Proposition de stage M2 *(Internship projects)*

Directeur du stage - Encadrement (*tutor - supervisor*) :
Nom/prénom/fonction (surname/first name/quality) : Jean-Christophe Meunier, CR INSERM
Nom/prénom/fonction (surname/first name/quality) : Lucie Rouzoulens, PhD Student
Laboratoire (laboratory) : Inserm U1092, RESINFIT
Adresse (address) : Centre de Biologie et de Recherche en Santé (CBRS), University of Limoges, Limoges France

Titre du stage (*Title*) **: Study of the interplay between cellular lipid metabolism and the human cytomegalovirus life cycle**

Description du sujet (*project presentation*)**:**

Human cytomegalovirus (HCMV) infection is asymptomatic in healthy individuals, but the virus often persist for life in adults. Reactivation is often observed in immunocompromised patients and can lead to severe organ damage and graft rejection. Futhermore, fetal infection is the leading cause of congenital malformations. Antivirals targeting HCMV are available, but their efficacy is largely partial and side effects are frequent. It is essential to develop safe, robust, and innovative therapeutic strategies.

It has been shown that infection with HCMV will be followed by an increase in lipogenesis, and a stimulation of the production of LDLR, CETP and apolipoproteins. These characteristics point to an interaction between HCMV and lipid metabolism components, as already demonstrated for many viruses. As an example, for the hepatitis C virus (HCV), it has shown that HCV life cycle was indeed deeply intertwined with the human lipoprotein metabolism.

Hijacking cellular proteins for any given virus, aiming at promoting its own life cycle, could also be its Achilles heel. Indeed, unlike viral protein targets, virus-associated cellular proteins are not involved in genetic variability. That may constitute very interesting non-viral and genetically stable anti-HCMV therapeutic targets.

Our preliminary results have shown that HCMV infection is strongly facilitated by human serum (as shown for HCV). We have also demonstrated that the apolipoprotein E is critical for this HCMV entry facilitation. This is the first time it has been shown that lipoprotein components associate with HCMV for supporting its life cycle.

The selected student will first confirm these results. She/He will then determine the nature of ApoE-carrying lipoproteins associated with HCMV (HDL, VLDL…) and if possible the HCMV envelope protein involved in this interaction. She/He will characterize the mechanism involving ApoE in HCMV infection stimulation, using purified ApoE and anti-ApoE Ab. She/He will verify if this association protect HCMV from neutralizing commercial antibodies or from HCMV-positive human serum. If time permits, She/He will compare therapeutic molecules-sensible and resistant HCMV variants for their interaction with lipoproteins and lipoproteins components.
In the near future, our goal is to determine if one, or several, of these lipoprotein components may constitute a relevant anti-HCMV therapeutic target.

Références associées au projet (5 max) (*references*)**:**

- Gudleski-O'Regan N, Greco TM, Cristea IM, Shenk T. Increased expression of LDL receptor-related protein 1 during human cytomegalovirus infection reduces virion cholesterol and infectivity. Cell Host Microbe. 2012 Jul 19;12(1):86-96. doi: 10.1016/j.chom.2012.05.012. PMID: 22817990; PMCID: PMC3405916.

- Boyer A, Dumans A, Beaumont E, Etienne L, Roingeard P, **Meunier JC**. The Association of Hepatitis C Virus Glycoproteins with Apolipoproteins E and B Early in Assembly is Conserved in Lipoviral Particles. J Biol Chem. 2014 May ; 289:18904-18913.

- Tréguier Y, Bull-Maurer A, Roingeard P. Apolipoprotein E, a Crucial Cellular Protein in the Lifecycle of Hepatitis Viruses. Int J Mol Sci. 2022 Mar 27;23(7):3676. doi: 10.3390/ijms23073676. PMID: 35409035; PMCID: PMC8998859.

- Farías MA, Diethelm-Varela B, Navarro AJ, Kalergis AM, González PA. Interplay between Lipid Metabolism, Lipid Droplets, and DNA Virus Infections. Cells. 2022 Jul 17;11(14):2224. doi: 10.3390/cells11142224. PMID: 35883666; PMCID: PMC9324743.

- The envelope protein of Zika virus interacts with apolipoprotein E early in the infectious cycle and this interaction is conserved on the secreted viral particles. Tréguier Y, Cochard J, Burlaud-Gaillard J, Lemoine R, Chouteau P, Roingeard P, **Meunier JC**, Maquart* M. Virol J. 2022 Jul. 19: 124.

Principales techniques utilisées (*main techniques used*)**:**

- Cell culture
- Neutralization assays
- Immunostaining
- Virus propagation and titration
- Western blotting

Nature de la gratification* (*bonus, if applicable)*: 596 euros par mois

*Les stages d'une durée de 6 mois font l'objet d'une gratification minimale équivalente à 15% du plafond de la sécurité sociale. Vous trouverez un simulateur à l'adresse suivante (if applicable, cost estimation can be calculated at the following address): https://www.service-public.fr/simulateur/calcul/gratification-stagiaire

Merci de renvoyer vos propositions de stage à l'adresse suivante (*please send your proposal to the following address*):

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