

INsTRuCT Consortium: Call for applications from Early Stage Researchers for 15 Doctoral (PhD) Training Positions in Basic, Translational and Computational Immunotherapy

INsTRuCT Consortium

INsTRuCT is an Innovative Training Network (ITN) funded by the European Union Horizon 2020 Programme. The INsTRuCT Consortium is a research network of leading European scientists from academia and industry focused on fundamental research and clinical translation of myeloid regulatory cell (MRC)-based immunotherapies. A total of **15 doctoral research projects** (PhD projects) for Early Stage Researchers (ESR) are offered across **13 institutes in Europe**. Research topics range from fundamental to translational science, all at the forefront in the field of MRC-based immunotherapies. Successful applicants will also receive expert training in **basic immunological research, preclinical pharmacological development, manufacturing processes, clinical trial design, healthcare economics, ethics and marketing**. The interaction of biologists, computational scientists, physicians and engineers is central to INsTRuCT and will challenge ESR to explore complex issues in bench-to-bedside research from different perspectives. Graduates of INsTRuCT will be well-prepared to enter the workplace with an innovative and beyond state-of-the-art view on **fundamental and translational science of cell-based therapies** that will accelerate the future of the field.

Participating in INsTRuCT offers early stage researchers many unique opportunities, including:

- A project as Marie Skłodowska Curie trainee in one of the participating institutions with the intention of receiving a doctoral degree (PhD).
- State-of-the art, exciting research in an international consortium with highly integrated research projects.
- Expert training in preclinical and clinical development of cell-based medicinal products.
- At least two months of research training in the lab of another consortium member, mostly in a different EU country than the country where most of the project will take place.
- Training in both academic and commercial research environments.
- Salary according to [EU guidelines](#) for Marie Skłodowska Curie trainees, including mobility payments and family allowances where applicable.

Eligible candidates must:

- hold a Master's degree or equivalent in a field of science relevant to their chosen project (see below)
- demonstrate a history of academic excellence
- demonstrate an affinity for Basic Immunology, Computational Biology, bio(medical / process) engineering or translational research
- speak and write fluently in English
- have less than 4 years' previous research experience and not hold a doctoral (PhD) title
- have not been resident in the country where the host institution is located for more than 12 months in the 3 years before recruitment.
- be available for a personal interview at the INsTRuCT recruitment meeting in **Barcelona, 23rd-25th March 2020**.
- be available to start their project no later than **1st September, 2020**.

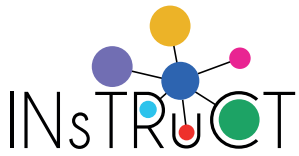


Application Process

INSTRuCT will select ESR through a 2-step recruitment process. Candidates should submit their application for their top two or three preferred research projects. Applications (in English) should include a CV, a Letter of Motivation and a Letter of Recommendation from two appropriate referees. **The closing date for applications is January 31st, 2020.** Application documents should be sent by email to Mrs. Christine Bayer, Project Administrator (christine.bayer@ukr.de) and the relevant project supervisors by email (see individual project descriptions). Applicants are advised to familiarise themselves thoroughly with projects for which they apply and be ready to answer questions on their chosen topics. After reviewing all project applications, supervisors of individual projects will contact selected applicants to organise an initial screening interview by telephone or videoconferencing. The most promising candidates will then be invited to a personal interview in a recruitment meeting of the whole consortium in Barcelona on **23rd - 25th March, 2020.** Approximately half of those interviewed in the second round will be offered a position.

Research projects offered by INSTRuCT

ESR	Project Title	Subject Area	Primary Supervisor	Institution	EU State
1	Metabolic Programming of Human Monocyte Differentiation	Molecular Immunology	ZASLONA, Z. zaslonaz@tcd.ie	Trinity College Dublin	IE
2	Mitochondrial and metabolic functions of tolerogenic myeloid cells	Molecular Immunology	SAWITZKI, B. birgit.sawitzki@charite.de	Berlin Charité	DE
3	Engineered Tolerogenic Dendritic Cells for Ag-Specific Immunotherapy	Molecular Immunology	GREGORI, S. silvia.gregori@hsr.it	Ospedale San Raffaele	IT
4	Trained Immunity in Regulatory Macrophages	Molecular Immunology	OCHANDO, J. jordi.ochando@mssm.edu	University of Madrid	ES
5	A data science approach to characterising myeloid regulatory cell therapies	Computational Biology	LORD, P. - HILKENS, C. phillip.lord@newcastle.ac.uk catharien.hilkens@newcastle.ac.uk	Newcastle University	GB
6	Investigating molecular mechanisms of human autologous tolerogenic DC	Cellular Biology	MOREAU, A. aurelie.moreau@univ-nantes.fr	University of Nantes	FR
7	Computational characterisation, classification and deconvolution of myeloid regulatory cells	Computational Biology	REHLI, M. - SPANG, R. michael.rehli@ukr.de rainer.spang@ukr.de	University Hospital Regensburg	DE
8	Development of Pharmaceutical Release Processes for DC-based Therapy	GMP Manufacturing	GERMERAAD, W. w.germeraad@cimaas.com	Cimaas BV	NL
9	Personalized MRC-based therapy: Innovative strategies to improve efficacy	Computational Biology	SANCHEZ FUEYO, A. sanchez_fueyo@kcl.ac.uk giovanna.lombardi@kcl.ac.uk	King's College London	GB
10	Development and validation of antigen-specific assays for T and B cell responses	Cellular Immunology	BRINKE, A. - van HAM, M. a.tenbrinke@sanquin.nl m.vanham@sanquin.nl	Sanquin Blood Supply and University of Amsterdam	NL
11	Development of an affordable & scalable process for tolDC manufacturing	GMP Manufacturing	COOLS, N. Nathalie.Cools@uza.be	University of Antwerp	BE
12	Classification of Human Myeloid Regulatory Cell Networks by Machine Learning	Computational Biology	KOLLET, J. jutta.kollet@miltenyibiotec.de	Miltenyi Biotec BV & Co. KG	DE
13	Genes & pathways associated with the tolerogenic capacity of tolDC-VitD3	Molecular Immunology	MARTINEZ, E. emmartinez.germanstrias@gencat.cat	Institute of the Germans Trias i Pujol Foundation	ES
14	Human Mreg-mediated conversion of naïve CD4+ T cells to iTreg	Cellular Immunology	HUTCHINSON, J. james.hutchinson@ukr.de	University Hospital Regensburg	DE
15	Route of delivery of tolerogenic dendritic cells	Clinical Immunology	HILKENS, C. catharien.hilkens@newcastle.ac.uk john.isaacs@newcastle.ac.uk	Newcastle University	GB



Further Information

Interested candidates are advised to visit the [INsTRuCT Consortium website](#) for further information about projects. Questions about recruitment, training opportunities and the scientific activities of the INsTRuCT Consortium should be directed to Dr. James Hutchinson, [Project Coordinator](#). INsTRuCT is committed to a fair, open, transparent and merit-based recruitment of researchers. To comply with Research Executive Agency policy, the INsTRuCT Consortium will retain copies of all documents submitted by all applicants at least until completion of the Project. In addition, INsTRuCT will retain copies of all evaluations made by project supervisors at every stage of the recruitment process. By submitting their application to INsTRuCT, candidates agree to their personal data being kept on record by University Hospital Regensburg and communicated to EU officials if demanded. The Data Protection Officer (DPO) at University Hospital Regensburg is Dr. Wolfgang Börner, who can be contacted by telephone on +49-(0)941 944 4420 or by sending an email to dsb@ukr.de.



