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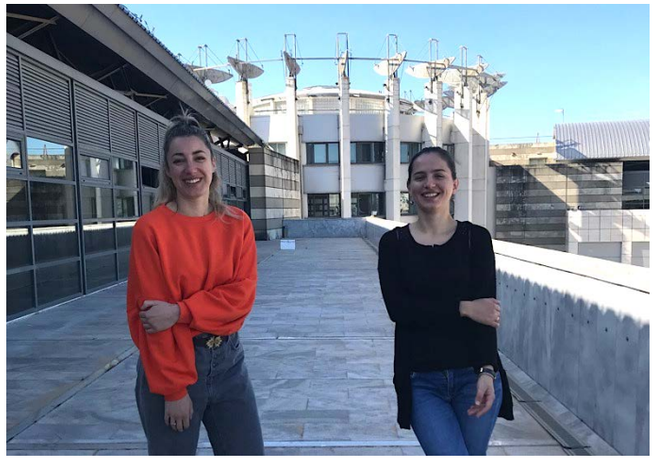
Description of the funded research project

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

Title of the research project: Dissecting the Regulatory T cell metabolic aberrancies in autoimmunity to empower their function

Principal Investigator: Themis Alissafi

Reader-friendly title: Treg cell metabolism as a potential therapeutic target for autoimmune diseases



Scientific Area: SA3 Life Sciences

Institution and Country: Biomedical Research Foundation Academy of Athens, Greece

Host Institution: Biomedical Research Foundation Academy of Athens

Collaborating Institution(s): Institute for Molecular Biology and Biotechnology, Aristotle University of Thessaloniki

Budget: 180.000 euro

Duration: 36 months

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Research Project Synopsis

Autoimmune diseases (ADs), comprise a heterogeneous group of poorly understood potentially life- threatening disorders that arise when immune tolerance against self is breached. Although much progress has been made in understanding the mechanisms of ADs and the nature of self-tolerance, effective and highly targeted treatments remain elusive. Therefore there is a presently urgent need to explore strategies to re-establish self-tolerance and provide long term disease suppression. This unmet need is becoming critical as the new era of cancer immunotherapy using immune-checkpoint inhibitors (ICI), induces a wide spectrum of severe autoimmune manifestations, collectively called immune-related adverse events (irAEs). We and others have shown that among the various mechanisms implicated in autoimmunity, immune suppression by endogenous regulatory T cells (Tregs) is indispensable. Importantly, our recent work unravelled that during ADs, Tregs are poorly functioning being unable to counterbalance the autoimmune responses. However, the pathogenic processes leading to Treg dysfunction during ADs remain largely obscure. Our preliminary data indicate significant alterations in Treg mitochondrial function and immunosuppressive nature both in mice and patients with ADs or irAEs. Building upon our extensive expertise on Tregs in ADs and cancer, AutoReg specifically proposes to: 1) integrate Treg metabolic and proteomic analysis as well as mitochondrial function towards the generation of an AutoReg signature, with the potential to identify Treg- based therapeutic targets; 2) utilize AutoReg signatures, to restore Treg function via innovative transgenic models and gene editing and 3) provide a translational spin by validating AutoReg signatures in patients with ADs and irAEs. Deciphering the cellular and molecular pathways that lead to Treg malfunction in ADs may unveil novel therapeutic targets for autoimmunity.

Project originality

Autoimmune diseases (ADs) comprise a heterogeneous group of poorly understood life-threatening disorders. Although the variety of therapeutic targets is enormous, a large number of patients fail to either respond or to achieve long-lasting remission. In addition, despite our increasing knowledge of the cellular and molecular processes involved in the development of ADs, the most effective targets for immunotherapy remain unknown. The goal therefore, would be to develop novel therapeutic protocols that could cure and not only palliate autoimmunity by resolving inflammation and establishing lasting tolerance.

Immune tolerance is critical to the avoidance of unnecessary responses against self antigens. Nevertheless, a large segment of the population is developing AD. Deciphering cellular and molecular pathways of immune tolerance is an important goal, with the expectation that understanding these pathways will lead to new advances in the treatment of these devastating diseases.

Among the various mechanisms of immunological self-tolerance, immune suppression by Foxp3+CD25+CD4+ Tregs is essential and indispensable as illustrated by spontaneous AD development when Tregs are rendered deficient [3]. This pivotal role of Tregs has generated an impetus for exploiting them as therapeutic targets in ADs. The clinical implementation of these therapies however, has been hampered by a lack of understanding on the mechanism of Treg action.

Our results recently demonstrated that during autoimmune manifestations Tregs are poorly functioning and cannot counterbalance autoimmune inflammation. **The specific pathogenic mechanisms leading to Treg dysfunction during autoimmune manifestations remain obscure.**

Among the many cellular and molecular processes involved in Treg cell fitness, their unique metabolic profile has recently gained a lot of attention. However, whether autoimmune environments induce differential metabolic rewiring and what aspects of it are critical for the function of Tregs is not understood. **Illuminating and targeting the mechanisms of Treg dysfunction in autoimmunity will open promising avenues for therapeutic interventions in ADs.**

Expected results & Research Project Impact

Autoimmune Diseases (ADs) affect approximately 40 million people worldwide, which translates into a total cost of several billion Euros per year deriving from their clinical management and the associated loss in work productivity. Clearly, based on these figures, the potential for societal impact of a commensurate action targeting ADs is extraordinary. The market for inflammatory diseases represents one of the fastest growing areas of pharmaceutical industry. Although biologic interventions targeting components of the immune response have replaced the generalized immunosuppressive strategies in the treatment of ADs, a significant portion of patients fails to achieve true remission. Therefore there is an increased interest in exploring strategies to provide long term disease suppression.

AutoReg intends to broaden our knowledge beyond the state of the art, using ground-breaking approaches in order to provide a comprehensive analysis of the mechanisms dictating Treg dysfunction during development of autoimmune responses that represent one of the main obstacles towards designing effective immunotherapies. Our findings will pave the way for the development of therapeutic protocols that exploit Tregs for the treatment of autoimmunity as well as diseases in which disturbed tolerance is a common denominator. Based on our solid preliminary data that highlight significant alterations in the mitochondrial function and the nature of Tregs in autoimmune mice and in patients with autoimmune manifestations, we propose to target Treg mitochondria function for therapeutic intervention of autoimmune responses. Furthermore, AutoReg will generate innovative tools for a) restoring Treg mitochondrial function such as the cutting edge generation of unique conditional knockin animal models and b) development of exclusive in vitro models to study immunotherapy induced toxicities.

The importance of this funding

The current proposal fulfills my vision as a scientist, as it provides the opportunity to combine my skills in basic immune regulation mechanisms, in order to uncover mechanisms of the immune system in health and disease with the goal these mechanisms to lead to therapeutic decisions for life threatening diseases. Since I am at the early stages of my career, I envision that AutoReg will equip me with the essential funding for a successful startup that will allow me to accomplish my scientific goals and pave the way towards my independence as a researcher in the field of immunology. Furthermore, data generated by AutoReg might create opportunities to apply for additional funds from national and international agencies. The proposed project will use, improve and develop state-of-the-art technologies and work with human samples in a Systems Medicine approach, which are highly relevant areas for building future careers.

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