Call for 8 PhD fellowships in

"An integrated approach to restore tolerance in autoimmune disease"

Introduction

TOLERATE training network aims at training Doctoral Candidates' (DCs) to acquire the skills to develop different innovative strategies to treat autoimmune diseases, to identify the most promising strategies or a combination of strategies, to setup clinical trials and to develop a roadmap to bring a novel therapeutic agent to the market. This all will be done in a highly interdisciplinary and intersectoral environment.

Interdisciplinarity allows to introduce innovative tolerogenic therapies developed for cancer, Chimer Antigen Receptor (CAR)-T cell therapies, into the world of autoimmune disease and to apply nanotechnology and protein-engineered tolerogenic vaccines to re-establish immune tolerance in autoimmune disease. Both the presence of academia and industry provides a platform for in-depth preclinical studies and a realistic possibility for future commercialization of the novel therapies. Clinicians in the consortium with expertise in setting-up and running clinical trials for novel drugs assure that developed novel therapies in TOLERATE will find their way to the clinic in the future. Developing novel therapies for autoimmune diseases goes close together with a thorough knowledge on the long-term consequences of living with an autoimmune disease. Since many autoimmune diseases are rare diseases, setting up international uniform databases and biobanks is crucial to understand the long-term pathophysiology of the disease and to guarantee optimal use of (novel) therapies. TOLERATE will train 8 DCs who will hence have the expertise and skills to work in and setup interdisciplinary and intersectoral projects. The ground-breaking training programme will provide the DCs with a unique clinical training.

Additional training in ethical, regulatory and legal aspects together with a training in innovation management of therapeutics and diagnostics for autoimmune diseases will prepare the DCs for the European job market.

Research projects

The research activities implemented in TOLERATE have the following objectives:

1. **To develop innovative CAR-T or T cell receptor (TCR)-engineered T cell therapies**
2. **To develop innovative therapies to restore antigen specific tolerance in autoimmune diseases**
3. **To study ADAMTS13 (targeted) clearance**
4. **To setup standardised medical databases and biobanks for long-term follow-up of autoimmune diseases to better understand the pathophysiology and optimize treatment**
5. **To integrate knowledge obtained in Objective 1 to 4 to identify the most promising (combined) innovative therapy**
6. **To provide a unique translational training programme with important links to clinic, academia, industry and patient organizations**

The 8 Doctoral Candidates (DCs)' projects are listed in the following table.

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DC	TITLE OF THE PROJECT	HOST INSTITUTION	SHORT NAME	SUPERVISOR	EXPECTED START DATE
1	**Long-term consequences of living with TTP: improve follow-up and design novel treatment regimens for iTTP to reduce comorbidities**	Assistance Publique Hopitaux De Paris	AP-HP	Paul Coppo, Agnès Veyradier paul.coppo@aphp.fr; agnes.veyradier@aphp.fr	1st April 2023
2	**UniCAR-T cell therapy to treat autoimmune disease: iTTP as the model system**	Katholieke Universiteit Leuven	KUL	Karen Vanhoorelbeke Karen.vanhoorelbeke@kuleuven.be	1st April 2023
3	**RevCAR-T cell therapy to treat autoimmune disease: iTTP as the model system**	Helmholtz-Zentrum Dresden-Rossendorf e.V.	HZDR	Michael Bachmann Interested candidates are invited to apply for this position via the HZDR career website	1st April 2023
4	**TCR-engineered Tregs to treat autoimmune disease: iTTP as the model system**	ANICELLS	ANI	Nathalie Cools nathalie@anicells.com	1st April 2023
5	**Engineered protein based tolerogenic vaccines: iTTP as the model system**	Stichting Sanquin Bloedvoorziening	SNQ	Jan Voorberg j.voorberg@sanquin.nl	1st April 2023
6	**Nanoparticle-mediated approaches to restore tolerance in iTTP**	AHEAD THERAPEUTICS SL	AHT	Marta Vives-Pi mvives@igtp.cat	1st April 2023
7	**ADAMTS13 (targeted) clearance**	Royal College of Surgeons in Ireland	RCSI	James O'Donnell jamesodonnell@rcsi.ie	1st April 2023
8	**Understanding the immune response during long term follow-up**	Semmelweis Egyetem	SMW	Zoltán Prohászka Prohaszka.zoltan@med.semmelweis-univ.hu	1st April 2023

