

**Project title: Immune mechanisms of liver damage in patients co-infected with HBV and HIV**

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Liver disease from viral hepatitis is now a leading cause of morbidity and mortality in HIV-infected patients. Patients with HIV are more likely to re-activate their HBV (1) and we have shown that this may be attributable to an impairment in the virus-specific T cell responses important for control (2). Although there is some reconstitution of these responses upon reduction of HBV load (3), this is insufficient to regain viral control off therapy. Patients who develop viral resistance are therefore at high risk of rebound viraemia precipitating flares of liver inflammation, with the risk of fatal hepatic decompensation.

We have recently described a novel immune mechanism activated during spontaneous hepatic flares, whereby the cytokine milieu promotes a pathway for NK cell-mediated liver damage (4). We hypothesise that this mechanism of liver damage may likewise be activated during co-infection with HBV/HIV. We therefore aim to investigate the contribution of innate immune mechanisms to hepatocyte death in patients with HIV infection who have evidence of HBV-related liver inflammation. We will sample co-infected patients with or without liver inflammation, including those developing drug-resistant flares, with both cross-sectional and longitudinal study designs. Levels of relevant cytokines will be quantified in the serum and liver, and NK cells, their receptors, ligands and effector functions analysed from the peripheral and intrahepatic compartments. An understanding of the role of innate mechanisms in mediating liver damage may open up new options for treatment of this increasingly common scenario in the co-infected population.

The candidate will join a lab that already has a strong translational focus on HBV pathogenesis, with a group leader who is also a clinician working in viral hepatitis clinics at both UCH and Royal Free Hospital sites. She has worked for many years with the secondary clinical supervisor Richard Gilson and they already have a track record of successfully co-supervising students between the lab and the clinic. They will specifically tailor a programme of additional training to suit this PhD programme, to include:

a) Involvement in patient recruitment: the student will have the opportunity to play a part in the selection and sampling of the HBV/HIV patients to be studied, sitting in on some of clinics from where they will be recruited before taking the blood straight back to

the bench. This will provide a unique continuity of understanding of the clinical context of the samples to be studied for a non-medical graduate.

b) Background clinical experience in HBV and HIV infection: to further enhance their understanding of the relevant disease pathogenesis and current treatment limitations, the student will have opportunities to sit in on in-patient and out-patient clinical case reviews/ward rounds, liver histopathology and radiology meetings. They will also have the chance to attend selected courses pertinent to the clinical and statistical aspects of their study, and to present their findings at multidisciplinary clinical meetings and conferences in addition to the usual scientific audiences.