HEPATOLOGY RESEARCH GROUP
INSTITUTE OF TRANSLATIONAL AND STRATIFIED MEDICINE, PLYMOUTH UNIVERSITY PENINSULA SCHOOLS OF MEDICINE AND DENTISTRY

Hepatology Research Group (HRG) structure:

*Head of group:*
Prof Matthew Cramp, Professor of Hepatology and Consultant Hepatologist

*Clinical Academics:*
Dr David Sheridan Associate Professor (Senior Lecturer) of Hepatology and Honorary Consultant Hepatologist,
Dr Ashwin Dhanda, Academic Clinical Lecturer

*Senior Scientists:*
Dr Daniel Felmlee, Lecturer,
Dr Doha Hegazy, HRG Manager

*Clinical Research Fellows:*
Dr Ollie Rupar – PhD student, Dr Asma Ahmed and Dr Evi Mandalou, MD students (writing up), Dr Maggie Ow – awarded MD in 2016

*PhD Fellows:*
Isaac Shawa, Paula Boeira


**Overview:**
2016 was a successful year for the group with continued growth and diversification of the research portfolio and a good number of publications and presentations. The HRG has developed its 3 main areas of research in 1) hepatitis C virus infection and protection from infection, 2) non-alcoholic fatty liver disease, 3) alcohol related liver disease, and is now developing a 4th strand of research studying liver cancer development and its prevention. A short summary of work in each of these areas is included in this report.

The research group together with the wider clinical team of the South West Liver Unit continue to be actively involved in many clinical trials and are major recruiters to a number of interventional studies including those for HCV infection, non-alcoholic fatty liver disease, alcoholic hepatitis, and advanced decompensated liver disease. In HCV studies the treatment success rates continue to astound, and every single patient recruited by the group to a HCV treatment trial in 2016 achieved virological cure, despite many of them having advanced liver disease.
A useful collaboration with Bath University saw 2 excellent undergraduates join us in September for one year laboratory based projects. This has proved very successful and we hope it continues.

**Hepatitis C Virus infection and Protection from Infection**  
**Leads: Matthew Cramp, Dan Felmlee**

The viral hepatitis laboratory research programme continues with the HCV exposed uninfected cohorts, and is revealing new insights into potential mechanisms of resistance. The study of immune correlates with direct acting antiviral treatment outcomes has again shown the importance of interactions between host and virus.

The whole-exome sequencing study of a small and very rare cohort of blood transfusion HCV exposed but uninfected cases has unearthed some fascinating genetic findings that are currently being verified. This group appear to have high level resistance against HCV infection and searching through their genomes has revealed a small number of candidate genes some of which have clear theoretical links to viral entry into hepatocytes. We are developing a cell culture model using CRISPR /Cas-9 to functionally validate the findings and clarify how resistance to HCV infection can be conferred. The establishment of a category 3 containment lab in the Derriford Research Facility, due to open in 2017, will be of great help in this work.

Isaac Shawa’s work on individuals who are exposed to HCV through injection drug use continues. His work with Imperial College London has further clarified the key link between lipids and outcomes following exposure to HCV infection. Isaac’s poster outlining his lipidomics findings was selected as a top scoring abstract for the national liver meeting and for publications in the journal *Clinical Liver Disease* as part of the Best of BASL (British Association for the Study of the Liver), 2016. Isaac is also completing work on innate immune responsiveness in this group of cases with work due for completion in mid 2017.

Asma Ahmed completed her detailed study of the evolution of adaptive and innate immune responses in patients undergoing anti-viral treatment and is currently analysing the findings to seek correlates of treatment success or failure. Some of this work has already been presented at national and international meetings with publications and MD submission anticipated in 2017.

**Non-alcoholic fatty liver disease**  
**Lead: David Sheridan, Dan Felmlee**

The HRG strategy is to develop this field of research and 2016 saw substantial investment with a focus on delivery of cutting edge translational research studies in non-alcoholic fatty liver disease (NAFLD) diagnostics, pathogenesis and treatment.
In NAFLD and its liver-damaging sequelae non-alcoholic steatohepatitis (NASH), we have completed recruitment to an international study investigating the utility of Controlled Attenuation Parameter (CAP) and Transient Elastography to diagnose and assess liver fat content using liver histology as the reference standard. The data has been accepted for oral presentation (co-author) at EASL 2017.

The HRG, with the income received from the clinical trials programme, was able to invest in the MRI infrastructure at Plymouth Hospitals NHS Trust to deliver state of the art non-invasive assessment of liver fat, including MRI-PDFF imaging and multiparametric MRI. We are now able to perform LiverMultiscan provided by Perspectum Diagnostics Ltd in the context of the Regenerate Trial, and are the only centre in the South West with the capability to do this.

