

AAP China Scholarship Council - CSC 2024 PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : Exploration of the pathophysiology of Immune Checkpoint Inhibitor-associated Myocarditis and development of personalized therapies

DIRECTION de THESE

Porteuse ou porteur du projet (*doit être titulaire de l'HDR*) :

NOM : SALEM

Prénom : Joe-Elie

Titre : PU-PH ou Autre :

Section CNU : Pharmacologie

Email : joe-elie.salem@aphp.fr

Unité de recherche : Code (ex. UMR xxx) et Intitulé : CIC1901 INSERM, Centre d'investigation Clinique Paris EST, Centre de recherche en myologie UMRS 974, Equipe 8 Muscle inflammatoire et thérapies innovantes ciblées, Sorbonne Université - Inserm

Ecole doctorale de rattachement : ED394 – P2T

Nombre de doctorants actuellement encadrés : 1

CO-DIRECTION de THESE (HDR) ou CO-ENCADREMENT (Non HDR) :

NOM :

Prénom :

Titre : Sélectionner ou Autre :

Section CNU :

Email :

Unité de recherche : Code (ex. UMR xxx) et Intitulé :

Ecole doctorale de rattachement Sorbonne Université : Sélectionner ou autre :

Nombre de doctorants actuellement encadrés :

CO-TUTELLE INTERNATIONALE envisagée : OUI NON

DESCRIPTIF du PRD :

Ce texte sera affiché en ligne à destination des candidates et candidats chinois : il ne doit pas excéder 2 pages doit être rédigé en ANGLAIS

Thesis project title

Exploration of the pathophysiology of Immune Checkpoint Inhibitor-associated Myocarditis and development of personalized therapies

Background

Immune checkpoint inhibitor (ICI) myocarditis are difficult to predict, diagnose and treat (30-50% fatality rate). First line treatment relies on corticosteroids but up to 60% are cortico-resistant requiring additional immunosuppressive treatments; of which none has been formally evaluated. Our team (Centre d'Investigation Clinique - CIC Paris Est/INSERM U1166), specialized in onco-cardiology, has shown that abatacept specifically reverse the pathways activated by ICI and is promising to treat ICI-myocarditis. In abatacept's approved indication (rheumatoid arthritis), CD86 receptor (abatacept's target) occupancy on circulating monocytes (CD86RO) is a relevant pharmacodynamic biomarker of clinical activity with a target threshold above 80%. A phase II dose finding trial studying various doses of abatacept to rapidly achieve a CD86RO \geq 80% has started in our center for severe /cortico-resistant ICI myocarditis. This study is nested in a prospective cohort including all patients referred for suspected ICI myocarditis.

Objectives

Our work will have several objectives:

- To evaluate the exact pharmacological immune and cardiac mechanisms and appropriate dose of abatacept's to be used through analysis of a phase II trial in the setting of cortico-resistant or severe ICI-myocarditis.
- Identify risk factors for developing ICI-myocarditis, improve their diagnostic and prognostic stratification. The clinical and bio-radiological covariates of interest will be identified using a local prospective cohort (Pitié-Salpêtrière, Paris) of ICI-treated patients suspected or not for ICI-myocarditis and then replicated in various inter(national) registries and pharmaco-epidemiological databases.

Faisibility

This original project is achievable given the fact that the phase II trial have currently starting since october 2022 (NCT05195645), as well as the prospective cohort with over 100 patients suspected for ICI-myocarditis included to date (NCT03393793). Moreover, our team is among the pioneers who defined the pathophysiology and described the clinical features of ICI myocarditis. Professor Salem lead or collaborate within several national and international consortia with all expertise and data required for this project readily accessible; of which an international redcap database with over 700 patients (NCT04294771). Of note, Professor Salem is a world-class leader on this specific topic (≥ 20 publications including NEJM, Cancer Discovery, Nature Medicine, Lancet, Lancet Oncology, JAMA Oncology, JAMA Cardiology, Circulation, ...).

5 major publications of the research unit

1. Fenioux, C. et al. Thymus alterations and susceptibility to immune checkpoint inhibitor myocarditis. *Nat. Med.* 29, 3100–3110 (2023).
2. Lehmann, L. H. et al. Cardiomyocardial Biomarkers in the Diagnosis and Prognostication of Immune Checkpoint Inhibitor Myocarditis. *Circulation* 148, 473–486 (2023).
3. Salem, J.-E. et al. Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis. *Cancer Discov.* 13, 1100–1115 (2023).
4. Power, J. R. et al. Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis. *Circulation* 144, 1521–1523 (2021).
5. Salem, J.-E. et al. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. *N. Engl. J. Med.* 380, 2377–2379 (2019).

Candidate's skills

We are looking for a motivated, hard-working student with an interest in science and immunology. He/She should be able to work in team and driven by natural curiosity for science. An independent profile in bio statistics would be interesting.

AVIS de l'Ecole Doctorale :

**Merci d'enregistrer votre fichier au format PDF sous la forme :
NOM Prénom_Projet CSC 2024.pdf**

**Fichier à envoyer par mail simultanément
à l'école doctorale de rattachement et à csc-su@listes.upmc.fr**