Ecole Doctorale COMPLEXITE DU VIVANT – Fiche Projet CONCOURS

Fiche à nommer selon le format Nom_Prenom (sans accents ni cédilles), à enregistrer en format PDF et à renvoyer à l'adresse : edcdv@sorbonne-universite.fr

Nom et prénom du directeur de thèse (et si besoin du co-directeur) : Combadiere Christophe
Le directeur de thèse et le co-directeur doivent impérativement avoir l'HDR ou équivalent
Coordonnées Tel : 01 40 77 98 97 e-mail : christophe.combadiere@upmc.fr

Nom et prénom du co-encadrant (*non HdR*) (s'il y a lieu) : NON
Coordonnées Tel :
e-mail :

Y-a-t-il un candidat déjà identifié pour le projet: NON

Nom et prénom du responsable de l'équipe : Boissonnas Alexandre

Intitulé de l'équipe : CHIPI
Nombre de chercheurs et enseignants-chercheurs statutaires de l'équipe titulaires d'une HDR (ou équivalent) : 3

Nom et prénom du responsable d'UMR: Combadiere Christophe

Intitulé et N° d'UMR ou de département : Cimi - Centre d'Immunologie et des Maladies Infectieuses- U1135

Titre du projet de thèse : Role of neutrophil subsets in severe COVID-19

Signature du directeur d'UMR ou de département (vaut avis favorable pour le dépôt du projet) :

Spécialité : Immunologie, Virologie

Résumé du projet de thèse *(1 page maximum, en anglais)*
Pour les thèses avec 2 co-directeurs, ou en partenariat entre 2 laboratoires ou structures, indiquer la participation de chaque co-directeur et structure dans la gestion du projet.

SARS-CoV-2 infection is characterized by a range of symptoms including fever, cough, fatigue and myalgia in the majority of cases. More severe cases of COVID-19 show development of acute respiratory distress syndrome (ARDS) leading to mortality. A high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. Increasing clinical data indicated that the neutrophil-to-lymphocyte ratio (NLR) is a powerful predictive and prognostic indicator for severe COVID-19. In an attempt to identify neutrophil surface markers that may help to predict severity of COVID-19 infection, we recently developed a multi-parametric neutrophil profiling strategy and revealed new immature neutrophil subsets. These markers were significantly correlated with disease severity. Whether these new tools may help monitor COVID-19 patients and improve clinical care remains to be determined. To test the hypothesis of a virally-driven neutrophil profile that could be a good COVID patients' disease-state indicator, we now propose to better characterize the neutrophil subsets in COVID-19 patients and how neutrophil dysregulation can result from an inappropriate functional differentiation to a critical clinical outcome with thrombotic complications. The proposed research program combines 1) ex vivo analysis in patients and 2) preclinical murine model of COVID-19. We will first provide a detailed molecular and cellular analysis of the neutrophil subsets in blood in both COVID-19 patients and controls using high-resolution single cell RNA sequencing (scRNAseq) analysis. We will confirm that the phenotype, the function and the dynamic of some neutrophil subsets is associated with COVID-19 and its complications in a murine model of Sars-Cov2 infection. The final ambition of the program is to propose drugs targeting neutrophil subsets fate and differentiation leading to inflammatory disorders. Globally, this research program is designed to better understand the role of neutrophil subsets in COVID-19 and to define therapeutic targets directed at facilitating inflammation resolution and improving COVID-19 complications.

The team of C. Combadiere recently performed a comprehensive evaluation of whole blood circulating neutrophils in septic (Meghraoui-Kheddar A. et al, manuscript submitted). High dimensional mass cytometry revealed a specific neutrophil signature of sepsis severity that does not overlap with other inflammatory biomarkers, and that distinguishes patients with infection from those with non-infectious inflammatory syndrome. Unsupervised analysis of 40-dimesional mass cytometry data characterized previously unappreciated heterogeneity within the CD64+ immature neutrophils and revealed new subsets. These immature neutrophils exhibited diminished activation and phagocytosis functions.

