ÉCOLE DOCTORALE UNIVERSITÉ PARIS-EST
Sciences de la Vie et de la Santé

Campagne de recrutement 2020

Titre du projet de Thèse
Development of broad-spectrum host-targeted antiviral agents against SARS-CoV-2 and other respiratory viruses

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Unité / laboratoire d'accueil

Intitulé de l'unité/laboratoire : INSERM U955

Nom du Directeur de l'unité / laboratoire d'accueil : Pr. Jorge Boczkowski

Contexte scientifique du projet et objectifs (0,5 page maximum)

Arial 11, interligne simple

RNA viruses responsible for acute lower respiratory tract infections (aLRTI) carry a significant medical burden. Common viruses causing aLRTIs in vulnerable populations include the human respiratory syncytial virus (hRSV), human metapneumovirus (hMPV), human parainfluenza viruses (hPIV) and human coronaviruses (hCoV). hCoV are generally responsible for benign infections, but they have a high potential for crossing species barriers and thus represent a permanent pandemic respiratory threat. In December 2019, an outbreak of pneumonia of unknown origin emerged in the Chinese city of Wuhan. A novel coronavirus was soon identified as the pathogen causing the disease, named COVID-19 for Coronavirus Disease 2019. This new virus was called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) because of its genetic proximity with SARS-CoV. COVID-19 is now pandemic and, on the day of writing this application, over 2 million people have been diagnosed with the infection worldwide, while over 200,000 of them have died from complications of the disease. No efficacious antiviral drugs or vaccines are available for any of these infections.

We raised the hypothesis that host-targeting agents active on cellular functions used by different RNA viruses in their lifecycles will provide broad-spectrum, high barrier-to-resistance antiviral solutions efficient against SARS-CoV-2 and aLRTIs for which virus-specific drugs or vaccines are unlikely to be developed. A very credible option is the use of cyclophilin inhibitors. Cyclophilins are host peptidyl-prolyl cis-trans isomerases (PPIases) that catalyze the interconversion of the two energetically preferred conformers (cis and trans) of the planar peptide bond preceding an internal proline residue. Cyclophilins play a very important role in the life cycle of many respiratory viruses. Our laboratory has been working for the past 10 years on the development of host-targeted approaches, in particular those based on cyclophilin inhibition, as broad-spectrum antiviral therapies.

The objectives of the candidate's project are: (i) to repurpose approved drugs and cyclophilin inhibitors for the treatment of COVID-19 and (ii) to use small molecule cyclophilin inhibitor developed in our laboratory to understand the key role played by Cyps in the lifecycles of different families of RNA viruses causing potentially severe aLRTIs, (iii) to develop new antiviral agent for aLRTIs treatment.

Compétences requises du candidat (5 lignes maximum)

Arial 11, interligne simple

The candidate shall: be autonomous in the acquisition of new knowledge, be able to research and mobilize scientific or technical resources, be adaptable to a wide range of applications, know how to work in a team, how to fit into an organization and its environment, have report writing skills, have strong technical skills in biochemistry, cellular culture, virology and cellular biology.

Publications de l'équipe d'accueil de ces 5 derniers années en lien avec le projet (5 publications maximum)

1. Ruiz, I., Nevers, Q., Hernandez, E., Ahnou, N., Brillet, R., Softic, L., Donati, F., Berry, F., Hamadat, S., Fourati, S., Pawlotsky, J.M., Ahmed-Belkacem, A., 2020. MK-571, a cysteinyl leukotriene receptor-1 antagonist, inhibits hepatitis C virus (HCV) replication. Antimicrobial agents and chemotherapy.

2. Panel, M., Ruiz, I., Brillet, R., Lafdil, F., Teixeira-Clerc, F., Nguyen, C.T., Calderaro, J., Gelin, M., Allemand, F., Guichou, J.F., Ghaleh, B., Ahmed-Belkacem, A.#, Morin, D., Pawlotsky.#, J.M., 2019. Small-Molecule Inhibitors of Cyclophilins Block Opening of the Mitochondrial Permeability Transition Pore and Protect Mice From Hepatic Ischemia/Reperfusion Injury. Gastroenterology 157, 1368-1382. # equal senior investigator

3. Nevers, Q., Ruiz, I., Ahnou, N., Donati, F., Brillet, R., Softic, L., Chazal, M., Jouvenet, N., Fourati, S., Baudesson, C., Bruscella, P., Gelin, M., Guichou, J.F., Pawlotsky, J.M., Ahmed-Belkacem, A., 2018. Characterization of the Anti-Hepatitis C Virus Activity of New Nonpeptidic SmallMolecule Cyclophilin Inhibitors with the Potential for Broad Anti-Flaviviridae Activity. Antimicrobial agents and chemotherapy 62.

4. Lahaye, X., Satoh, T., Gentili, M., Cerboni, S., Silvin, A., Conrad, C., Ahmed-Belkacem, A., Rodriguez, E.C., Guichou, J.F., Bosquet, N., Piel, M., Le Grand, R., King, M.C., Pawlotsky, J.M., Manel, N., 2016. Nuclear Envelope Protein SUN2 Promotes Cyclophilin-A-Dependent Steps of HIV Replication. Cell reports 15, 879-892.

5. Ahmed-Belkacem, A., Colliandre, L., Ahnou, N., Nevers, Q., Gelin, M., Bessin, Y., Brillet, R., Cala, O., Douguet, D., Bourguet, W., Krimm, I., Pawlotsky, J.M., Guichou, J.F., 2016. Fragment-based discovery of a new family of non-peptidic small-molecule cyclophilin inhibitors with potent antiviral activities. Nature communications 7, 12777.