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Training Programme

All the selected students will be involved in a highly stimulating training programme, both at the **local and at the network-wide level.**

TOLERATE aims to deliver highly skilled professionals. This will require training of our DCs in:

- **clinical, biotechnological** and **technical** aspects of therapeutics and diagnostics for autoimmune diseases
- **ethical, administrative, regulatory** and **legal** aspects in developing and implementing of therapeutics and diagnostics for autoimmune diseases
- **innovation management** of therapeutics and diagnostics for autoimmune diseases

The training programme comprises:

1) The implementation of the individual research project at the host institution. The research project will involve collaborations with other TOLERATE institutions, to be implemented through secondments.
2) Each researcher will be involved in local training sessions.
3) Joint scientific courses and meetings will be organised by the TOLERATE consortium, together with short courses for transferable skills training.
4) Enrolment in PhD programmes of the following universities:

DC	HOST INSTITUTION	UNIVERSITY RELEASING THE PhD TITLE
1	AP-HP	Sorbonne Universite (SU)
2	KUL	Katholieke Universiteit Leuven (KUL)
3	HZDR	Technische Universitaet Dresden (TUD)
4	ANI	Universiteit Antwerpen (AU)
5	SNQ	Academisch Medisch Centrum bij de Universiteit van Amsterdam (AMC)
6	AHT	Universidad Autonoma de Barcelona (UAB)
7	RCSI	Royal College of Surgeons in Ireland (RCSI)
8	SMW	Semmelweis Egyetem (SMW)

Recruitment

The DCs will be contractually employed for 36 months by the recruiting organisation and will be covered under the related national social security scheme. DCs will receive the fellowship within the Marie Skłodowska-Curie Actions Program and will receive a Monthly Living Allowance plus a Mobility and Family allowance (where applicable) compliant with the applicable EC Marie Skłodowska - Curie Actions - DN (https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2021-2022/wp-2-msca-actions_horizon-2021-2022_en.pdf pp 78-80).

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Eligibility Rules

At the time of recruitment applicants must fulfil the following rules:

Experience:

- Applicants must be in possession of the degree (usually the Master Degree) which would formally entitle them to embark on a doctorate, either in the country in which the degree was obtained or in the country in which the researcher will be recruited. In case the degree has not been obtained yet, it is necessary to send a declaration of the university stating that the degree will be obtained before the expected starting date
- Eligible applicants must not hold a Doctoral degree already.

Mobility:

- The applicants must not have resided in the country where the research training activities will take place for more than 12 months in the 3 years immediately prior to the recruitment date, and must not have carried out their main activity (work, studies, etc.) in that country.
- Exceptions International Organisations: Eligible researchers must not have spent more than 12 months in the 3 years immediately prior to the date of selection in the same appointing international organisation.

How to apply

TOLERATE will select DC through a 2-step recruitment process.

Candidates should submit their application for their top two preferred research projects.
Application documents should be sent by email to the relevant project supervisors (see emails indicated in the individual project descriptions below).

Applications (in English) should indicate the preferred research project(s) and should include:
1) an updated CV; the CV must be without gaps, in order to easily check the mobility and experience requirements. CVs that either do not clearly show the applicant's past experience, or have gaps, will be considered ineligible.
2) a letter giving reason for his/her motivation for the position;
3) at least 1 reference letter (in English) from one former supervisor and/or lecturer;
4) the scan of the degree (usually the Master Degree) which would formally entitle him/her to embark on a doctorate, either in the country in which the degree was obtained or in the country in which the researcher will be recruited. In case the degree has not been obtained yet, it is necessary to send a declaration of the university stating that the degree will be obtained before the expected starting date;
5) transcripts of records (document indicating their ranking and marks within their last year at their Master Degree as well as the courses/modules they have followed).

Applications must be in English and will be evaluated against the following criteria:

- educational record;
- scientific quality of the applicant's CV;
- expected individual impact and benefit to the fellow and to the project;
- previous experience in the subject of TOLERATE research programme.