Individual Project Descriptions

ESR1	
Metabolic Programming of Human Monocyte Differentiation	
Host Institution	Trinity College Dublin, Ireland
Primary Supervisor	Dr. ZASLONA, Zbignew
Email address	zaslonaz@tcd.ie
Planned duration	36 months
Subject Area	Molecular Immunology; Cellular Metabolism
<p>Introduction: After emigrating from the blood to tissues, monocytes continue their maturation and undergo final differentiation into long-lived tissue-specific macrophages. Immune-metabolites, such as succinate and itaconate, markedly influence monocyte-to-macrophage transition and functional polarisation; however, we do not fully understand the mechanistic links between these metabolites and macrophage differentiation. A deeper appreciation of metabolic control of macrophage polarisation will lead to superior MRC-based therapies.</p>	
<p>Aims: A1: We will assess how immunometabolites affect monocyte-to-macrophage differentiation using in vitro systems; A2: We will study the effects of immune-metabolites on monocyte recruitment and differentiation into macrophages in a mouse model of LPS-induced peritonitis. A3: In an OVA-induced murine asthma model, macrophages accumulate by local proliferation. We will explore how this process is affected by succinate and itaconate.</p>	
<p>Expected Results: R1: The role of succinate and itaconate in regulation of monocyte differentiation and macrophage maturation will be elucidated. R2: We will define mechanisms by which these immunometabolites affect the process of monocyte recruitment and macrophage proliferation in vivo. Since succinate and itaconate production is altered by disease states, and because maturation status influences macrophage functions, our findings will have broad clinical implications.</p>	
<p>Planned secondment: (1) An international 3-month secondment to Regensburg, Germany is planned as a networking, technical and scientific exchange. (2) An international, intersectoral 3-month secondment to GSK is planned, giving the ESR an opportunity to work with diseased human material.</p>	
<p>Enrolment in Doctoral degree(s): Trinity College Dublin</p>	
<p>Project-specific selection criteria: Desirable experience in molecular biology laboratory, preferable experience with techniques, such as Western Blotting, flow cytometry and qPCR. Knowledge of Immunology and in particular innate immunity preferable.</p>	
<p>Recommended reading: [1] Ginhoux, F., and M. Guilliams. 2016. Tissue-Resident Macrophage Ontogeny and Homeostasis. <i>Immunity</i> 44: 439-449. [2] Varol, C., et al. 2015. Macrophages: development and tissue specialization. <i>Annu Rev Immunol</i> 33: 643-675. [3] Tannahill, G. M., et al. 2013. Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha. <i>Nature</i> 496: 238-242. [4] Mills, E. L., et al. 2018. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. <i>Nature</i> 556: 113-117. [5] Murphy, M. P., and L. A. J. O'Neill. 2018. Krebs Cycle Reimagined: The Emerging Roles of Succinate and Itaconate as Signal Transducers. <i>Cell</i> 174: 780-784.</p>	

ESR2	
Mitochondrial and metabolic functions of tolerogenic myeloid cells	
Host Institution	Charité University Hospital, Berlin, Germany
Primary Supervisor	Prof. SAWITZKI, Birgit
Email address	birgit.sawitzki@charite.de
Planned duration	36 months
Subject Area	Molecular Immunology; Cellular Metabolism
<p>Introduction: Recent evidence indicates that mitochondrial function controls macrophage and DC activity. By regulating substrates for histone acetylation and methylation, cellular metabolism controls transcription through epigenetic mechanisms. Mitochondrial dynamics control metabolic programming, hence immune cell differentiation. We hypothesise that mitochondrial fission underlies the shift towards glycolysis and inflammatory phenotype in DCs and macrophages, whereas enforced mitochondrial fusion maintains a stable regulatory phenotype. Our work suggests innovative approaches for developing more stable MRC that could be used as safer or more potent cell-based immunotherapies.</p>	
<p>Aims: A1: To study mitochondrial dynamics, function and cellular metabolism in various MRC populations, including DC10, Tol-DC, ATDC and Mregs. A2: To explore the possibility of interfering with proteins regulating mitochondrial dynamics to generate more stable MRC.</p>	
<p>Expected Results: R1: Characterising mitochondrial functions and cellular metabolism of different MRC subtypes will lead to a more complete scientific understanding of their interrelationships; R2: This work will determine whether a stable, maturation-resistant phenotype in MRC is dependent upon fusion-like morphology of mitochondria and their oxidative phosphorylation activity; R3: Small molecule inhibitors and genetic engineering will be used to reinforce mitochondrial fusion in MRC products; R4: As a pharmacodynamic indicator, immune monitoring methods will be implemented to analyse mitochondrial morphology and functions following in vivo transfer of MRC.</p>	
<p>Planned secondment: An international, intersectoral 3-month secondment to Sanofi is planned to support preclinical development of gene therapy approaches to stabilising MRC function.</p>	
<p>Enrolment in Doctoral degree(s): Charité University Hospital, Berlin</p>	
<p>Project-specific selection criteria: Experience with primary cell culture, flow cytometry and an interest in bioinformatics / R programming</p>	
<p>Recommended reading: [1] Vogel SZ, [...] and Sawitzki B. TCAIM decreases T cell priming capacity of dendritic cells by inhibiting TLR-induced Ca²⁺ influx and IL-2 production. <i>J Immunol.</i> 2015 Apr 1;194(7):3136-46. doi: 10.4049/jimmunol.1400713. [2] Angajala A, et al.. Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism. <i>Front Immunol.</i> 2018 Jul 12;9:1605. doi: 10.3389/fimmu.2018.01605. eCollection 2018. Review. PubMed PMID: 30050539; PubMed Central PMCID: PMC6052888. [3] Rambold AS and Pearce EL. Mitochondrial Dynamics at the Interface of Immune Cell Metabolism and Function. <i>Trends Immunol.</i> 2018 Jan;39(1):6-18. doi: 10.1016/j.it.2017.08.006. Epub 2017 Sep 8. Review. PubMed PMID: 28923365.</p>	

