School of LifeSciences
Global Health Institute

Thursday, January 30, 2020 **14h00, SV 1717**

GHI Floor Seminars

Special seminar by invited speaker

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The host cell signalome as a target for chemotherapy of infectious diseases

Host-directed therapy (HDT) is gaining traction as a strategy to combat infectious diseases. It provides (i) untapped targets to limit cross-resistance to existing antimicrobials, and (ii) reduced susceptibility to the emergence of *de novo* resistance. Protein kinases have proven druggability in the context of cancer chemotherapy, and we propose that host cell kinases required for the replication of pathogens are attractive targets for HDT.

We have recently implemented an antibody microarray-based approach to systematically assess the host cell signalling response to intracellular pathogens; most of the antibodies on the array are phospho-specific, allowing to monitor the activation of signalling pathways by infections. We first provided proof of principle, using a Hepatitis C virus/ hepatocyte model, that this can lead to the identification of druggable host targets (protein kinases) and lead molecules to prevent infection (1). We also used this technology to identify the Insulin receptor as a mediator of the block of viral superinfection in mosquitoes infected by *Wolbachia* (2), and to show that a small molecule inhibitor of the insulin receptor impairs Zika virus replication in live mosquitoes.

We have now completed a system-wide study of host erythrocyte response to infection with the malaria parasite *Plasmodium falciparum* and identified several human kinases that are activated by infection; furthermore, inhibitors against some of these kinases display high potency against parasite proliferation *in vitro* (3). We were unable to raise resistant parasite lines against some of these inhibitors, validating that notion that targeting the host limits the ability of the parasite to develop resistance. However, resistance against Trametinib, an inhibitor of the host cell kinase MEK, appeared rapidly, suggesting there is a parasite-encoded off-target for this compound. Unexpectedly, some of the Trametinib-resistant lines have become addicted to the inhibitor, suggesting that the inhibitor interferes with a host cell defense mechanism against the parasite.

Several of the host kinases required for *Plasmodium* proliferation in erythrocytes are also implicated in the replication of other pathogens; for example, c-MET is implicated in infections with *Plasmodium*, the bacterium *Listeria*, as well as Influenza and Ebola viruses (4). This raises the prospect of broad-spectrum anti-infective based on inhibitors of selected kinases.

1. Haqshenas G, Wu J, Simpson KJ, Daly RJ, Netter HJ, Baumert TF, Doerig C. (2017) Signalome-wide assessment of host cell response to hepatitis C virus. **Nature Communications** 8:15158. doi: 10.1038/ncomms15158
2. Haqshenas G, Terradas G, Paradkar PN, Duchemin JB, McGraw EA, Doerig, C. (2019) A Role for the Insulin Receptor in the Suppression of Dengue Virus and Zika Virus in Wolbachia-Infected Mosquito Cells. **Cell Reports** 26(3):529-535.e3.
3. Adderley et al., under review
4. Haqshenas &Doerig (2019) Targeting of host cell receptor tyrosine kinases by intracellular pathogens. **Science Signaling** 12:599

Host: Bruno Lemaitre