to immunodeficiency, leukaemia or autoimmune disorders. Thus, it is of both fundamental and clinical relevance to comprehend how to harness and repair thymopoiesis. Our proposal is focused on studying primordial molecular events that take place during thymic organogenesis and become deterministic of its function. Within the thymus, the generation of T cells is not a cell-intrinsic process and depends on interactions with resident thymic stromal cells. Particularly, thymic epithelial cells (TECs) constitute the main functional stromal component of the vertebrate thymus. TECs play a non-redundant role in T cell development, expressing key cytokines, chemokines and ligands that control thymocyte survival, commitment, division, migration and selection. Abnormal differentiation of TECs cause immunodeficiency or autoimmunity, which makes the study of these cells of basic importance to understand the foundations of immunity and develop new therapeutics for pathologies couple to dysfunctional T cell responses.

An essential step during early stages of TEC development is the induction of the transcription factor Forkhead box N1 (Foxn1), which remains to date as the sole determinant of thymic epithelium lineage specification. The functional relevance of Foxn1 to the development of the thymus is typified by the athymia of mice and human carrying mutations in Foxn1 gene. Genetic defects in Foxn1 abrogate thymus development, due to a primitive arrest in TEC differentiation. As result, disruptive Foxn1 mutations prevent T cell production and cause a Severe Combined Immunodeficient phenotype. Importantly, Foxn1 is not only essential at the onset of thymus organogenesis, but is also continuously required to sustain TEC homeostasis throughout life. Moreover, fluctuations in Foxn1 levels are linked to the degeneration of the thymus and immune senescence. Yet, our understanding of the chief transcriptional network that controls Foxn1 expression in TECs remains elusive. Here, we outline research approaches that can potentially close this gap. Understanding the

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Rua Alfredo Allen, 208
4200-135 Porto
Portugal
+351 220 408 800
info@i3s.up.pt
www.i3s.up.pt

fundaments underlying thymic organogenesis is key not only to comprehend normal organ development but also to develop new therapeutics for thymus regeneration.

Our project aims at defining the molecular determinants and pathways that regulate Foxn1 induction in TECs. We propose an integrative research program that extends beyond the current state-of-the-art, proceeding from an innovative in vivo reporter model to advanced genome-wide genetic analyses and high-content molecular deconvolution methods, culminating with in vivo functional validation studies. We have generated a novel mouse model where in Foxn1-reporter mice were crossed onto a Nude (Foxn1-deficient) background. Although Foxn1 protein is absent in compound Foxn-1-reporter:Nude mice as a result of Foxn1 mutation, our preliminary results have validated that TECs arrested at early stages of development are competent to initiate Foxn1 transcription. Pilot single cell RNA sequencing (scRNAseq) analysis revealed that Nude TEC compartment hides a heterogeneity hitherto unknown, and confirmed that Foxn1 reporter gene faithfully replicate the activity of Foxn1 promoter. Employing this model, we will delineate the genome-wide epigenomic (ATAC-seq) and transcriptomic (bulk and scRNAseq) signatures that govern Foxn1 expression during TEC specification in vivo (GOAL1). Subsequent bioinformatics analysis, combined with in vitro and in vivo functional validation studies will allow us to evaluate the role of newly identified genes in Foxn1 expression, TEC differentiation and thymus function (GOAL2).

Notably, thymic function declines with age, infection, or cytoablative regimens, contributing to poor T cell responses and increased risk of autoimmunity and malignancy in the elderly or immunodeficient patients. These deficits have been associated to alterations in the homeostasis and function of TEC microenvironments. Our proposal has the potential to contribute to solve one of the great challenges of modern immunology – control of thymic function. The discovery of molecular elements involved in the control of Foxn1 expression can be integrated into therapeutics to repair thymic activity via the functionalization of TEC. Collectively, our project is of fundamental and clinical importance to understand how T cell-mediated immunity and tolerance are established in vivo, and therefore, represents a major advance in Health Sciences.

2. Applicable Portuguese legislation

Decree no. 57/2016, of August 29 - Legal Regime of Scientific Employment RJEC - in its current wording

Portuguese Labor Code, in its current wording

3. Jury

Chairman: Pedro Mendes Rodrigues; Other Members: Nuno Lages Alves and Rute Pinto.

Substitute: Margarida Saraiva

4. Workplace

i3S - Rua de Alfredo Allen, 208 Porto

Research group: Thymus Development and Function

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5. Professional category and monthly remuneration

Junior Researcher

€2.228,11, corresponding to index 33 of the Tabela Remuneratória Única, whose application is intended for PhD holders with reduced post-doctoral experience or without a post-doctoral scientific curriculum.

