ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Erasmus Medical Center Rotterdam Dept. of Internal Medicine-Nephrology & Kidney Transplantation The Netherlands
Project Title:	**Humoral rejection in organ transplantation: new concepts in treatment to improve allograft survival**
Abstract:	Annually, 40.000 kidney transplantations are performed worldwide. However, 50% of the transplanted organs are lost within 10 years after transplantation. In particular, antibodies directed against the transplanted organ drives this irreversible and non-treatable process of allograft rejection. Because of its association with preformed antibodies to HLA in recipients, vascular presence of complement fragment C4d has been assumed to represent humoral immune reaction against graft endothelial cells. Analysing the cellular composition of rejection biopsies display a mixture of CD4+ T helper, CD8+ cytotoxic T cells and CD20+ B cells. These poorly defined T and B cell responses persist at a low-grade level during the entire life span of the graft and are refractory to treatment with conventional immunosuppression. Therefore, detailed knowledge of the mechanisms that initiate and maintain B cell driven anti-donor reactivity is required to design therapeutic strategies that specifically target antibody-mediated humoral rejection in organ transplant patients. Recently, a novel specialized T cell subset has been identified, the T follicular helper (Tfh) CXCR5+ cell, which is required for the generation of efficient antibody responses. These Tfh cells that are present in the transplanted organ and in the circulation, support activated B cells via IL-21 after binding to the IL-21Receptor (R) expressed by these B cells. **We hypothesize that blockade of the IL-21/IL-21R pathway reduces the incidence and the severity of antibody-mediated rejection after kidney transplantation.** We will examine I. the development of antigen specific IL-21+CXCXR5+Tfh in relation to humoral rejection in patients after kidney transplantation and II. study in a pre-clinical transplant model the direct effects of anti-IL-21R blockade on the Tfh cell directed antibody rejection process (proof of concept). We will deliver functional characterization of IL-21+CXCR5+Tfh cells that will show the potential of a novel therapeutic approach for treatment of humoral rejection after organ transplantation. **The primary objectives of the project are** 1. To determine the interplay between IL-21/IL-21R signaling and B cell mediated immune responses in patients after kidney

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	transplantation 2. To identify a signature that differentiates antibody mediated rejection from non-B cell mediated alloreactivity 3. To examine the efficacy immune modulation by IL-21R blockade in pre-clinical transplant models **This proposal will elucidate the role of the IL-21/IL-21R pathway in antibody mediated rejection after organ transplantation**
Requirements of candidate:	Master degree: Yes Background: candidate should be educated in *Immunology, Medicine or Biology* and be trained in laboratory techniques like flow cytometry, cell culture and RNA/DNA assays. Also experience with small animals is appreciated. IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*
Supervisor information:	This project is a collaboration between the departments of **Internal Medicine** (prof Baan), **Surgery** (dr Dor) and **Pulmonary Diseases** (prof Hendriks) For information contact: Prof dr. Carla.C. Baan, E-mail: c.c.baan@erasmusmc.nl Erasmus Medical Center Rotterdam Dept of Internal Medicine-Nephrology & Transplantation P.O.Box 2040, Room Nc508, 3000 CA Rotterdam The Netherlands Website: http://nl.linkedin.com/pub/carla-baan/8/a19/960 **Publications by the Rotterdam Research Team (dr Dor, prof Hendriks and prof Baan)** *Selected references* 1. Bouvy AP, Klepper M, Kho MM, Boer K, Betjes MG, Weimar W, **Baan CC**. The impact of induction therapy on the homeostasis and function of regulatory T cells in kidney transplant patients.

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