ESR3	
Engineered Tolerogenic Dendritic Cells for Ag-Specific Immunotherapy	
Host Institution	Ospedale San Raffaele, Milan, Italy
Primary Supervisor	Dr. GREGORI, Silvia
Email address	silvia.gregori@hsr.it
Planned duration	36 months
Subject Area	Molecular & Cellular Immunology; Epigenomics
<p>Introduction: DC-10 is a promising example of tolDC-based cell therapy, representing a subset of DC that spontaneously releases IL-10 and induces Ag-specific T regulatory cells (Tregs). This project pursues an innovative strategy for engineering a more stable and potent MRC-based therapy. Forced over-expression of IL-10 and nominal antigens in genetically engineered DC using state-of-the-art lentiviral vector (LV) technology allows us to generate functionally stable human DC (known as IL-10-tolDC) that suppress antigen-specific Teff cells and promote antigen-specific Tregs</p>	
<p>Aims: A1: To define in vitro stability and in vivo biodistribution of IL-10-tolDC; A2: To investigate the tolerogenic potential of IL-10-tolDC, their mode of action and ability to promote/restore tolerance in vitro and in pre-clinical models; A3: To define the genetic/epigenetic landscape of IL-10-tolDC.</p>	
<p>Expected Results: R1: Characterization of IL-10-tolDC bio-distribution, stability, survival, and function in pre-clinical models; R2: Preclinical development of a IL-10-tolDC-based cell therapy; R3: Better understanding of the molecular mechanisms underlying regulatory DC biology and identification of targetable pathways to boost IL-10-mediated tolerance.</p>	
<p>Planned secondment: (1) An international 2-month secondment to Prof. Jordi Ochando's lab is planned as a networking, technical and scientific exchange. (2) An international, intersectoral 2-month secondment to Cimaas BV is planned to support preclinical development of gene therapy approaches to stabilizing MRC function.</p>	
<p>Enrolment in Doctoral degree(s): University Vita Salute</p>	
<p>Project-specific selection criteria: Degree in Biological Sciences, Biotechnology or related disciplines with skills in molecular and cellular biology as well as primary human cell culture and manipulation. The use of FACS/sorter and experience in animal handling is a significant plus.</p>	
<p>Recommended reading: doi: 10.1182/blood-2009-07-234872; doi: 10.3389/fimmu.2018.00682; doi: 10.1038/s41423-019-0218-0</p>	

ESR4 Trained Immunity in Regulatory Macrophages	
Host Institution	Instituto de Salud, Carlos III, Madrid, Spain
Primary Supervisor	Prof. OCHANDO, Jordi
Email address	jordi.ochando@mssm.edu
Planned duration	36 months
Subject Area	Molecular & Cellular Immunology; Epigenomics
<p>Introduction: The innate immune system displays long-term changes in its functional capacities through epigenetic programming of macrophages and monocytes, a phenomenon known as ‘trained immunity.’ Trained immunity is likely to be a critical issue in MRC-based therapy, affecting the quality of therapeutic cell products, their functional stability and their effects in patients. This project concerns an innovative treatment paradigm in which innate immune cells are specifically targeted and “untrained” using drug-loaded nanobiologics. A trained immunity-inhibiting nanobiologic library of high-density lipoprotein (HDL) derived nanomaterials with different immunomodulatory payloads will be created using advanced microfluidics technology. These highly innovation nanobiologics will complement future cell-based therapeutic approaches, both in terms of producing superior MRC-based products and co-treatment of patients receiving MRC-based therapies.</p>	
<p>Aims: A1: To develop nanobiologic library technology to regulate trained immunity; A2: To evaluate the robustness of our trained immunity-inhibitory nanobiologics to prevent organ transplant rejection; A3: To test trained immunity-inhibitory nanobiologics as substances added to cell cultures during manufacture of MRC-based therapeutic products.</p>	
<p>Expected Results: R1: Development of optimized nanoformulations that target different molecular pathways associated with trained immunity. This program’s successful completion will yield targeted immunotherapies not only to potentially treat transplant patients, but also autoimmune disorders and allergies.</p>	
<p>Planned secondment: An international, intersectoral 6-month secondment to the non-academic group of Dr. Gregori (OSR, M22) is planned to support preclinical development of gene therapy approaches to stabilising MRC function.</p>	
<p>Enrolment in Doctoral degree(s): Complutense University of Madrid</p>	
<p>Project-specific selection criteria: Practical experience of common techniques in Molecular Biology and Cellular Immunology.</p>	
<p>Recommended reading: [1] Ochando, J. et al. Trained immunity in organ transplantation. <i>Am J Transplant</i>. 2019 Sep 27. doi: 10.1111/ajt.15620. [2] Braza, MS. et al. Inhibiting Inflammation with Myeloid Cell-Specific Nanobiologics Promotes Organ Transplant Acceptance. <i>Immunity</i>. 2018 Nov 20;49(5):819-828.e6. doi: 10.1016/j.immuni.2018.09.008.</p>	