6. Obligatory requirements for admission

1. PhD degree in "Life and Health Sciences", "Biomedical Sciences", or similar areas. If a foreign higher education institution has conferred the degree, it must comply with the provisions of Decree-Law 66/2018, of 16th August, and any formalities established therein must be fulfilled by the date of signing the contract.
2. Highly motivated candidates with experience in the area of Immunology. Particularly, T cell development and function or related areas.
3. Publication track record in peer-reviewed journals: First author of, at least, 1 peer-review research manuscript on a top tier journal in the area of Immunology and/or related fields.
4. Experience and Accreditation to perform animal (mice) experimentation – The FELASA B or C certificate must be provided with the application.
5. Hands-on experience in multi-colour flow cytometry analysis and cell culture. Proven laboratory experience with other techniques will be valued.
6. Participation in national and/or international conferences in the area.
7. Proficiency in English (written and spoken).

7. Evaluation of the applications and publication of the results

Under the terms of article 5 of RJEC, the evaluation of the scientific and curricular background of the candidates should focus on the activity of the last five years that the candidate considers most relevant. The five-year period may be extended by the jury, at the candidates request, when justified by suspension of scientific activity for socially protected reasons, namely for reasons of parental leave, prolonged serious illness, and other situations of unavailability for work that are legally protected.

Weight of the different curricular valuation criteria:

a) Detailed Curricula (70%)

- List of scientific publications and their impact factor (25%)
- Experience in animal (mice) experimentation in immunological models (20%)
- Relevant research experience in the project area (25%)

b) Motivation Letter (20%)

- Interest and motivation for the research area framing the position to be hired.

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If the jury decides to obtain further clarifications and additional information about the curricular elements presented, the best candidates classified on the basis of the curriculum may be called for an interview. In this case, the curricular evaluation will weight 90% for all candidates and the interview will weight 10%.

Candidates are excluded from admission to this call if they do not fill out their application correctly or do not meet the obligatory admission requirements. If in doubt, the jury may ask any candidate additional documents in support of their statements.

False statements made by candidates will be sanctioned in accordance with the law.

The jury will take minutes of their meetings, which may be consulted by candidates upon request.

The jury deliberates by means of a justified nominal vote according to the evaluation criteria, with no abstentions allowed, and draws up a list of excluded and admitted candidates, ranked by the respective classification after the curricular evaluation. I3S publishes the list on the i3S website, www.i3S.up.pt and candidates will be notified by e-mail.

After publication of the ranking list, if their wish to do so, the candidates have 10 working days to submit comments.

In the 90 days following the deadline for submission of applications, the jury's final decision is communicated to the candidates and made public. Subsequently the institute Director, who is also responsible for the final decision of hiring, will ratify the decision of the jury.

This call is intended exclusively to fill the indicated position on offer and may be canceled before the final ranking list of candidates is ratified by the Director. Accordingly, the position will no longer be available.

8. Submission of applications

Applications must include all the documents proving that they fulfill the admission requirements, namely:

a) Copy of certificate or diploma of PhD;
b) Detailed Curriculum Vitae;
c) Motivation Letter (English);
d) FELASA B or C certificate.

The submission of applications is digital, in pdf format, from 23 May to 5 June 2023, in the following link:

https://dozer.i3s.up.pt/applicationmanagement/#/addpositions

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9. Start and duration of the contract

The expected start date of the contract is 01/07/2023, being subject to budget availability. The maximum duration of the contract will be 24 months; however, it cannot overlap the end date of the project, presently scheduled for 28/02/2025.

10. Non-discrimination and equal access policy

i3S actively promotes a policy of non-discrimination and equal access. No applicant shall be privileged, benefited, prejudiced, or deprived of any right or exempted from any duty on the basis of ancestry, age, gender, sexual orientation, marital status, family situation, economic situation, education, origin or social condition, genetic heritage, reduced work capacity, disability, chronic illness, nationality, ethnic origin or race, territory of origin, language, religion, political or ideological beliefs, or trade union membership.

Within the framework of the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers, i3S adopts the Open, Transparent and Merit-based (OTM-R) principles for the recruitment of researchers, with the aim of conducting fair and transparent recruitment processes, bringing equal opportunities to all candidates.

11. Applicants with disabilities

Under the terms of Decree-Law 29/2001, of February 3, the candidate with a disability is given preference in equal ranking, which takes precedence over any other legal preference. Candidates must declare under oath their degree of disability, the type of disability and the means of communication/expression to be used in the selection process, under the terms of the aforementioned decree.

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