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The closing date for applications is 15/12/2022

Candidates will be evaluated by the recruiting institution on the basis of the received documents.

The best **4** candidates for each position will be invited for a Skype (or face to face) interview (in the period **15-31 January 2023**). Interviews will be held by the recruiting institution and at least one other member of the respective DC Board, preferably from the industry.

For each position a short list of top candidates will be prepared and notified to the applicants.
The top candidates will be asked to provide a written acceptance of the studentship; then the following ranked candidates will be requested to confirm. If a successful candidate declines the offer, the studentship will be offered to the next ranked candidate.

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Individual Project Descriptions

DC1 Long-term consequences of living with TTP: design novel treatment regimens for iTTP to reduce comorbidities	
Host Institution	Assistance Publique Hopitaux De Paris (France)
Primary Supervisor	Paul Coppo, Agnès Veyradier
Email address	Paul.coppo@aphp.fr; agnes.veyradier@aphp.fr
Planned duration	36 months
Subject Area	Immune-mediated TTP, ADAMTS13, cardiovascular risk factors, comorbidities, relapse, refractoriness, life expectancy, registry cross-sectional analysis, biobank collection and analysis, clinical trials

Introduction: *Immune-mediated TTP has become a disease of favorable prognosis at the acute phase. However, relapses and comorbidities are prevalent after the acute phase. Comorbidities, especially cardiovascular risk factors, combined with relapses in patients unresponsive to usual immunosuppressive strategies, shorten life expectancy in these patients. These unmet needs will be addressed here.*

Aims: Science: 1. To identify risk factors associated with morbidity and shortened life expectancy following an acute iTTP episode. 2. To address whether ADAMTS13 activity levels are predictive of morbidity and shortened life expectancy. 3. To gain clinical experience in the use of immunomodulators for the prevention of clinical relapses in patients refractory to rituximab. 4. To address whether newest therapeutic regimens at the acute phase and preemptive treatments during follow-up can reduce the incidence of comorbidities and prevent premature death. **Training:** 1. Experience in clinical diagnosis, treatment and follow-up of patients with iTTP. 2. Learn how to approach a patient suffering of iTTP. 3. Management of clinical databases and statistical analyses; design and execution of research based on registry data.

Expected Results: To identify risk factors linked to morbidity and shortened life expectancy; adapt treatment to improve life expectancy and quality of life. To provide definitive evidence about whether abnormal ADAMTS13 levels during follow-up exposes patients to more comorbidities, such as ischemic stroke, and if ADAMTS13 activity improvement affects the prevalence of comorbidities.

Planned secondment(s): 1: **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP.; 2: **SMW**, 6 months: to understand the immune response in iTTP during long-term follow-up. 3: **Werfen** (Biokit Research & Development S.L.U.), 1 month: to get acquainted with commercialization of commercial assays

Enrolment in Doctoral degree(s): DC will be enrolled at Sorbonne Université

Project-specific selection criteria: Good skills/experience in medical data analysis and innovative treatments concepts (Monoclonal antibodies area and recombinant proteins).

Recommended reading:
1. Jestin, M; *et al.* Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. *Blood,* 132, 2143-2153 (2018).
2. Prevel,, R; *et al.* Immune thrombotic thrombocytopenic purpura in older patients: prognosis and long-term survival. *Blood.* 134(24), 2209-2217 (2019).
3. Mariotte, E; *et al.* French Reference Center for Thrombotic Microangiopathies. Epidemiology and pathophysiology of adulthood-onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. *Lancet Haematol.* 3(5), e237-45 (2016).