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Faisabilité du projet de thèse (*1/2 page maximum, en anglais)*

Expliciter la faisabilité du projet en terme d'expertise de l'équipe d'accueil, des collaborations potentielles qui pourront être mises en place pour certains aspects du projet, de la disponibilité des appareils nécessaires au bon déroulement du projet...

There remain unmet needs for specific and rapid prognostic tests for COVID-19 severity and complications, which directly reflects the inflammatory status of patients and discriminate patients that will develop severe symptoms from those that will develop critical symptoms requiring intensive medical care. Our ambition is to better characterize the neutrophil subsets in COVID-19 patients and how neutrophil dysregulation can result from an inappropriate functional differentiation to a critical clinical outcome. The proposed research program is organized in three main tasks and combines 1) ex vivo characterization of the neutrophil diversity in patients and controls, 2) characterization of the neutrophil dynamic in SARS-CoV2 preclinical murine model, and 3) functional modulation of the neutrophil subsets for therapeutic approaches.

The task 1 will provide a detailed molecular and cellular analysis of the neutrophil subsets in both patients and controls. It mainly will rely on a high-resolution single cell RNA sequencing (scRNAseq) analysis of neutrophil subsets in the peripheral blood.

The task 2 will study the phenotype, the function and the dynamic of the neutrophil subsets in the murine Sars-Cov2 infection and complications. Major assets to address this issue is our expertise in infectious murine models, and the large numbers of tools that we developed to characterize pathophysiological complications in murine models.

The final ambition of the team is to propose drugs targeting neutrophil subsets fate and differentiation leading to inflammatory disorders. It will help define therapeutic targets directed at facilitating inflammation resolution and improving COVID-19 complications. We already identified 2 targets described as potent prognosis markers of Covid-19 severity (CD123) and thrombotic complications (LOX-1). In both cases, monoclonal antibodies have been already used with success in murine model of sepsis.

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Thèses actuellement en cours dans l'équipe

Tous les encadrements doivent être indiqués (y compris les co-directions avec un autre HDR pour des doctorants d'une autre ED, et les encadrements dans le cadre de programmes doctoraux tels qu'IPV, FDV...)

Nom et Prénom du doctorant	Directeur(s) de thèse	Année de 1ère inscription	ED	Financement
Eleonore WEBER-DELACROIX	Alexandre Boissonnas	2021	ED515	Contrat Sorbonne Partenariat International

Trois publications récentes du directeur de thèse (du co-directeur ou du co-encadrant s'il y a lieu). Mettre en gras le nom du directeur de thèse.

1. Combadiere B., Adam L., Guillou N., Quentric P., Rosenbaum P., Dorgham K., Bonduelle O., Parizot C., Sauce D., Mayaux J, Luyt C-E., Boissonnas A., Amoura Z., Martinez V., Miyara M., Gorochov G., Guihot A. and **Combadière C.** LOX-1-expressing immature neutrophils identify critically-ill COVID-19 patients at risk of thrombotic complications. Front. Immunol. 2021 Sep 20;12:752612.
2. Meghraoui-Kheddar A., Chousterman B.G., Guillou N., Barone S.M., Granjeaud S., Vallet H., Corneau A., Guessous K., Boissonnas A., Irish J.M. and **Combadière C.** Two new immature and dysfunctional neutrophil cell subsets define a predictive signature of sepsis useable in clinical practice. Am. J. Respir. Crit. Care Med. 2022 Jan 1;205(1):46-+.
3. Boissonnas A., Louboutin F., Laviron M., Loyher P-L, Reboussin E., Barthelemy S., Reaux A., Lobsiger C., Combadiere B., Melik-Parsadaniantz S. and **Combadiere C**. Imaging resident and recruited macrophage contribution to Wallerian degeneration. **J. Exp. Med.,** 2020. (doi.10.1084/jem.20200471; in press).