In NASH therapeutics, we are successfully contributing to several phase 2 and 3 clinical trials, and are amongst the largest recruiters in Europe.

A major industrial collaboration has been established with the Oxford University spin-out company CNBio Innovations Ltd to utilise 3D Primary Hepatocyte culture for investigation of the role of mitochondrial function in the progression from NAFLD to NASH. This state-of-the-art culture system has the potential to investigate liver disease in the laboratory like never before. The mitochondrial work involves close collaboration with Dr Affourtit and the mitochondrial lab currently based in the main Plymouth University campus. In 2016 we were awarded a PhD stipend from Plymouth University and welcomed a new PhD student (Paula Boeria) into the group in January 2017 to work on this project. This work is integrated with the Inflammatory Liver Disease Biobank and extensive work has been undertaken to set up the Human Tissue Authority approved biobank, hosted by PUPSMD.

2016 saw the completion of the first national survey for NAFLD care standards completed and accepted for publication.

**Alcohol related liver disease**

**Lead: Ashwin Dhanda**

This is another area of strategic development for the HRG and in 2016 Ashwin focussed on raising the groups national profile and impact in the field of alcohol related liver disease. He has been appointed as a Topic Expert for the NICE Clinical Guidelines Update Committee for Alcohol Use Disorders and is a member of the British Society of Gastroenterology Liver Clinical Research Group which develops collaborative clinical trial proposals.

Laboratory work in this field has started with patients cared for by the South West Liver Unit recruited into a study investigating the immune dysregulation that contributes to alcohol related liver disease.

Work on further developing and validating a novel bioassay to predict response to corticosteroid treatment continues. This is work started by Ashwin in Bristol with the assay protocol recently published (Williams et al, Biomarker Research 2016). The
group are co-applicants on a large national collaborative grant application to the Medical Research Council to improve outcomes in patients with alcoholic hepatitis, and seeking to validate the use of this assay as a clinically useful tool to predict mortality and response to current treatment.

**HRG Management and teaching**
**Lead: Doha Hegazy**

The group structure has significantly expanded over the last few years - the current team consists of 5 senior staff members, 3 PhD/MD students in the writing stage of the research projects and 2 students from Bath University for 1 year research projects as part of their degree course. In addition, we have appointed two new research fellows in 2016 who will start in January and February 2017 and expect to appoint a new NIHR (National Institute for Health Research) Academic Clinical Fellow post in early 2017.

Doha’s focus on supporting postgraduate research students has facilitated good progress in all areas of laboratory work. All HRG members are trained to meet the required standards including information governance, ICH-GCP (for clinicians involved in clinical trials), and to meet all the requirements of the Human Tissue Act which is especially important with the development of a biobank for liver disease. With the expansion of the group and diversification of the research portfolio, data security has been a focus this year. All group members are aware of their obligations and we have established a secure electronic database accessible only by fully trained members of the group. Health and safety in the research environment is important and Doha leads on ensuring all group members work strictly to agreed protocols and follow appropriate standard operating procedures.

Inspiring the next generation of researchers is key and the group, led by Doha, remains actively involved in teaching medical students and other undergraduates. We run a number of Special Study Units to introduce students to the laboratory and to foster interest in translational research.

**Research Outputs for 2016 – see appendix**

**Future Plans**

2017 will see the opening of the Derriford Research Facility (DRF), a landmark £14.8 million investment by Plymouth University in biomedical research infrastructure, providing state-of-the-art laboratories and a rich, collaborative environment for University researchers and our partners. The DRF is located adjacent to the main Plymouth University Peninsula Schools of Medicine and Dentistry (PUPSMD) building and the neighbouring Derriford Hospital and is part of the University’s £25 million investment in medical research to accelerate translation into patient care and improved outcomes for people living with devastating conditions. The DRF will bring
together Plymouth University’s medical, dental and biomedical laboratory-based research under one roof facilitating enhanced interdisciplinary working and clinical collaborations.

The DRF will very significantly expand the laboratory facilities at the medical school site and includes a containment level 3 laboratory which will allow the HRG to develop cell culture techniques to fully understand the mechanisms of HCV resistance identified in the blood transfusion cohort of cases. Excitingly the expanded laboratory facilities will see the transfer of researchers from the main university campus to facilitate collaborations in all areas of our laboratory research.

A new area of research is starting in 2017 to investigate the pathogenesis of liver cancers, both primary and secondary, and the role of universal tumour antigens in tumour behaviour and treatment response. This project is a collaboration between Matthew Cramp and Michael Jarvis (Associate Professor in Virology and Immunology, School of Biomedical & Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry). Dr Ollie Rupar joins the group in Feb on this NIHR funded PhD research project which is ultimately aimed at developing a vaccination strategy to prevent tumour development and to enhance cancer treatment response rates.