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Individual Project Descriptions

DC2 **UniCAR-T cell therapy to treat autoimmune disease: iTTP as the model system**	
Host Institution	Katholieke Universiteit Leuven (Belgium)
Primary Supervisor	Karen Vanhoorelbeke
Email address	karen.vanhoorelbeke@kuleueven.be
Planned duration	48 months
Subject Area	Genetic engineering, UniCAR-T-cell therapy, mouse models, autoimmune disease immune-mediated thrombotic thrombocytopenic purpura

Introduction: *Universal chimeric antigen receptor (UniCAR)-T cell therapy was originally developed to treat cancer by HZDR. Here UniCAR-T cell therapy will be introduced for the first time to treat autoimmune diseases. The disease model used will be the autoimmune disease iTTP, The efficacy of the UniCAR-T cell therapy will be studied in vitro and in vivo in a mouse model of iTTP.*

Aims: **Science:** 1. To generate UniCAR-T cells and the CS- and CUB-targeting modules, 2. To study in vitro efficacy as well as the in vivo efficacy of UniCAR-T cell therapy in a mouse model of iTTP; 3. To compare UniCAR-T cell therapy with other innovative immune therapies (WP2 and WP3). **Training:** 1. to learn to generate UniCAR-T cells via lentiviral transduction and transduce T cells, to isolate T cells via FACS sorting to learn to perform cytotoxicity assays and how to use the preclinical mouse model for iTTP (trigger, sign and symptoms)

Expected Results: Expected Results: Having designed human and murine UniCAR-T cells and CS-and CUB-targeting modules; Having realized in vitro cytotoxicity using the UniCAR-T cell therapy; Having demonstrated the UniCAR-T cell therapy reduces signs and symptoms in the mouse model of iTTP

Planned secondment(s): 1. **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP; 2: **HZDR**, 3 months: being trained UniCAR-T cell therapy; 3: **Immudex,** 3 months: trained in Klickmer technology to follow depletion of antigen specific B cells

Enrolment in Doctoral degree(s): DC will be enrolled at Katholieke Universiteit Leuven

Project-specific selection criteria: Master degree with distinction required. Good skills/experience in molecular biology, fluorescent cell sorting, working with mouse models, generation/expression recombinant proteins.

Recommended reading: 1. Hovinga, J. A. K. *et al.* Thrombotic thrombocytopenic purpura. *Nat Rev Dis Primers 3*, 17020 (2017).
2. Vanhoorelbeke, K. & Meyer, S. F. Animal models for thrombotic thrombocytopenic purpura. *J Thromb Haemost 11*, 2–10 (2013).
3. Deforche, L. *et al.* Generation of Anti-Murine ADAMTS13 Antibodies and Their Application in a Mouse Model for Acquired Thrombotic Thrombocytopenic Purpura. Plos One 11, e0160388 (2016).
4. Cartellieri, M. et al. Switching CAR T cells on and off: a novel modular platform for retargeting of T cells to AML blasts. *Blood Cancer* J 6, e458–e458 (2016).

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Individual Project Descriptions

DC3 RevCAR-T cell therapy to treat autoimmune disease: iTTP as the model system	
Host Institution	Helmholtz-Zentrum Dresden-Rossendorf e.V. (Germany)
Primary Supervisor	Michael Bachmann
Email address	Interested candidates are invited to apply for this position via the HZDR career website
Planned duration	36 months
Subject Area	Genetic engineering, RevCAR-T cell therapy, mouse models, autoimmune disease immune-mediated thrombotic thrombocytopenic purpura

Introduction: *Reverse chimeric antigen receptor (RevCAR)-T cell therapy was originally developed to treat cancer by HZDR. Here RevCAR-T cell therapy will be introduced for the first time to treat autoimmune diseases. The disease model used will be the autoimmune disease iTTP. The efficacy of the RevCAR-T cell therapy will be studied in vitro and in vivo in a mouse model of iTTP*

Aims: **Science:** 1. To generate RevCAR-T cells and CS- and CUB-targeting modules, 2. To study in vitro efficacy and in vivo efficacy of RevCAR-T cell therapy in a mouse model of iTTP; 3. To compare RevCAR-T cell therapy with other innovative immune therapies (WP2 and WP3). **Training:** 1. Learn to generate RevCAR-T cells via lentiviral transduction and to isolate T cells via MACS/FACS sorting, 2. Learn to perform cytotoxicity assays; 3. Learn how to use the preclinical mouse model for iTTP (trigger, sign and symptoms)

Expected Results: Having designed human and murine RevCAR-T cells and CS-and CUB-targeting modules. Having proven in vitro cytotoxicity using the RevCAR-T cell therapy. Having demonstrated the RevCAR-T cell therapy reduces signs and symptoms of iTTP in the mouse model.