ESR5	
A data science approach to characterising tolerogenic myeloid regulatory cell therapies in a standardised manner	
Host Institution	Newcastle University, United Kingdom
Primary Supervisor	Dr. LORD, Phillip (primary) Dr. HILKENS, Catharien
Email address	phillip.lord@newcastle.ac.uk - catharien.hilkens@newcastle.ac.uk
Planned duration	36 months
Subject Area	Computational Biology; Data Science
<p>Introduction: Basic and translational research in immunoregulatory cell-based therapy has been limited by the intrinsically small-scale of clinical trials, which hampers comparison, standardization and reproducibility. Our group has spearheaded initiatives to define reporting guidelines for cell-based therapies, which serve as a foundation for further standardization efforts. This project aims to combine data from consortium partners with publically available knowledge to achieve two main goals: firstly, to unify descriptions of the pharmacological properties of tolerogenic cell products in order to support standardisation of their quality-control; secondly, to predict the immune regulatory effects of tolerogenic cell products, which will inform the design of standardised immunomonitoring in clinical trials.</p>	
<p>Aims: A1: To build a warehouse of publically available data on tolerogenic cell therapies and incorporating relevant background resources, including pathway, cell development and pharmacological data sets. A2: To embed good data management practice, enabling reproducibility and data sharing as the default behaviour within the consortium. A3: To enable semantic descriptions to cell products and immunomonitoring read-outs. A4: To predict optimal strategies for quality-control and immunomonitoring by using a combination of semantic similarity, rule-based learning and other computational learning techniques.</p>	
<p>Expected Results: This research provides an innovative solution for predicting the immune regulatory effects of tolerogenic MRC-based products by creating an integrated, big data set scale through standardisation and data warehousing. R1: The proposed 'data warehouse' will represent a major scientific output of this project, which will be an extremely value resource for INSTRuCT partners and the wider field. R2: Development of recommendations about quality-control testing of MRC products; R3: Development of recommendations about the optimal conditions for ex vivo generation of MRC products.</p>	
<p>Planned secondment: (1) 3-month secondment to SciBite (Cambridge, UK, M18) to learn new tools for the curation and management of biomedical data. (2) An international, 2-month secondment to Prof. Nathalie Cools' lab to learn about new GMP-compliant technologies and regulations for manufacturing of MRC-based products.</p>	
<p>Enrolment in Doctoral degree(s): Newcastle University</p>	
<p>Project-specific selection criteria: As this is a cross-disciplinary project, a Masters degree or equivalent in bioinformatics, or computational biology is preferable. Also acceptable, a BSc or equivalent in Computing Science, a BioMedical Science (inc. Immunology), with a strong and demonstrable interest in the other discipline. Experience with (some of) knowledge representation, biological data handling, databases or data integration.</p>	
<p>Recommended reading: [1] Lord P, [...], and Hilkens CM. Minimum information about tolerogenic antigen-presenting cells (MITAP): a first step towards reproducibility and standardisation of cellular therapies. PeerJ 2016, 4, 1-14. [2] Misirli G et al. Data Integration and Mining for Synthetic Biology Design. ACS Synthetic Biology 2016, 5(10), 1086–1097. [3] Bandrowski A, et al. The Ontology for Biomedical Investigations. PLoS ONE 2016, 11(4), e0154556.</p>	

ESR6	
Investigating molecular mechanisms of human autologous tolerogenic DC	
Host Institution	University of Nantes, France
Primary Supervisor	Dr. MOREAU, Aurélie
Email address	aurelie.moreau@univ-nantes.fr
Planned duration	36 months
Subject Area	Molecular & Cellular Immunology; Cellular Metabolism
<p>Introduction: Autologous Tolerogenic Dendritic Cells (ATDC) exhibit tolerogenic properties in vitro and in vivo. Human ATDCs are currently being investigated in a Phase I/II clinical trial in kidney transplantation. ATDC produce high levels of lactate that steer T cell responses towards tolerance. This project concerns further investigation of molecular mechanisms of ATDC action using cutting-edge techniques in order to develop of innovative methods for quantifying therapeutic effects of ATDC in solid organ transplant recipients.</p>	
<p>Aims: A1: To examine the phenotypic and functional heterogeneity of ATDC by single cell RNASeq and epigenetic profiling studies. A2: Using LV coding for shRNA, we will delete molecules thought to be relevant to the regulatory function or stability of ATDCs. Gene-edited ATDCs will then be examined in vitro and in vivo using established assays and animal models. A3: The utility of functionally important molecules as biomarkers of ATDC effects in vivo will be explored using archived blood samples from patients treated with ATDCs or other immune regulatory cells.</p>	
<p>Expected Results: R1: Understanding of the molecular mechanisms of ATDC action, allowing us to systematically compare ATDC function with other MRC products. R2: Novel molecules contributing to ATDC action will be mechanistically investigated. R3: Innovative tests for ATDC pharmacodynamic effects will be developed, standardised and clinically validated.</p>	
<p>Planned secondment: (1) An intersectoral secondment of 2-months to Immunotech which produces CE/IVD-marked reagents and assays. (2) A 2-month intersectoral secondment to Silvia Gregori's lab is critical to aim A1.</p>	
<p>Enrolment in Doctoral degree(s): University of Nantes</p>	
<p>Project-specific selection criteria: Master degree in Science, strong knowledge in immunology and experience with (or interest for) bioinformatic tools.</p>	
<p>Recommended reading: [1] Marin et al. Human tolerogenic dendritic cells regulate immune responses through lactate synthesis. Cell Metabolism. 2019 Dec 3. [2] Marín E, Cuturi MC, Moreau A. Tolerogenic Dendritic Cells in Solid Organ Transplantation: Where Do We Stand? Front Immunol. 2018 Feb 19;9:274. doi: 10.3389/fimmu.2018.00274</p>	

ESR7	
Computational characterisation, classification and deconvolution of myeloid regulatory cells	
Host Institution	University of Regensburg, Germany
Primary Supervisor	Prof. REHLI, Michael - Prof. SPANG, Rainer
Email address	michael.rehli@ukr.de - rainer.spang@ukr.de
Planned duration	36 months
Subject Area	Computational Biology; Transcriptomics
<p>Introduction: The distinctive tolerogenic signatures of MRC (as well as the signals required to induce and maintain them) are poorly understood, as are the fate and phenotypic stability of adoptively transferred cells in vivo. This predominantly computational project is concerned with improving our understanding of differentiation routes, transcriptional and epigenetic features of MRCs in vitro, as well as their adaptation in vivo to optimize tolerogenic cell products.</p>	
<p>Aims: A1: To devise computational methodology for the quantification and molecular characterization of MRC subsets in transcriptome or epigenome profiles from bulk samples such as blood or tissue. We will build on established deconvolution methods such as Cyber Sort and our in-house adaptive deconvolution algorithm based on loss-function learning. The method will be applied to public and consortium data. A2: Modelling myeloid differentiation both in vitro and in vivo from transcriptome and epigenetic data to unravel regulatory networks, co-expression modules and corresponding pathways important for tolerogenicity of myeloid cell products. SB considers the implementation risk of this project is low because all required data are public or already shared.</p>	
<p>Expected Results: R1a: Novel deconvolution algorithms for an improved quantification of regulatory immune cells in bulk samples will be developed and implemented. The method will be open source and freely available to the scientific community. R1b: Annotation of existing bulk profile data sets from transcriptomics and epigenomics resources such as TCGA with computationally estimated immune cell composition. These will be made freely available in web applications and in portable containerized data warehouses that we will develop using the in-house LYRA system. R2a: Identification of latent factors that drive myeloid differentiation in cell therapy settings. These factors will inform the deconvolution models and guide their learning phase. R2b: Identification of signaling and regulatory pathways controlling tolerogenic features of cell products and computational prediction of candidate drugs that may improve the phenotypic stability or tolerogenic functions.</p>	
<p>Planned secondment: The ESR will undertake a 2-month secondment at Miltenyi Biotec to expand their knowledge of management and analysis of immune cell-related NGS data.</p>	
<p>Enrolment in Doctoral degree(s): University of Regensburg</p>	
<p>Project-specific selection criteria: Degree in Mathematics, Computer Science, Physics or other project-relevant subject.</p>	
<p>Recommended reading: Görtler, F. et al. (2019) Loss-function learning for digital tissue deconvolution. https://arxiv.org/pdf/1801.08447.pdf</p>	