Docteurs encadrés par le directeur de thèse ayant soutenu entre la date de dépôt de ce dossier et il y a 5 ans et publications relatives à leur sujet de thèse. Mettre en gras le nom du directeur de thèse et celui du docteur.

Nom Prénom : **Baudesson de Chanville Camille**

Date de soutenance : NOV 2018

Durée de thèse (en mois): 37

Ecole Doctorale : ED515

Publications :

1. **Baudesson de Chanville C**, Chousterman BG, Hamon P, Laviron M, Guillou N, Loyher PL, Meghraoui-Kheddar A, Barthelemy S, Deterre P, Boissonnas A and **Combadière C**. Sepsis Triggers a Late Expansion of Functionally Impaired Tissue-Vascular Inflammatory Monocytes During Clinical Recovery. Front. Immunol. 2020 11:675. doi: 10.3389/fimmu.00675.
2. Loyher PL, Hamon P, Laviron M, Meghraoui-Kheddar A, Goncalves E, Deng Z, Torstensson S, Bercovici N, **Baudesson de Chanville C**, Combadière B, Geissmann F, Savina A, **Combadière C**, Boissonnas A. Macrophages of distinct origins contribute to tumor development in the lung. J Exp Med. 2018 Oct 1;215(10):2536-2553.
3. Parillaud VR, Lornet G, Monnet Y, Privat AL, Haddad AT, Brochard V, Bekaert A, **de Chanville CB**, Hirsch EC, **Combadière C**, Hunot S, Lobsiger CS. Analysis of monocyte infiltration in MPTP mice reveals that microglial CX3CR1 protects against neurotoxic over-induction of monocyte-attracting CCL2 by astrocytes. J Neuroinflammation. 2017 Mar 21;14(1):60.
4. Hamon P, Loyher PL, **Baudesson de Chanville C**, Licata F, **Combadière C**, Boissonnas A. CX3CR1-dependent endothelial margination modulates Ly6Chigh monocyte systemic deployment upon inflammation in mice. Blood. 2017 Mar 9;129(10):1296-1307
5. Loyher PL, Rochefort J, **Baudesson de Chanville C**, Hamon P, Lescaille G, Bertolus C, Guillot-Delost M, Krummel MF, Lemoine FM, **Combadière C**, Boissonnas A. CCR2 Influences T Regulatory Cell Migration to Tumors and Serves as a Biomarker of Cyclophosphamide Sensitivity. Cancer Res. 2016 Nov 15;76(22):6483-6494

6. Auvynet C, **Baudesson de Chanville C**, Hermand P, Dorgham K, Piesse C, Pouchy C, Carlier L, Poupel L, Barthélémy S, Felouzis V, Lacombe C, Sagan S, Chemtob S, Quiniou C, Salomon B, Deterre P, Sennlaub F, **Combadière C**. ECL1i, d(LGTFLKC), a novel, small peptide that specifically inhibits CCL2-dependent migration. FASEB J. 2016 Jun;30(6):2370-81
7. Arnold L, Perrin H, **de Chanville CB**, Saclier M, Hermand P, Poupel L, Guyon E, Licata F, Carpentier W, Vilar J, Mounier R, Chazaud B, Benhabiles N, Boissonnas A, Combadiere B, **Combadiere C**. CX3CR1 deficiency promotes muscle repair and regeneration by enhancing macrophage ApoE production. Nat Commun. 2015 Dec 3;6:8972.
8. Chousterman BG, Boissonnas A, Poupel L, **Baudesson de Chanville C**, Adam J, Tabibzadeh N, Licata F, Lukaszewicz AC, Lombès A, Deterre P, Payen D, **Combadière C**. Ly6Chigh Monocytes Protect against Kidney Damage during Sepsis via a CX3CR1-Dependent Adhesion Mechanism. J Am Soc Nephrol. 2016 Mar;27(3):792-803.