Planned secondment(s): 1: **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP; 2: **KUL**, 3 months: test RevCAR-T cell therapy in the mouse model for iTTP; 3: **Immudex**, 1 month: trained in Klickmer technology to follow depletion of antigen specific B cells

Enrolment in Doctoral degree(s): DC will be enrolled at Technische Universitaet Dresden

Project-specific selection criteria: The Applicants must hold a master's degree in the field of Biology, Biotechnology, (Bio-) Chemistry or equivalent (e.g., must have completed their medical studies) and must have a solid knowledge of immunology and/or protein biochemistry. Good skills/experience in molecular biology, protein biochemistry, generation of recombinant proteins, working with cell cultures, flow cytometry and mouse models.

Recommended reading:
1. Kittel-Boselli, E. *et al.* Targeting Acute Myeloid Leukemia Using the RevCAR Platform: A Programmable, Switchable and Combinatorial Strategy. *Cancers 13*, 4785 (2021).
2. Feldmann, A. *et al.* Versatile chimeric antigen receptor platform for controllable and combinatorial T cell therapy. *OncoImmunology 9*, 1-15 (2020).
3. Arndt, C. *et al.* Adaptor CAR Platforms-Next Generation of T Cell-Based Cancer Immunotherapy. *Cancers 12*, 1302 (2020).
4. Bachmann, M. *et al.* The UniCAR system: A modular CAR T cell approach to improve the safety of CAR T cells. *Immunol Letts 211*, 13-22 (2019).

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Individual Project Descriptions

DC4 **TCR-engineered Tregs to treat autoimmune disease: iTTP as the model system**	
Host Institution	ANICELLS (Belgium)
Primary Supervisor	Nathalie Cools
Email address	nathalie@anicells.com
Planned duration	48 months
Subject Area	Genetic engineering, Treg-cell therapy, mouse models, autoimmune disease immune-mediated thrombotic thrombocytopenic purpura

Introduction: *To date, cell therapies are also being evaluated to treat autoimmune diseases, such as type I diabetes, rheumatoid arthritis and multiple sclerosis. In this perspective, the essential role of regulatory T cells (Tregs) in preventing autoimmunity and controlling responses to self-antigens is well established. In current proposal, we aim to develop "designer" Tregs that are engineered to express a disease-specific TCR to enforce cell interactions that may play a key role in resolving the disease pathogenesis. The disease model used will be the autoimmune disease iTTP, The efficacy of the TCR-engineered Tregs will be studied in vitro and in vivo in a mouse model of iTTP*

Aims: Science: 1. Having generated TCR transgenic Tregs and tested their stability, 2. Having tested the functionality and suppressive potential of TCR transgenic Tregs towards key immune cells. **Training:** 1. Having learned to isolate Tregs via FACs, expand them and study their stability, 2. Having learned how to generate TCR transgenic Tregs via T cell electroporation with mRNA. 3. Having learned how to study the suppressive effect of the TCR transgenic Tregs on selected immune cells

Expected Results: Having generated TRC transgenic Tregs that are suppressive towards key immune cells

Planned secondment(s): 1: **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP; 2: **SQN**, 4 months: to understand and study T cell responses in iTTP patients

Enrolment in Doctoral degree(s): DC will be enrolled at Universiteit Antwerpen

Project-specific selection criteria: Good skills/experience in molecular biology, sterile cell culture, flow cytometry and cell sorting Master degree with distinction required.

Recommended reading:
1. Janssens I, Cools N. Regulating the regulators: Is introduction of an antigen-specific approach in regulatory T cells the next step to treat autoimmunity? *Cell Immunol. 358*:104236 (2020).
2. Janssens I *et al.* Engineering of regulatory T cells by means of mRNA electroporation in a GMP-compliant manner. *Cytotherapy. 24*(6), 659-672 (2022).
3. Trzonkowski P, *et al.* Hurdles in therapy with regulatory T cells. *Sci Transl Med. 7*(304), 304ps18 (2015).