ESR8	
Development of Pharmaceutical Release Processes for DC-based Therapy	
Host Institution	Cimaas BV, The Netherlands
Primary Supervisor	Prof. GERMERAAD, Wilfred
Email address	w.germeraad@cimaas.com
Planned duration	48 months
Subject Area	GMP Manufacturing; Quality Control; Cellular Immunology
<p>Introduction: In order to ensure safety and clinical efficacy, stringent criteria for the identity, purity, potency sterility and stability of therapeutic cell-based products must be established, implemented and validated as part of sterile pharmaceutical manufacturing processes. Cimaas specializes in manufacture of myeloid cell-based therapies using fully-closed, automated systems. In particular, CIM has developed innovative, GMP-compliant approaches for mRNA transfection of monocyte-derived cells. This project concerns integration of cutting-edge assays of regulatory macrophage (Mreg) and DC phenotype and function into semi-automated, fully closed manufacturing procedures to deliver robust, informative, scalable and cost-effective quality-control tests for process intermediates and cell products. Current QC protocols involve open handling steps but through this project, Cimaas aims to establish automated assays connected into a closed system workflow.</p>	
<p>Aims: A1a: To assimilate and adapt novel assays for myeloid cell phenotype and function that provide a minimal adequate profile of a cell product's identity, potency and stability in the shortest time. A1b: To define a uniform set of release criteria in MRC-based therapies. A2: To participate in development of a final formulation of a frozen DC-based product that is free of animal components. A3: To characterize the MHC class II peptide presentation profile by mRNA electroporated DC. This project exemplifies how INSTRuCT can accelerate innovation in MRC-based therapy through commercial adoption of basic scientific discoveries. Cimaas already exchanged know-how with SQ, UA, UHREG and OSR. Further collaborations are anticipated with UNEW, Miltenyi and IGTP. SB has minimized project implementation risks through detailed planning of collaborations and ensuring sufficient redundancy in scientific deliverables.</p>	
<p>Expected Results: R1: Implementation and validation of QC assays for myeloid cell products within automated, closed manufacturing systems, including release testing for identity, purity, potency, sterility and stability. R2: Approval for an end-to-end sterile manufacturing process that can be used to produce animal component-free, frozen Mreg- and DC-based products with high viability and functionality after thawing. R3: Profiling of peptides in MHCII molecules expressed by mRNA electroporated DC.</p>	
<p>Planned secondment: The ESR will undertake a 2-month secondment at Sanquin to master DC-CD4 T cell co-cultures and optimized release assays (ie. MHC-II multimer analyses) to develop antigen-specific release assays for electroporated DC.</p>	
<p>Enrolment in Doctoral degree(s): University of Maastricht</p>	
<p>Project-specific selection criteria: Strong background in Immunology; Interest in product development; main competencies: flexibility, creativity, can-do mentality</p>	
<p>Recommended reading: [1] Oth T., et al. Pathogen recognition by NK cells amplifies the pro-inflammatory cytokine production of monocyte-derived DC via IFN-γ. BMC Immunol. 2018 Feb 13; 19(1):8. [2] Oth T., et al. Pathogen-Associated Molecular Patterns Induced Crosstalk between Dendritic Cells, T Helper Cells, and Natural Killer Helper Cells Can Improve Dendritic Cell Vaccination. Mediat Inflamm: 2016; 2016:5740373. [3] Oth T., et al. Potency of Both Human Th1 and NK Helper Cell Activation is Determined by IL-12p70-Producing PAMP-Matured DCs. J Interferon Cytokine Res. 2015 Sep;35(9):748-58.</p>	

ESR9	
Personalized MRC-based therapy: innovative strategies to improve efficacy	
Host Institution	King's College London, United Kingdom
Primary Supervisor	Prof. SANCHEZ FUEYO, Alberto - Prof. LOMBARDI, Giovanna
Email address	sanchez_fueyo@kcl.ac.uk - giovanna.lombardi@kcl.ac.uk
Planned duration	36 months
Subject Area	Computational Biology; Personalized Medicine
<p>Introduction: We propose to create a highly personalised approach based on surrogate immunological biomarkers to assess tolerance induction in order to direct treatment with MRC-based therapies according to patients' individual needs.</p>	
<p>Aims: A1: To perform sequential high-throughput phenotypic analysis of peripheral blood leucocytes from liver transplant recipients performing immunosuppression withdrawal to achieve tolerance by CyTOF, RNASeq and epigenetic landscaping (LIFT trial, >100 patients enrolled and centralized by KCL). A2: To evaluate antigen-specific responses in the same patients using in vitro functional assays, as well as profiling TCR repertoires of Tregs and effector T cells. A3: To correlate the distribution of antigen-specific effector and regulatory T cells based on TCR sequencing with peptide-specific MHC II tetramer staining in flow cytometry. A4: To develop bioinformatic tools to integrate phenotypic, transcriptional and epigenetic patterns in order to evaluate the function and stability of mixed leucocyte populations. A5: To apply the designed tolerogenic signatures and specific immune cell characterization methods to evaluate and compare the immunological effects of MRC-based and Treg-based therapies in liver (ThRIL, LITE studies at our center) and kidney transplant recipients (archived samples from UHREG, UN-CRTI).</p>	
<p>Expected Results: R1: The immunomonitoring techniques established and validated on clinical trials will provide new tools to study immunological mechanism of tolerance, monitor disease progression, evaluate therapeutic effect, stratify candidates for MRC-based immunotherapy, and serve as prognostic markers of clinical outcome. R2: The implementation of bioinformatic platforms to improve the identification and characterization of regulatory and effector cells in complex multicellular samples, such as peripheral blood or biopsies, will identify novel biomarkers that can be developed as innovative clinical assays.</p>	
<p>Planned secondment: An intersectoral secondment of 5-months to UCB Pharma is planned to provide the student with experience in market-driven biomarker research and to pursue aims A1 and A2.</p>	
<p>Enrolment in Doctoral degree(s): King's College London</p>	
<p>Project-specific selection criteria: Desirable experience in molecular biology laboratory, preferable experience with techniques, such as Western Blotting, flow cytometry and qPCR. Knowledge of Immunology and in particular innate immunity preferable.</p>	
<p>Recommended reading: [1] Feng, S., [...] and Sánchez-Fueyo, A. Evidence of Chronic Allograft Injury in Liver Biopsies From Long-term Pediatric Recipients of Liver Transplants. <i>Gastroenterology</i>. 2018; 155(6):1838-1851.e7. doi: 10.1053/j.gastro.2018.08.023. [2] Sánchez-Fueyo, A. et al. Applicability, Safety And Biological Activity Of Regulatory T Cell Therapy In Liver Transplantation. <i>Am J Transplant</i>. 2019. doi: 10.1111/ajt.15700.</p>	

