BIOGRAPHICAL SKETCH

NAME: **Luis GRACA**

eRA COMMONS USER NAME (credential, e.g., agency login): LGraca

POSITION TITLE: Full Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Faculty of Medicine, University of Lisbon, Portugal	M.D.	07/1995	Medicine
Hospital Santa Maria, Lisbon, Portugal	-	09/1997	Medical Internship
Sir William Dunn School of Pathology, University of Oxford, UK	D.Phil.	07/2002	Immunology Transplantation
University of Oxford, UK	Postdoc	07/2004	Immunology Immunotherapy
Telethon Institute for Child Health Research, University of Western Australia, Perth, Australia	Postdoc	09/2005	Immunology Allergy
Faculty of Medicine, University of Lisbon, Portugal	Habilitation	03/2010	Immunology

A. Personal Statement

The main focus of my research has been directed at understanding the regulation of immune pathology. I acquired unique expertise with therapeutic monoclonal antibodies (under H. Waldmann) and regulatory T (Treg) cells, which I have used to study human immunology and immune pathology. Recently I made significant contributions related to the regulation of humoral responses in human individuals, and the pathogenesis of human autoimmunity. I have been exploring the concept that in the same way specialized inflammatory responses are necessary for optimal immunity, specialized regulatory mechanisms ought to be also present. While probing this concept I discovered the existence of Foxp3+ iNKT cells and, more recently, T follicular regulatory (Tfr) cells specialized in regulating humoral responses. The recognition of my research has led to invitations to review the field, presentations in major conferences, as well as election as president of the Portuguese Society of Immunology, and more recently as president of the Portuguese Medical Sciences Society (the oldest medical society in Europe).

- Deng J, Wei Y, Fonseca VR, **Graca L***, Yu D* (2019) “Follicular helper and follicular regulatory T cells in autoimmune rheumatic diseases: phenotype, pathogenesis and targeted immunotherapies”. *Nature Rev Rheumatol*. 15:475-490. (* joint senior/corresponding authors)
- Fonseca VR, Ribeiro F, **Graca L** (2019) “Dissecting the Complexity of T Follicular Regulatory Cells”. *Immunol Rev*. 288:112-127.
- Fonseca VR, Agua-Doce A, Maceiras AR, Pierson W, Ribeiro F, Romão VC, Pires AR, Silva SL, Fonseca JE, Sousa AE, Linterman MA, **Graca L** (2017) “Human Blood CXCR5+Foxp3+ T cells Are Indicators of Ongoing Humoral Activity Not Fully Licensed With Suppressive Function”. *Science Immunol*. 2: eaan1487.
- Maceiras R, Almeida SCP, Mariotti-Ferrandiz E, Chaara W, Jebbawi F, Six A, Hori S, Klatzmann D, Faro J, **Graca L** (2017) “T follicular helper and T follicular regulatory cells from the same germinal centers have different TCR-specificity”. *Nature Commun*. 8: 15067.

B. Positions and Honors

Positions held

•	2019-	Full Professor	Faculty of Medicine, University of Lisbon, Portugal
•	2005-	Head of research group	Instituto de Medicina Molecular, Lisbon, Portugal
•	2013-19	Associate Professor	Faculty of Medicine, University of Lisbon, Portugal
•	2005-13	Assistant Professor	Faculty of Medicine, University of Lisbon, Portugal
•	2004-05	Post-doctoral fellow Patrick G. Holt group	University of Western Australia, Perth, Australia Telethon Institute for Child Health Research
•	2002-04	Post-doctoral fellow	University of Oxford, UK

Honors and awards

•	2019	Research Excellence Award	Univ. Lisbon / Caixa Geral de Depositos
•	2017	Innovators Award	TwinToInfect, IMM Portugal
•	2011	Award in Autoimmunity Research	NEDAI, Portuguese Society of Internal Medicine
•	2010	Venture Competition Award	ISCTE-IUL MIT-Portugal Venture Competition
•	2010	Young Entrepreneur Award	National Society of Entrepreneurship (ANJE)
•	2010	National Innovation Award for Health Technologies;	Espirito Santo Bank (BES)
•	2009	Professor Heimburger Award in Coagulation Diseases;	CSL – Behring, Germany
•	2002-04	Junior Research Fellowship	Wolfson College, University of Oxford, UK
•	1995	Clinical Research Prize	Society of Medical Sciences / Pfizer

Commissions of trust

•	2013-16	Board of scientific counselors for Health Sciences	Portuguese Research Council (Fundação para a Ciência e Tecnologia, FCT), Portugal
•	2015-18	President	Portuguese Society for Immunology
•	2012-18	Board of Directors	Portuguese Society for Immunology
•	2017-	President	Portuguese Medical Sciences Society (Sociedade das Ciências Médicas de Lisboa; *established 1822*)
•	2006-	Board of Directors	Sociedade de Ciências Médicas de Lisboa

