Project Proposal

Project title: The cellular interactions in a steatotic and inflammatory liver microenvironment that drives the progression and regression of hepatic fibrosis progression.

Supervision:

Primary Supervisor: Prof Eleanor Barnes, Professor of Hepatology and Experimental Medicine and Hon. Consultant Hepatologist, Nuffield department of Medicine (EB)
Oxford Co-lead Supervisors: Emma Culver, Consultant Hepatologist, John Radcliffe Hospital (EC); Alex Gordon Weeks, Consultant Hepato-Biliary Surgeon, Nuffield Department of Surgical Scientists (AGW)
Oxford Collaborators: Tamsin Cargill, Academic Clinical Lecturer; Bioinformatician (appointed by AGW)
External collaborators: Hussein Abbas, Hepatobiliary and liver transplant surgeon, Royal Free Hospital, UK (HA)
GSK Supervisor: Steve Atkinson
GSK Collaborators: Project developed with Katherine Bull and Richard Turner

Background Summary:

Metabolic associated fatty liver disease (MAFLD) is a multisystem disorder defined by hepatic steatosis with at least one trait of the metabolic syndrome, excluding significant alcohol intake or secondary steatosis. Metabolic dysfunction–associated steatotic liver disease (MASLD) affects up to 38% of adults worldwide (1). Disease initiates with steatosis, progressing to inflammation and fibrosis (MASH), cirrhosis, and hepatocellular carcinoma (HCC). HCC risk rises with advanced fibrosis and cirrhosis: a meta-analysis of 64 studies estimated 1.25 HCC cases per 1000 person-years in MASLD and 20 per 1000 in MASLD-related cirrhosis (2). However, the cellular interactions linking steatosis, fibrosis, and carcinogenesis remain poorly defined.

Clinically significant fibrosis (≥F2) strongly predicts mortality and liver-related complications. “At-risk MASH” (MASH with ≥F2 fibrosis) is the main treatment target in clinical trials. Fibrosis regression is associated with improved prognosis, and both fibrosis reduction and MASH resolution are regulatory endpoints for drug approval. Recently, resmetirom (a thyroid hormone receptor beta agonist) (3) and semaglutide (a GLP-1 receptor agonist) (4,5) received conditional FDA approval for non-cirrhotic MASH with fibrosis. Yet, no liver-directed therapies exist for MASLD-related cirrhosis, and the mechanisms by which drugs confer hepatoprotection remain unclear.

The liver microenvironment and the development and reversal of fibrosis is orchestrated by crosstalk among heterogeneous immune, parenchymal, and stromal populations (6-9). This immunological niche must balance tolerance to gut-derived antigens with inflammation against pathogens (10-11).

We hypothesise that: the cellular phenotype, location, and cell-cell interactions in the background liver in patients with steatotic liver disease, irrespective of its cause, have shared characteristics that promote the development of liver-related complications and malignancy within the liver niche. In particular, interactions between fibroblasts, parenchymal, myeloid, and/or regulatory T cells may favour fibrotic progression and/or tumorigenesis, and disruption of such interactions may result in fibrosis regression.

In this DPhil, you will aim to assess:

(1) The mechanistic similarities and differences between steatotic liver diseases due to metabolic (MASLD), alcohol (ALD) and combined MetALD, with an emphasis on more advanced liver disease (stage ≥F2 or cirrhosis).
(2) The mechanistic influence on the development of HCC in these cohorts.
(3) The mechanistic basis for fibrosis regression within the context of a variety of therapeutic interventions (diet/exercise, bariatric surgery, drugs) in advanced fibrotic liver disease.
(4) Evaluate circulating and imaging-based biomarkers indictive of therapeutic efficacy on fibrosis and inflammation.

Approach and pre-existing infrastructure/cohorts:

The DPhil will focus on the use of multi-omic methods including single-cell sequencing, proteomics, and spatial transcriptomics. You will apply a patient-centric approach to understanding human disease endotypes and pathological mechanisms of steatotic liver disease, thus enhancing future patient stratification and precision medicine strategies in drug development.
Ethical approvals are already in place for the DeLIVER CRUK funded program in advanced fibrosis and HCC (https://deliver.cancer.ox.ac.uk/EB as CI, EC as Oxford PI) and the NIHR Oxford BRC-funded TGLU Biobank (EC PI for “at-risk” cirrhosis). Amendments will enable data sharing with GSK. Data will be shared publicly following high-impact publications.