ESR10	
Development and validation of antigen-specific assays for T and B cell responses following tolerance-inducing treatments with MRC-based therapies	
Host Institution	Sanquin Blood Supply and University of Amsterdam, The Netherlands
Primary Supervisor	Prof. ten BRINKE, Anja - Prof. van HAM, Marieke
Email address	a.tenbrinke@sanquin.nl - m.vanham@sanquin.nl
Planned duration	48 months
Subject Area	Cellular Immunology; Personalized Medicine
<p>Introduction: This project aims to develop versatile peptide-specific MHCII tetramers to increase the number of specific T cell responses that can be analysed in patients with autoimmune diseases. In addition, we will perform antigen-specific T cell receptor (TCR), B cell receptor (BCR) and single cell RNA sequencing. These innovations will allow more complete interpretation of the immunological and therapeutic impact of MRC-based therapies in clinical trials.</p>	
<p>Aims: A1: To establish standardised and validated immunomonitoring assays of CD4+ T cell responses against disease-relevant antigens that will be useful for evaluating the efficacy and safety of tolerance-inducing MRC-based therapies. A2: To assess the effects of MRC-based therapies on auto-, allo- or recall- Ag-specific CD4+ T cell responses using new or archived samples from consortium partners; A3: To develop standardised and validated assays to measure Ag-specific memory B cell and Ag-specific antibody formation. Analysis of patient cohorts not treated with MRC-based therapies might be performed as an alternative proof-of-concept.</p>	
<p>Expected Results: R1: Standardization of proliferation dye-based assay to monitor ag-specific CD4+ T cell responses; R2: Up-scaling production of patient and antigen-tailored in house developed peptide-exchangeable MHCII tetramers; R3: Establishment of an assay to measure antigen-specific antibody and memory B cell responses; R4: Analysis of Ag-specific T and B cell responses before, during and after tolerance inducing cell therapy to study safety and efficacy and to obtain insights in the mode-of-action of the applied immunotherapy.</p>	
<p>Planned secondment: (1) An international 2-month secondment is planned to the lab of Dr. Nathalie Cools (Belgium) to provide the ESR with training in METC application and clinical trial immunomonitoring, as well as logistics of sample retrieval and clinical database registration during conduct of clinical trials. (2) An international, 2-month industrial secondment to Miltenyi (Germany) will support preclinical development of commercially viable antigen-specific immune monitoring assays.</p>	
<p>Enrolment in Doctoral degree(s): University of Amsterdam, the Netherlands</p>	
<p>Project-specific selection criteria: [1] A Master degree in Biomedical Sciences or a similar education level. [2] Knowledge of Immunology is required and a proven track record in research in cellular immunology is a prerequisite. [3] Team player with good communication skills.</p>	
<p>Recommended reading: [1] Ten Brinke A., et al. Monitoring T-Cell Responses in Translational Studies: Optimization of Dye-Based Proliferation Assay for Evaluation of Antigen-Specific Responses. <i>Front Immunol.</i> 2017; 8:1870. doi: 10.3389/fimmu.2017.01870. [2] Lighaam LC., et al. . In vitro-Induced Human IL-10+ B Cells Do Not Show a Subset-Defining Marker Signature and Plastically Co-express IL-10 With Pro-Inflammatory Cytokines. <i>Front Immunol.</i> 2018; 9:1913. doi: 10.3389/fimmu.2018.01913. [3] Willekens B., et al. Tolerogenic dendritic cell-based treatment for multiple sclerosis (MS): a harmonised study protocol for two phase I clinical trials comparing intradermal and intranodal cell administration. <i>BMJ Open.</i> 2019;</p>	

ESR11	
Development of an affordable & scalable process for tolDC manufacturing	
Host Institution	University of Antwerp, Belgium
Primary Supervisor	Prof. COOLS, Nathalie
Email address	nathalie.cools@uza.be
Planned duration	48 months
Subject Area	GMP Manufacturing; Quality Control; Cellular Immunology
<p>Introduction: Development of MRC-based products has been restricted by their cost and complexity. This is especially true when a unique batch is manufactured for each patient using labor-intensive, multiple-step processes. Successful future commercialization of cell-based, patient-specific products will require innovative solutions to unique manufacturing challenges and constraints; critically, any technological solutions will have to be affordable, reliable and not introduce new process-related risks. In this project, we aim to unlock new opportunities for the development of commercially viable and safe cell-based treatments by co-development of next generation technologies to facilitate lean, cost-effective manufacturing of MRC products, in particular tolDC. In collaboration with Antleron, an end-to-end closed and automated cell culture system will be developed that contains all features essential for safe production of cell therapies: precise control over temperature and fluid flow, mixing and cell seeding capability, internal refrigeration, light protection, various sterile access points to verify cell differentiation, biosensors to monitor cell performance and automated computer-controlled record keeping.</p>	
<p>Aims: A1: To identify biological factors contributing to the optimal micro-environment for MRC generation that will allow redesign of MRC manufacturing processes to ensure product consistency and quality. A2: To engineer 4D environments for MRC generation that increase process reproducibility and robustness, and optimize roll-out of MRC products to the market.</p>	
<p>Expected Results: R1: Novel biological insights into the differentiation process of tolDC and other MRC types, such as the influence of environmental factors (e. g. cell density, growth surface material, pH, dissolved oxygen and shear stress) affect quality-control measures and potency of MRC-based products. This information will be invaluable for the parallel development of a scalable and automated process. R2: Development of an R&D scale proof-of-concept bioreactor-driven tolDC differentiation process with integrated up- and down-stream unit operations, and built-in quality control measures to monitor critical cell culture parameters. R3: Mapping of cost of goods in order to transition from R&D scale to an industrialized process.</p>	
<p>Secondments: (1) An intersectoral secondment of 6 months to Antleron is planned to provide the ESR with training in cell growth micro-environments and experience in designing scale-up and scale-out procedures in GMP conditions. Aim 2 is dependent upon this secondment. (2) An international, intersectoral secondment of 2 months to CiMaas BV will provide the ESR with a market-oriented perspective of manufacturing and roll-out of MRC-based products.</p>	
<p>Enrolment in Doctoral degree(s): University of Antwerp</p>	
<p>Project-specific selection criteria: Master's degree in Bio(medical) Engineering, Biotechnology, Mechanical Engineering or equivalent qualifications. Practical laboratory experience preferred.</p>	
<p>Recommended reading: [1] Willekens B, et al. Tolerogenic dendritic cell-based treatment for multiple sclerosis (MS): a harmonised study protocol for two phase I clinical trials comparing intradermal and intranodal cell administration. <i>BMJ Open</i>. 2019 Sep 9;9(9):e030309. doi: 10.1136/bmjopen-2019-030309. [2] Derdelinckx J, et al. Clinical and immunological control of experimental autoimmune encephalomyelitis by tolerogenic dendritic cells loaded with MOG-encoding mRNA. <i>J Neuroinflammation</i>. 2019 Aug 15;16(1):167. doi: 10.1186/s12974-019-1541-1. [3] Lee WP, et al. Immunomodulatory Effects of 1,25-Dihydroxyvitamin D(3) on Dendritic Cells Promote Induction of T Cell Hyporesponsiveness to Myelin-Derived Antigens. <i>J Immunol Res</i>. 2016;2016:5392623.</p>	