Institutional responsibilities

•	2017-	Member of the Academic Council, Faculty of Medicine, University of Lisbon, Portugal
•	2017-18	Member of the Scientific Council, Faculty of Medicine, University of Lisbon, Portugal
•	2013-	Member of the board of the IMM PhD Program
•	2016-	Member of the General Assembly (supervisory council) of IMM
•	2014-17	Member of Conselho de Escola (supervisory Council), Fac. Medicine, Univ. Lisbon
•	2009-14	Member of the Scientific Council, Faculty of Medicine, University of Lisbon, Portugal
•	2010-	Member of the scientific committee of the rodent facility at the IMM
•	2014-17	Head of the users' committee of the Flow Cytometry unit at the IMM

C. Contributions to Science

a) My independent research was initially based on my expertise in tolerance induction and peripherally induced Treg cells. *I decided to investigate the concept that different specialized populations of regulatory cells ought to be necessary, in the same fashion different pro-inflammatory cell types can be found*.

I studied several models of *tolerance induction to foreign antigens*, namely immunogenic therapeutics (i.e. factor VIII in hemophilia) or allergens (house dust mite, lactoglobulin). My group found that mechanisms leading to tolerance can change depending on the nature of the antigen: tolerance can rely on Foxp3-induction or on IL-10-dependent mechanisms that are Foxp3-independent and, paradoxically, adjuvants can facilitate tolerance induction by promoting adequate antigen presentation (*1-3*). Thus, the context can select the most appropriate regulatory cell population.

We were the first to show that murine and human iNKT cells can acquire Foxp3-expression and immune-suppressive properties (*4*), a population we termed NKTreg, that opened a new field, being subsequently studied by other groups. This observation led us to pursue the controversial notion that functional iNKT cell subsets

(namely iNKT17) can also be peripherally induced (*5*). Our NKTregs studies had great impact being highly cited and highlighted in commentaries, namely in *New Scientist* and *SciBX*, due to potential usefulness as an immunosuppressive cell therapy (as an alternative to Treg cells that have been used in trials to prevent GVHD). Our current research (in mice) suggests that indeed NKTreg cells, due to preferential homing into the liver, can prevent rejection of islet allografts delivered by the clinically relevant intra-portal route without preventing extra-hepatic immunity (*unpublished*).

1. Oliveira VG, Agua-Doce A, Curotto de Lafaille M, Lafaille JJ, **Graca L**. (2013) "Adjuvant facilitates anti-CD4 mediated immune tolerance to recombinant factor VIII in hemophilia through a Foxp3-independent mechanism that relies on IL-10". *Blood* 121: 3938-3945.
2. Oliveira VG, Paiva RS, Demengeot J, **Graca L**. (2011) "Sub-optimal CD4 T cell activation triggers TGF-β-dependent conversion to Foxp3$^+$ regulatory T cells". *Eur J Immunol* 41:1249-55.
3. Agua-Doce A, Caridade M, Oliveira VG, Bergman L, Curotto de Lafaille M, Lafaille JJ, Demengeot J, **Graca L** (2018) "Route of antigen presentation can determine the selection of Foxp3-dependent or Foxp3-independent immune tolerance". *J Immunol*. 200:101-109.
4. Monteiro M, Almeida CF, Caridade M, Ribot JC, Duarte J, Agua-Doce A, Wollenberg I, Silva-Santos B, **Graca L**. (2010) "Identification of Regulatory Foxp3+ Invariant NKT Cells Induced by TGF-β". *J Immunol* 185: 2157-2163.
5. Monteiro M, Almeida CF, Agua-Doce A, **Graca L**. (2013) "Induced IL-17-producing invariant Natural Killer T cells require activation in presence of TGF-β". *J Immunol* 190: 805-811.

b) We were also among three groups that independently discovered Foxp3$^+$ Tfr cells and their role in regulating GC responses (*6*). This paper (we rushed it to *J Immunol* as the other two independent reports appeared in *Nat Med*) has been highly cited (over 350 citations), and is generally considered (together with the other two reports) as the initial finding.

Following the discovery of Tfr cells, I established their biology in mice and humans. First, I decided to investigate whether Tfh and Tfr cells from the same germinal centre have different TCR specificity. I postulated that if we believe Tfr cells prevent autoimmunity while Tfh cells are involved in the selection of B cells with high affinity to the immunogen (affinity maturation), then Tfr cells should recognize self-antigens while Tfh should be specific to the immunizing antigen. We have shown that this hypothesis is indeed correct and that Tfr cells derive mostly from thymus-derived Treg cells (suggesting a reason for the TCR-repertoire bias) (7).