Cohorts:

1. DeLIVER cohort: CRUK-funded since 2020 to detect primary liver cancer in cirrhosis and non-cirrhotic MASLD. Includes the PEARL cohort (>2300 patients with cirrhosis of MASLD, ALD, MetALD, or viral hepatitis; 5-year follow-up with biomarkers and clinical data). Also includes DELPHI: single-cell sequencing of blood and tissue from 15 patients with advanced fibrosis at risk of HCC.
2. Celeste cohort: Investigates transcriptomic and proteomic changes in cirrhosis and non-cirrhotic MASLD at high HCC risk. Forty FFPE liver resections (including cancers) have undergone multiplexed ion beam imaging (MIBI) and Xenium spatial transcriptomics. The MIBI panel builds on validated CellDive platforms.
3. NIHR Oxford BRC-funded TGLU Biobank: Collects data and samples from MASLD-cirrhosis, non-cirrhotic MASLD, and other liver disease patients for storage and analysis.
4. Oxford Centre for Histopathology Research (OCHRe): Provides samples pre- and post-weight loss via (1) lifestyle change, (2) bariatric surgery, or (3) GLP-1 therapy (semaglutide). Three longitudinal cases per group will be studied for fibrosis regression. Samples include FFPE tissue (OUH histopathology) and/or snap-frozen surgical tissue.
5. De-fatted liver samples (access HA): A cohort of transplant-rejected livers due to steatosis. These have undergone normothermic machine perfusion over a 3-day period, during which, tissue biopsies were taken before, during and after de-fatting with a combination of L-carnitine and Forskolin. This provides a unique and powerful patient-matched before and after cohort from which mechanistic insights can be gained with regards the effect of reducing liver fat on tissue microenvironment composition and cell-cell interactions at the transcriptome level. The cohort size is 30 patients with at least 3 samples per patient.

Project delivery:

Experimental methodology to address objectives: Multi-omic analysis on liver tissue using sc-sequencing technology, proteomics and spatial transcriptomics. Spatial proteomics has to date used Multiplexed Ion Beam Imaging (MIBI)), and for spatial transcriptomics we are applying Xenium technologies. Biomarker analysis using whole blood/PBMC will be determined in the same patients. These platforms have already been worked up and optimised on liver tissues but collaborators within the group.

Facilitate fellow's training in research methods related to data science: technical skills in wet lab support provided to develop bioinformatic computational skills to interrogate spatial data

Deliverables will be developed with the applicant with clear milestones against which to assess progress, but will include analysis of i) existing (MASLD) and alcohol (ALD) MIBI and spatial transcriptomic data sets ii) pre and post steatotic regression (using human liver FFPE tissue and the ex-vivo transplant rejected whole livers).

L**everages existing Oxford-GSK infrastructure and/or builds new capabilities:** This project leverages BRC and DeLIVER resources, plus Oxford–GSK expertise. Pipelines for spatial proteomics and transcriptomics integrate cellular and acellular analyses, neighbourhood/community mapping, and normalization. These have already been established by the collaborating groups for the CosMx spatial transcriptome and MIBI proteome imaging platforms (EC and AGW DPhil student). Together, they will enable the most detailed analysis of commonalities and differences across liver environments.

Research environment (see embedded links):

There is exceptional access to a range of prospective biobanks (INTEGRATOR/TGLU/ORB) and diagnostic archive tissue samples (OCHRe). This studentship would also leverage existing data and banked samples from a range of large well-annotated liver cohorts including DeLIVER, PEARL and CELESTE. The CELESTE Project is supported by a pump priming grant from the Oxford Cancer Centre. Collection and analysis of these bespoke samples is supported by various infrastructure grants (e.g. CRUK Oxford Cancer Centre of Excellence, NIHR-BRC Oxford), existing personnel (e.g. postdoctoral researchers and research assistants), and discounted access to on-site platforms (e.g. Xenium). Downstream analysis of spatial data will be supported by our collaborators in mathematics and engineering, who have developed pipelines such as MuSpAn and SpatioEV. The CRUK Centre further provides dedicated support to ensure that research remains representative and aligned to patient priorities (Oxford Cancer Patient and Public Involvement Committee). To unite multi-disciplinary expertise around liver disease, we recently established the Oxford Liver Cancer Centre of Excellence (OLivE). We are well placed to translate findings through Oxford's multiple clinical trials units, including our Hepatology Clinical Trials Department based in the John Radcliffe Hospital supporting a range of steatotic liver disease (MASLD, ALD) studies.

Extent and frequency of any clinical commitments expected of the fellow

This would be a full-time DPhil position, and the focus will be on the development of scientific skill. Attending clinics (where this benefits the research program) e.g. the weekly joint Hepatology-Endocrine Metabolic Liver Clinics at OUH to better understand patient risk factors and treatment targets would be encouraged.

References

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