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Individual Project Descriptions

DC5 **Engineered protein based tolerogenic vaccines: iTTP as the model system**	
Host Institution	Stichting Sanquin Bloedvoorziening (The Netherlands)
Primary Supervisor	Jan Voorberg
Email address	j.voorberg@sanquin.nl
Planned duration	48 months
Subject Area	Tolerogenic vaccines, genome-engineered red blood cells, tolerance, autoimmune disease, immune thrombotic thrombocytopenic purpura

Introduction: *DC5 will develop a novel strategy to induce antigen-specific tolerance in iTTP based on targeting of surface receptors on highly tolerogenic liver sinusoidal endothelial cells (LSEC). In addition, CRISPR/Cas9 mediated genome engineering of red blood cell precursors will be employed to hijack the tolerogenic properties of ageing red blood cells.*

Aims: **Science:** 1. to design novel protein-based tolerogenic vaccines based on our current knowledge of B cell and T cell epitopes involved in iTTP. 2. Design peptide-based tolerogenic vaccines that hijack the tolerogenic properties of ageing red blood cells. 3. Provide in vivo proof of the efficacy of "designer" tolerogenic vaccines for the treatment of iTTP in a mouse model. **Training:** 1. Rational design of tolerogenic vaccines to treat autoimmune disorders. 2. Characterize the tolerogenic properties of LSEC and different macrophage populations. 3. To learn how to use the preclinical mouse model for iTTP (trigger, sign and symptoms).

Expected Results: Having designed tolerogenic vaccines that can potentially be used for treatment of autoimmune disorders. Having designed peptide-based vaccines that have the potential to re-direct CD4+ T cells towards a regulatory phenotype thereby restoring tolerance in autoimmune disorders like iTTP. Having tested the tolerogenic vaccines in the mouse model of iTTP

Planned secondment(s): 1: **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP; 2: **AHT:** 3 months: to test whether incorporation of tolerogenic vaccines in nanoparticles will provide a novel treatment option for autoimmune disorders; 3: **KUL**, 4 months: test tolerogenic vaccines in the mouse model for iTTP

Enrolment in Doctoral degree(s): DC will be enrolled at Academisch Medisch Centrum bij de Universiteit van Amsterdam

Project-specific selection criteria: DC5 will develop novel tolerogenic approaches to treat autoimmune disease using immune-mediated thrombotic thrombocytopenic purpura (iTTP) as a model disease. Liver directed tolerogenic vaccines targeting surface receptors on liver sinusoidal endothelial cells (LSEC) will be employed as well as genome-engineered red blood cell based tolerogenic vaccines will be generated. The novel tolerogenic therapies will be tested in vitro and in vivo in a mouse model of iTTP. Master degree with distinction required.

Recommended reading:
1. Laghmouchi A, *et al.* Emerging Concepts in Immune Thrombotic Thrombocytopenic Purpura. *Front Immunol 12,* 757192 (2021).
2. Sorvillo, N. *et al.* Preferential HLA-DRB1*11-dependent presentation of CUB2-derived peptides by ADAMTS13-pulsed dendritic cells. *Blood 121*(17), 3502-10 (2013).
3. Verbij, F.C. CD4+ T cells from patients with acquired thrombotic thrombocytopenic purpura recognize CUB2 domain-derived peptides. *Blood 127*(12), 1606-9 (2016).

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Individual Project Descriptions

DC6 **Nanoparticle-mediated approaches to restore tolerance in iTTP**	
Host Institution	AHEAD THERAPEUTICS SL (Spain)
Primary Supervisor	Marta Vives-Pi
Email address	mvives@igtp.cat
Planned duration	36 months
Subject Area	Liposomes, antigen specific tolerance induction, autoimmune disease immune-mediated thrombotic thrombocytopenic purpura

Introduction: *Ahead's PS-liposomes induce antigen specific immune tolerance by biomimicry, stopping the autoimmune reaction. The immunotherapy was preclinically developed for type 1 diabetes and has been successfully validated in other autoimmune diseases. Considering the potential of PS-liposomes therapy, it is worth exploring the use of this technology platform to solve the autoimmune attack that undergoes in iTTP. Liposomes will be generated and tested both in vitro and in vivo in iTTPs patients' lymphocytes and in a mouse model of iTTP respectively.*