In humans, we provided the first comprehensive characterization of circulating Tfr cells, in a study where we analyzed paired samples of blood and tonsils, as well as human thymus, in influenza vaccinated individuals and B cell-deficient patients (8). This publication was highlighted in a commentary in *Nature Immunol.* In parallel, we investigated the participation of Tfr cells (and other Tfh subsets) in patients with Sjögren's syndrome (where we had access to paired samples of blood and salivary gland biopsies with ectopic lymphoid structures) (9), rheumatoid arthritis (10), and thyroiditis (*unpublished*). Our observations were subsequently reproduced in three other patient cohorts (Netherlands, Sweeden, and China) and our article was highlighted by commentaries in *Nature Reviews in Rheumatology* and *Arthritis and Rheumatology.*

6. Wollenberg I, Agua-Doce A, Hernández A, Almeida C, Oliveira V, Faro J, **Graca L**. (2011) "Regulation of germinal centre reaction by Foxp3+ follicular regulatory T cells". *J Immunol* 187: 4553-4560.
7. Maceiras R, Almeida SCP, Mariotti-Ferrandiz E, Chaara W, Jebbawi F, Six A, Hori S, Klatzmann D, Faro J, **Graca L** (2017) T follicular helper and T follicular regulatory cells from the same germinal centers have different TCR-specificity. *Nature Commun*. 8: 15067.
8. Fonseca VR, Agua-Doce A, Maceiras AR, Pierson W, Ribeiro F, Romão VC, Pires AR, Silva SL, Fonseca JE, Sousa AE, Linterman MA, **Graca L** (2017) "Human Blood CXCR5+Foxp3+ T cells Are Indicators of Ongoing Humoral Activity Not Fully Licensed With Suppressive Function". *Science Immunol*. 2: eaan1487.
9. Fonseca VR, Romão VC, Agua-Doce A, Santos M, López-Presa D, Ferreiras AC, Fonseca JE, **Graca L** (2018) "The Ratio of Blood T Follicular Regulatory Cells to T Follicular Helper Cells Marks Ectopic Lymphoid Structure Formation While Activated Follicular Helper T Cells Indicate Disease Activity in Primary Sjögren's Syndrome". *Arthritis Rheumatol*. 70:774-784.
10. Romão VC, Agua-Doce A, Fonseca JE, **Graca L** (2018) "T follicular regulatory cells are decreased in established treated rheumatoid arthritis patients with active disease". *Arthritis Rheumatol*. 70:1893-1895.

c) Early in my career, I made seminal contributions to the understanding of the role of Treg cells in transplantation. In the early 2000s, there was skepticism within the transplantation community regarding the role of Treg cells (the alternative model to explain tolerance was activation-induced cell death of alloreactive T cells), therefore the first demonstration that co-stimulation blockade could lead to Treg cell induction (*11*) was a breakthrough. I moved on to show, for the first time, that Treg cells infiltrate transplants that are tolerated (*12*) supporting long term graft survival (also relevant for cancer immunotherapy) – this paper was highlighted in commentaries in *Science* and, together with (*13*) were considered two "landmark papers" in the Treg field in a special issue on Treg cells by *Nature Immunol*.

I also found, at a time when Foxp3 role in Treg cells was still unknown, that Treg cells could be found within the $CD4^+CD25^-$ subset (*14*); and that the cross-reactivity of Treg cells (possibly due to a mechanism we termed *linked suppression*) could prevent rejection of transplants not initially tolerized (*15*). During this period, I became recognized as an expert on Treg-mediated transplantation tolerance, and also on the use of monoclonal antibodies (MAbs) for immunotherapy (one licensed patent). Thus, I was invited to speak at several conferences dedicated to Treg cells and immunotherapy.

11. **Graca L**, Honey K, Adams E, Cobbold SP, Waldmann H. (2000) Cutting Edge: Anti-CD154 Therapeutic Antibodies Induce Infectious Transplantation Tolerance. *J Immunol* 165: 4783-4786. (226 citations)
12. **Graca L**, Cobbold SP, Waldmann H. (2002) Identification of regulatory T cells in tolerated allografts. *J Exp Med* 195: 1641-1646. (618 cit.)
13. **Graca L***, Lin C-Y*, Cobbold SP, Waldmann H. (2002) Dominant transplantation tolerance impairs CD8+ T cell function but not expansion. *Nat Immunol* 3: 1208-1213. (*) Joint first authors (183 cit.)
14. **Graca L**, Thompson S, Lin C-Y, Cobbold SP, Waldmann H. (2002) Both CD4+CD25+ and CD4+CD25- regulatory cells mediate dominant transplantation tolerance. *J Immunol* 168: 5558-5565. (426 cit.)
15. **Graca L**, Le Moine A, Lin C-Y, Cobbold SP, Waldmann H. (2004) Donor-specific transplantation tolerance: the paradoxical behavior of $CD4^+CD25^+$ T cells. *Proc Nat Acad Sci USA* 101:10122-26. (122 cit)