We continue to look for new and innovative ways to fund service developments and research, and together with the SW Academic Health Science Network, David Sheridan has facilitated progression of the Devon Outcomes Based Commissioning Demonstrator to apply for Social Impact Bond funding streams to develop alcohol services across Devon. This has the potential to unlock a significant investment in new services for the region.

Many new clinical trials are envisaged for 2017 with novel interventional studies in alcoholic hepatitis, non-alcoholic fatty liver disease as well as viral hepatitis all due to commence.

Financial sustainability of the group remains a key priority and 2017 is going to see a specific drive to bring together pilot data from the recent investments in NAFLD and alcohol related liver disease to support Research Council Grant Funding applications.

We remain immensely grateful to all the patients and their families who have supported us by getting involved in clinical trials and consenting to the research work, to all our collaborators across the UK and abroad, and to our major sponsor, the Mary Kinross Trust for their continued generosity and support of Dr Doha Hegazy and the Hepatology Research Group.
Appendix 1:

Research Outputs for 2016:

Publications:


Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes.
_Hepatology_. 2016 Jul;64(1):34-46

New perspectives for preventing hepatitis C virus liver graft infection.
Felmlee DJ, Coilly A, Chung RT, Samuel D, Baumert TF.

FibroGENE: A gene-based model for staging liver fibrosis.
_J Hepatol_. 2016 Feb;64(2):390-8

Apolipoprotein E Mediates Evasion From Hepatitis C Virus Neutralizing Antibodies.
_Gastroenterology_. 2016 Jan;150(1):206-217

A targeted functional RNA interference screen uncovers glypican 5 as an entry factor for hepatitis B and D viruses.
_Hepatology_. 2016 Jan;63(1):35-48

Conference Presentations:

**European Association for the Study of the Liver Annual Meeting, Barcelona April 2016:**

- Dhanda AD, Collins PL. Infection is common in patients with severe alcoholic hepatitis treated with steroids but not associated with poor outcome. J Hepatol 2016; 64: S228
  - Presented as poster. Received Young Investigator award for registration

**British Association for the Study of the Liver Annual meeting, Manchester Sept 2016**
Ahmed A, Dhanda A, Hegazy D, Felmlee D, Sheridan D, Cramp ME. Sustained viral clearance of HCV with DAA treatment is associated with restoration of effector T cell phenotype
Presented as poster.

Isaac Thom Shawa; Maria Gomez Romero; Alexandros Pechlivanis; Daniel J Felmlee; Mary Crossey; Elaine Holmes; Margaret Bassendine; Simon Taylor Robinson; David A Sheridan; Matthew E Cramp. Serum lipid profiling using Ultra-performance liquid chromatography mass spectrometry (UPLC/MS) discriminates HCV exposed uninfected injection drug users from those susceptible to infection.
Presented as poster.

Isaac Thom Shawa, I.Jane Cox, Antonio Riva, James N Fullerton, Daniel J Felmlee, David A Sheridan, Shilpa Chokshi, Matthew E Cramp. Urine metabolomics profiling distinguishes HCV exposed uninfected injection drug users from those with chronic infection or resolved HCV infection.
Presented as poster.

American Association for the Study of Liver Disease Annual Meeting
Boston, US Nov 2016

Ahmed A, Dhanda A, Hegazy D, Felmlee D, Sheridan D, Cramp ME. Sustained viral clearance of HCV with DAA treatment is associated with restoration of effector T cell phenotype
Presented as poster.

Foster GR, Agarwal K, Cramp M, Moreea S, Barclay ST, Collier J, Brown AS, Ryder SD, Ustianowski A & Forton DM 'C-ISLE: Grazoprevir/Elbasvir plus Sofosbuvir in Treatment-naive and Treatment-experienced HCV GT3 Cirrhotic Patients Treated for 8, 12 or 16 weeks'
Presented as poster

Staging fibrosis and excluding advanced fibrosis in patients with NAFLD: comparison of non-invasive markers in an interim analysis from a prospective multicentre study
Peter J. Eddowes, Quentin Anstee, Indra Neil Guha, David A. Sheridan, Emmanouil Tsochatzis, Jeremy Cobbold, Michael E. Allison, Valerie Paradis, Pierre Bedossa, Philip N. Newsome
Presented as poster

Novel Fibroscan-Based Score to Diagnose NASH and its severity in A Multi-centre UK Cohort of Patients with Suspected NAFLD
Peter J. Eddowes, Quentin Anstee, Indra Neil Guha, David A. Sheridan, Emmanouil Tsochatzis, Jeremy Cobbold, Michael E. Allison, Victor de
Ledinghen, Magali Sasso, Celine Fournier, Véronique Miette1, Valerie Paradis, Pierre Bedossa, Philip N. Newsome
Presented as poster

FOCIS (Federation of Clinical Immunology Societies):