ESR12 Classification of the human Myeloid Regulatory Network using Machine Learning on Multiparametric Immunofluorescence Image Data	
Host Institution	Miltenyi Biotec BV & Co. KG , Bergisch Gladbach, Germany
Primary Supervisor	Dr. KOLLET, Jutta
Email address	jutta.kollet@miltenyibiotec.de
Planned duration	36 months
Subject Area	Computational Biology; Image Analysis
<p>Introduction: It is critical to understand differences between myeloid cell populations in the context their surrounding tissue microenvironments. This project will identify and systematically characterize the MRC networks in tissues through development of computational methods to analyze multiparametric immunofluorescence image data (MACSima™ technology). The composition and spatial distribution of MRC subsets in tissues will be classified using machine learning on a knowledge database.</p>	
<p>Aims: A1: To apply model-based machine learning algorithms on multiparametric immunofluorescence image data of pancreatic cancer sections to identify and characterize the tolerogenic myeloid regulatory network. A2: To generate experimental image datasets from unrelated tissue sections to validate and optimize the initially generated classifier. A3: To optimize predictions and analysis tools by inclusion of self-learning components.</p>	
<p>Expected Results: R1: The phenotype and spatial network of MRC in tissues (eg. tumour, transplant) will be characterized; thereby phenotypically distinct subpopulations of MRC will be identified. R2: Understanding of the correlation of transcriptome and proteome data and of the function of cell types will be obtained from collaborations with UHREG. This is particularly important, since public NGS datasets are frequently used for biomarker/ target discovery. R3: Data-driven marker collections ('self-learning' algorithms will automatically update a data base) will be used for identification and prediction of cell composition. R4: Optimization and commercialization of antibody panels for kits and diagnostics for use in identifying or isolating MRC subsets using the newly developed software tools. R5: Software for automated annotation and cell type classification in immunofluorescence images and novel visualization methods for multiparametric datasets will be established.</p>	
<p>Planned secondment: A 2-month secondment to the labs of Professors Spang and Rehli is planned to train the ESR in analyzing different types of 'Big Data' in order to make correlations with imaging-based proteome data.</p>	
<p>Enrolment in Doctoral degree(s): University of Regensburg</p>	
<p>Project-specific selection criteria: Degree in Bioinformatics , Computer Science, or Biology with project-relevant subject.</p>	
<p>Recommended reading: Lin et al., 2018: eLife 2018;7:e31657; Ronneberger et al., 2015: arXiv:1505.04597; MACSima technology: https://www.miltenyibiotec.com/DE-en/products/macs-imaging-and-microscopy/ultra-high-content-imaging.html</p>	

ESR13

Genes & pathways associated with the tolerogenic capacity of tolDC-VitD3

Host Institution	Institute of the Germans Trias i Pujol Foundation, Barcelona, Spain
Primary Supervisor	Prof. MARTINEZ CACERES, Eva
Email address	emmartinez.germanstrias@gencat.cat
Planned duration	36 months
Subject Area	Molecular & Cellular Immunology; Translational Research

Introduction: Our research group has developed an autologous, antigen-specific cell-based therapeutic product for treatment of multiple sclerosis (MS) known as, “tolDC-VitD3.” We are now conducting a **Phase-I dose-escalation** clinical trial of **tolDC-VitD3 therapy in patients with MS** (EUDRA CT 2015-003541-26). 12 patients with active MS will receive tolDC-VitD3 by intranodal injection, followed by a 24-month observation and immune monitoring period. This project investigates pharmacodynamic effects of tolDC-VitD3 treatment in patients enrolled in this clinical trial.

Aims: **A1:** To perform silencing /downmodulation of candidate molecules on cells at different stages during the differentiation of monocytes into tol-DC-vitD3 or stimulatory DC with the aim of identifying transcriptional regulatory factors (TFs) governing the tolerogenic DC programme. **A2:** To analyse the contribution of TFs identified in A1 to overall tolerogenic phenotype human tolDC-vitD3 using established co-culture assays looking at T cell differentiation and effector functions. **A3:** To analyse the functional effect of tolDC VitD3 on peripheral blood T cells of multiple sclerosis patients compared to those of healthy donors. **A4:** To examine antigen-specific T and B cell responses of MS patients in the tolDC-VitD3 clinical trial (before, during and after cell therapy) as a low-risk project.

Expected Results: **R1:** New potential therapeutic targets involved in tolerance induction by tolDC-VitD3 will be identified through our in vitro experiments and analysis of patient samples. **R2:** Strategies will be developed to support tolDC-VitD3 treatment using drugs that interact with immunological networks affected by tolDC-VitD3 administration. **R3:** Novel clinical indications for tolDC-VitD3 will be investigated, especially other neuroinflammatory diseases and solid organ transplantation.

Planned secondment: **(1)** An international secondment of 2-months to Prof. van Ham is planned to undertake collaborative work on aim A4. **(2)** A 2-month intersectoral secondment to Aniling is planned. **(3)** An intersectoral secondment of 2-months will be spent in the academic department of Prof. Ochando where the student will learn about Transplant Immunology and solid organ transplant models.

Enrolment in Doctoral degree(s): **Autonomous** University of Barcelona

Recommended reading: **[1]** Navarro-Barriuso J, et al. MAP7 and MUCL1 Are Biomarkers of Vitamin D3-Induced Tolerogenic Dendritic Cells in Multiple Sclerosis Patients. *Front Immunol.* 2019. **[2]** Navarro-Barriuso J, et al. Searching for the Transcriptomic Signature of Immune Tolerance Induction-Biomarkers of Safety and Functionality for Tolerogenic Dendritic Cells and Regulatory Macrophages. *Front Immunol.* 2018 Sep 19;9:2062. **[3]** Navarro-Barriuso J et al. Comparative transcriptomic profile of tolerogenic dendritic cells differentiated with vitamin D3, dexamethasone and rapamycin. *Sci Rep.* 2018 Oct 8;8(1):14985.