d) I am very keen on translational science and how the findings from mice and basic human immunology can be translated to clinical practice, thus I have four patents related to the field of immune tolerance. One patent with the postdoc supervisor (H. Waldmann), where we found a strategy to overcome the immunogenicity of therapeutic antibodies by modifying the structure (16); and three patents from the Graca laboratory (17-19). We found that adjuvants can be used to facilitate the induction of immune tolerance to therapeutic proteins (for instance clotting factors in hemophilia, or in cases of enzyme replacement therapy) (17). Our studies with iNKT cells also led to the filing of a patent on the in vitro induction of Foxp3+ regulatory iNKT cells (18). Finally, our technology transfer office protected intellectual property on the use of Tfh and Tfr-related markers as a way to stratify patients with autoimmune diseases (19) – something that can potentially lead to companion diagnostics. Finally, our work related to iNKT cells and patent (18) led to a start-up company: Acellera Therapeutics.

16. **Graca L**, Frewin M, Gilliland L, Waldmann H. 2002. *Therapeutic Antibodies*. Isis Innovation Ltd, University of Oxford. WO2004009638
17. Agua-Doce A, **Graça L**. 2009. *The use of adjuvant to facilitate the induction of tolerance to proteins*. Universidade de Lisboa and Instituto de Medicina Molecular. WO2010056143
18. Monteiro M, **Graça L**. 2009. *Foxp3+ regulatory natural killer T cells and a method for their generation*. Universidade de Lisboa and Instituto de Medicina Molecular. WO2010056144
19. Fonseca V, Romão V, Fonseca JE, **Graça L**. 2018. *Blood biomarkers for autoimmunity*. Universidade de Lisboa and Instituto de Medicina Molecular. PCT/EP2018/064789

Overall, Graca's research led to 95 publications, with combined 3539 citations.
Full publication list: https://scholar.google.com/citations?user=DUYZctUAAAAJ&hl=pt-PT&authuser=2

D. Additional Information: Research Support and/or Scholastic Performance

Major competitive funding

Research from Graca's group has been funded by national public funds, European grants, competitive funding from private organizations, and industry contracts.

- 2020/22 Thymic Abnormalities in Rare Immunological Diseases (TARID). European Joint Programme – Rare Diseases. Partner.
- 2018/20 T-Cell Connect Europe. European Network of Experts on T cell Biology. European Federation for Immunology Societies. Partner.
- 2015/19 European Network linking informatics and genomics of helper T cells. ENLIGHT-TEN. Marie Sklodowska-Curie Innovative Training Network (EU). Partner (€434,000 of €3.3M).
- 2016/19 Immunomodulatory effect of CD6-targeting in neuroinflammation. PTDC/DTP-FTO/3080/2014. Fundação para a Ciência e Tecnologia Portugal. PI €200,000
- 2016/19 Multidisciplinary approach for the development of immune-modulatory nanoparticles. UTAP-ICDT/DTP-FTO/0016/2014. Fundação para a Ciência e tecnologia Portugal. Co-PI. €200,000
- 2016/18 Characterization of Tfh cells and B cell isotype switching induced by type 1 and type 2 adjuvants (FAPESP – FCT collaborative grants). Coordinator of network €200,000.
- 2016/18 Twinn-to-Infect. Network with Infection and immunology at IMM, Pasteur (FR), Crick (UK). H2020 Twinning (EU). Partner (€1M).
- 2015/17 Targeting germinal centre dysregulation in allergy. Harvard Medical School – Portugal. Coordinator of network €300,000.
- 2012/14 Regulation of germinal centre reaction by Foxp3+ follicular T cells (FCT Portugal) €198,000 coordinator
- 2011/14 Boosting dendritic cell function to facilitate tolerance induction to clotting factors. Bayer Global Hemophilia Awards. US$170,000
- 2012/14 Cellular therapy to induce local immune suppression in islet transplantation. Novo Nordisk/ European Foundation for the Study of Diabetes), €100,000 - coordinator

Public understanding of science

Graca is committed to promoting the understanding of scientific research in society. Therefore, he has been very involved in activities to increase scientific literacy, especially among young people. This has included open days, public lectures, and appearances in the media (radio, television, and printed press). He has a long-standing collaboration with visual artists interested in developing artworks exploring the interface between art and biomedical sciences. Graca has hosted over 10 visual artists in the lab over the years and participated in collaborative artworks with artist Marta de Menezes subsequently exhibited internationally. Graca was the scientific advisor for several cultural initiatives including Guimarães European Capital of Culture, international art-science festivals, and conferences, and authored several articles on the intersection of art and biology.