Aims: Science: 1. to design, synthesize, characterize (composition, charge, size) and optimize iTTP PS-Liposomes. 2. to validate PS-Liposomes potential for iTTP treatment. 3. to validate tolerogenicity using mouse model of iTTP and ex-vivo using human dendritic cells from 10 patients with iTTP. **Training:** Acquisition of full competence in laboratory work, cytometer sample processing, nanoparticle preparation, animal manipulation, data analysis as well as acquisition of industrial skills.

Expected Results: Having designed and manufactured iTTP PS-liposomes. Having selected the peptide to boost a tolerance signal. Both laboratory scale and scalable production process. Having produced 2 or 3 iTTP PS-liposome candidates. Having validated iTTP PS-Liposomes potential for treatment in the mouse model for iTTP, and in vitro via autologous proliferation assays with iTTPs patients' lymphocytes.

Planned secondment(s): 1: **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP; 2: **KUL**, 4 months: test PS-liposomes in the mouse model for iTTP; 3: **RCSI,** 1 month: to get insight into how ADAMTS13 can be retargeted to antigen presenting cells

Enrolment in Doctoral degree(s): DC will be enrolled at Universidad Autonoma de Barcelona

Project-specific selection criteria: Good skills/experience in immunology, cell culture, molecular biology, flow cytometry, working with mouse models, nanoparticles. Master degree with distinction required.

Recommended reading:
1. Hovinga, J. A. K. *et al.* Thrombotic thrombocytopenic purpura. *Nat Rev Dis Primers 3*, 17020 (2017).
2. Vanhoorelbeke, K. & Meyer, S. F. Animal models for thrombotic thrombocytopenic purpura. *J Thromb Haemost 11*, 2–10 (2013).
3. Pujol-Autonell, I. *et al.* Use of Autoantigen-Loaded Phosphatidylserine-Liposomes to Arrest Autoimmunity in Type 1 Diabetes. PLOS One 10(6):e0127057 (2015).
4. Rodriguez-Fernandez S, et al. Impaired phagocytosis in dendritic cells from pediatric patients with type 1 diabetes does not hamper their tolerogenic potential. *Frontiers in Immunology 10*:2811 (2019).

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Individual Project Descriptions

DC7 ADAMTS13 (targeted) clearance	
Host Institution	Royal College of Surgeons in Ireland (Ireland)
Primary Supervisor	James O'Donnell
Email address	jamesodonnell@rcsi.ie
Planned duration	36 months
Subject Area	Molecular medicine and cellular biology, including genetic engineering and protein biochemistry

Introduction: *The metalloprotease ADAMTS13 plays a key role in preventing the development of pathological thrombosis. ADAMTS13 deficiency is associated with life-threatening microvascular thrombosis in patients with TTP. In addition, variation in plasma ADAMTS13 levels has been implicated in the pathogenesis of other important human diseases including myocardial infarction, stroke, cerebral malaria and sickle cell disease. This project will investigate the biological clearance mechanisms involved in regulating ADAMTS13 half-life.*

Aims: Science: 1. Characterize the biological mechanisms underlying ADAMTS13 clearance in vivo; 2. Based on clearance biology, retarget ADAMTS13 to specific clearance pathways to promote tolerance. **Training:** 1. Having learned how to study in vivo regulation of ADAMTS13 clearance; 2. Having learned how to retarget ADAMTS13 to specific clearance pathways to promote tolerance

Expected Results: Having defined the role of macrophages and specific macrophage receptors in modulating ADAMTS13 clearance; Having investigate the importance of specific ADAMTS13 domains and glycan determinants in triggering clearance. Having identified how to retarget ADAMTS13 to specific clearance pathways to promote tolerance

Planned secondment(s): 1: **AP-HP**, 6 weeks: To gain understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP; 2: **KUL**, 2 months: to learn mouse model for iTTP; 3: **AHT,** 3 months: study targeting liposomes to dendritic cells

Enrolment in Doctoral degree(s): DC will be enrolled at Royal College of Surgeons in Ireland

Project-specific selection criteria: Good skills/experience in medical data analysis and innovative treatments concepts (Monoclonal antibodies area and recombinant proteins).