ESR14 Therapeutic Targeting of Mreg - T cell Interactions	
Host Institution	University Hospital Regensburg, Germany
Primary Supervisor	Dr. HUTCHINSON, James Alexander
Email address	james.hutchinson@ukr.de
Planned duration	36 months
Subject Area	Molecular & Cellular Immunology; Immunopharmacology
<p>Introduction: Administration of human regulatory macrophages (Mreg) has shown early clinical promise as an adjunct immunosuppressive cell-based therapy in solid organ transplantation. This project proposal addresses the hypothesis that recipient T cell immunity is actively regulated through direct allorecognition of donor-derived Mregs and conversion of naive CD4+ T cells to FoxP3+ induced regulatory T cells. A sensitive and rapid functional screening assay has been developed to measure Mreg-mediated conversion of naïve CD4+ to FoxP3+ iTregs (miTregs). We propose to use this in vitro assay system to define novel mechanisms contributing to generation, stabilization or expansion of miTregs.</p>	
<p>Aims: A1: To screen libraries of antibodies and small molecules for substances that affect miTreg generation using our established miTreg assay. A2: To investigate the contribution of Mreg-specific or miTreg-specific genes identified from previous transcriptional profiling studies to Mreg-induced Treg generation using gene-editing or -silencing techniques in our established assay system. A3: To investigate the pharmacological effects of substances identified by our screening assays in a human-into-mouse reconstitution model of human Mreg-driven allogeneic Treg conversion.</p>	
<p>Expected Results: R1: Original basic scientific insights into the suppressor functions of Mregs, including identification of new suppressive mechanisms, will follow from the functional screening experiments; R2: agents that enhance or repress miTreg generation will be identified and their effects characterized; R3: New Mreg-specific mAbs and clinical tests will be developed.</p>	
<p>Planned secondment: (1) An international, intersectoral secondment of 3 months to AstraZeneca will provide the ESR with an industrial perspective of drug screening and a broader view of pharmaceutical development.</p>	
<p>Enrolment in Doctoral degree(s): University of Regensburg</p>	
<p>Project-specific selection criteria: Practical experience of common techniques in Molecular Biology and Cellular Immunology.</p>	
<p>Recommended reading: Riquelme, P. et al. TIGIT+ iTregs elicited by human regulatory macrophages control T cell immunity (2018) Nature Communications. 9, 2858. https://doi.org/10.1038/s41467-018-05167-8</p>	

ESR15	
Route of delivery of tolerogenic dendritic cells	
Host Institution	Newcastle University, United Kingdom
Primary Supervisor	Dr. HILKENS, Catharien - Prof. ISAACS, John - Dr. THELWALL, Pete
Email address	catharien.hilkens@newcastle.ac.uk - john.isaacs@newcastle.ac.uk - pete.thelwall@newcastle.ac.uk
Planned duration	36 months
Subject Area	Cellular Immunology; Translational Research
<p>Introduction: We have developed a robust, GMP-compatible process to generate stable tolDC from patients with rheumatoid arthritis (RA). We recently completed a phase I trial showing that tolDC administration into an inflamed knee joint is safe. Diminished synovial inflammation was observed in the knee joint of patients treated with the highest tolDC dose; however no systemic changes were observed, either in overall disease activity or immune markers in blood. RA is a systemic disease, so tolDC may be more effective if they migrated to secondary lymphoid tissue. Therefore, we need to know (i) where tolDC migrate to after injection and (ii) whether they modulate T cell responses systemically. The aim of this clinically orientated project is to develop and validate tools required for addressing these questions in on-going clinical studies.</p>	
<p>Aims: A1: To assess the distribution of tolDC loaded with relevant citrullinated peptides (citP) injected via different routes into patients by 19F-magnetic resonance imaging (MRI); A2: To assess whether tolDC treatment modulates citP-specific T cell responses assayed by the use of MHCII-citP tetramers.</p>	
<p>Expected Results: R1: Determination of the sensitivity of detecting 19F-labelled tolDC by MRI; R2: Confirmation that 19F-labelling of tolDC does not affect their migratory ability and tolerogenic functions; R3: Establishment of an immunomonitoring protocol to assess functional properties (e.g. cytokine production, suppressive capability) of citP-specific T cells from RA patients. For this work we will make use of relevant citP-MHCII tetramers provided by our partners of the RTCure consortium and collaborations with ESR10. R4: Application of these immunomonitoring protocols to samples obtained from RA patients before and after tolDC administration.</p>	
<p>Planned secondment: An intersectoral secondment of 6 months to Alcyomics will provide the ESR with a perspective of a commercial pre-clinical service provider. Specifically, the ESR will define efficacy and safety of tolDC in a validated skin explant model.</p>	
<p>Enrolment in Doctoral degree(s): Newcastle University</p>	
<p>Project-specific selection criteria: Masters degree in a biological or biomedical science with laboratory experience in immunological techniques preferable.</p>	
<p>Recommended reading: Spiering R, Jansen MAA, Wood MJ, Fath AA, Eltherington O, Anderson AE, Pratt AG, van Eden W, Isaacs JD, Broere F, Hilkens CMU. Targeting of tolerogenic dendritic cells to heat-shock proteins in inflammatory arthritis. <i>J Transl Med.</i> 2019 Nov 14;17(1):375. doi: 10.1186/s12967-019-2128-4; Anderson AE, Swan DJ, Wong OY, Buck M, Eltherington O, Harry RA, Patterson AM, Pratt AG, Reynolds G, Doran JP, Kirby JA, Isaacs JD, Hilkens CM. Tolerogenic dendritic cells generated with dexamethasone and vitamin D3 regulate rheumatoid arthritis CD4(+) T cells partly via transforming growth factor-β1. <i>Clin Exp Immunol.</i> 2017 Jan;187(1):113-123. doi: 10.1111/cei.12870; Bell GM, Anderson AE, Diboll J, Reece R, Eltherington O, Harry RA, Fouweather T, MacDonald C, Chadwick T, McColl E, Dunn J, Dickinson AM, Hilkens CM, Isaacs JD. Autologous tolerogenic dendritic cells for rheumatoid and inflammatory arthritis. <i>Ann Rheum Dis.</i> 2017 Jan;76(1):227-234. doi: 10.1136/annrheumdis-2015-208456.</p>	