Recommended reading: 1. O'Sullivan JM, *et al.* Von Willebrand factor clearance – biological mechanisms and clinical significance. British *Journal of Haematology,183*(2), 185-195 (2018).
2. O'Sullivan JM, *et al.* Emerging roles for haemostatic dysfunction in malaria pathogenesis. *Blood, 12*;127(19), 2281-8. PMID: 26851291 (2016).

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Call for 8 PhD fellowships in

"An integrated approach to restore tolerance in autoimmune disease"

Individual Project Descriptions

DC8 Understanding the immune response during long term follow-up	
Host Institution	Semmelweis Egyetem (Hungary)
Primary Supervisor	Zoltán Prohászka
Email address	prohaszka.zoltan@med.semmelweis-univ.hu
Planned duration	48 months
Subject Area	Immunoassay development, ADAMTS13, cytokine and complement determinations, autoimmune disease immune-mediated thrombotic thrombocytopenic purpura

Introduction: *Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is mediated by anti-ADAMTS13 antibodies, however, the mechanism and course of the development of these antibodies are not yet elucidated. Here novel immunoassays will be developed and performed in sets of longitudinal iTTP samples and the role of antibody-, antigen- and host related factors will be studied in the anti-ADAMTS13 immune response.*

Aims: Science: 1. To develop a novel immunoassay for patient-derived "opening" antibodies that modulate ADAMTS13 conformation. 2. To measure opening, inhibitory and total anti-ADAMTS13 IgG antibodies in longitudinal samples. 3. To study the role of antigen-related and host-related factors in the anti-ADAMTS13 immune response. 4. To study the relationship between changes in anti-ADAMTS13 antibody concentrations, complement and cytokine parameters and the development of clinical endpoints. **Training:** 1. Learn how to develop immunoassays to determine the concentration of opening ADAMTS13-antibodies and antibodies against citrullinated or differently glycosylated ADAMTS13. 2. Learn how to study host factors that modulate autoimmunity.

Expected Results: Having identified host- and antigen-related factors that could drive autoimmunity against ADAMTS13 in iTTP, and having explored how opening, inhibiting or binding autoantibodies are related to the development of an acute iTTP episode.

Planned secondment(s): 1: **AP-HP**, 6 weeks: Understanding of the medical needs of patients with iTTP and challenges linked to diagnosis and treatment of patients with iTTP. To gain skills in the standardisation of clinical databases and ADAMTS13 measurements. 2: **Werfen** (Biokit Research & Development S.L.U.), 3 months: skills on regulatory/quality requirements to develop/market diagnostic assays. 3: **RCSI,** 1 month: to learn how to measure glycoforms of ADAMTS13

Enrolment in Doctoral degree(s): DC will be enrolled at Semmelweis Egyetem

Project-specific selection criteria: DC8 will develop an assay to measure opening antibodies in the iTTP patient's samples. A complex clinical study with measurement of cytokine profiles, complement profiles, ADAMTS13 antigen, ADAMTS13 autoantibody (total and inhibitory) levels will also be executed in iTTP to understand the complex immune pathophysiology in this disease. DC8 should have expertise in immunoassays, FACS analysis, multiplex assays, protein analysis techniques, molecular biology, clinical and laboratory immunology training, medical training.

Recommended reading: 1. Roose E, *et al.* Open ADAMTS13, induced by antibodies, is a biomarker for subclinical immune-mediated thrombotic thrombocytopenic purpura. *Blood.136*(3), 353-361 (2020).
2. Réti M, *et al.* Complement activation in thrombotic thrombocytopenic purpura. *J Thromb Haemost. 10*(5), 791-8 (2012).
3. Sinkovits G, *et al.* The role of human leukocyte antigen DRB1-DQB1 haplotypes in the susceptibility to acquired idiopathic thrombotic thrombocytopenic purpura. *Hum Immunol. 78*(2), 80-87 (2017).

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