007

FXR ANTAGONISTS AS NEW AGENTS FOR COVID19

Teresa Brevini^{1*}, Mailis Maes², Gwilym J Webb³, William TH Gelson³, Sally Forrest², Petra Mlcochova², Scott Dillon¹, Sagar Varankar¹, Mahnaz Darvish-Damavandi⁴, Victoria L Mulcahy⁵, Rhoda E Kuc⁶, Thomas L Williams⁶, Vasileios Galanakis¹, Marta Vila-Gonzalez¹, Olivia C Tysoe^{1,7}, Daniele Muraro⁸, Thomas WM Crozier², Johannes Bargehr¹, Sanjay Sinha¹, Sara S Upponi⁹, Lisa Swift⁷, Kourosh Saeb-Parsy⁷, Susan E Davies¹⁰, Thomas Marjot¹¹, Eleanor Barnes¹¹, Ansgar W Lohse¹², Andrew M Moon¹³, A Sidney Barritt IV¹³, Ravindra K Gupta², Stephen Baker², Anthony P Davenport⁶, Gareth Corbett¹⁴, Simon JA Buczacki⁴, Joo-Hyeon Lee¹, Paul Gibbs⁷, Andrew J Butler⁷, Christopher JE Watson^{7,15}, George F Mells³, Gordon Dougan², Ludovic Vallier^{1,7}, Fotios Sampaiziotis^{1,3,5}.
¹Wellcome-MRC Cambridge Stem Cell Institute, University Of Cambridge, Cambridge, UK; ²Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), Department of Medicine, University of Cambridge, Cambridge, UK; ³Cambridge Liver Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ⁴Nuffield Department of Surgical Sciences, Old Road Campus Research Building, Oxford, UK; ⁵Department of Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ⁶Experimental Medicine and Immunotherapeutics, University of Cambridge, Addenbrooke's Hospital, Cambridge UK, Cambridge, UK; ⁷Department of Surgery, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ⁸Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, Cambridge, UK; ⁹Department of Radiology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ¹⁰Department of Histopathology, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK; ¹¹Oxford Liver Unit, Translational Gastroenterology Unit, Oxford University Hospitals NHS Foundation Trust, University of Oxford, Oxford, UK; ¹²University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ¹³Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, USA; ¹⁴Cambridge University Hospital NHS Foundation Trust, Cambridge, UK; ¹⁵National Institute of Health Research (NIHR) Cambridge Biomedical Research 2 Centre, and the NIHR Blood and Transplant Research Unit (BTRU) at the University of 3 Cambridge in collaboration with Newcastle University and in partnership with NHS Blood and 4 Transplant (NHSBT), Cambridge, UK

10.1136/gutjnl-2021-BASL.7

Introduction The management of COVID19 is complicated by vaccine availability, the modest efficacy of existing treatments, and the potential for viral resistance. Therefore, there is a pressing need for new prophylactic and therapeutic agents. The viral receptor ACE2 is an ideal target as it is required for SARS-CoV-2 entry in host cells. Modifying ACE2 expression could prevent infection and/or limit disease progression. Nevertheless, the mechanisms controlling ACE2 expression remain elusive.

Aims To identify pathways controlling the transcriptional regulation of ACE2, and exploit them to reduce SARS-CoV-2 infection.

Methods Organoids from primary biliary, intestinal and pulmonary epithelia were derived and cultured as previously described. Single-cell RNA sequencing, QPCR, immunofluorescence and flow cytometry were used to assess marker expression. Chromatin immunoprecipitation was used to assess FXR binding on DNA. Bronchoalveolar lavage SARS-CoV-2 patient isolates were used for infection experiments. Human livers not used for transplantation were connected to the metra (OrganOx) normothermic perfusion device and perfused ex-situ using therapeutic doses of UDCA for 12 hours. ACE2 activity was measured following manufacturer's instructions. Patient data from the COVID-Hep and SECURE-Liver registries were compared using propensity score matching for sex, age and Child-Turcotte-Pugh score.

Results We first demonstrated that cholangiocytes are susceptible to SARS-CoV-2 infection in vivo and in organoid culture. We then used cholangiocyte organoids to identify FXR

as a transcriptional regulator of ACE2. We validated our results in pulmonary and intestinal organoids, showing that ACE2 regulation by FXR represents a broad mechanism present in multiple COVID19-affected tissues. We then demonstrated that approved FXR inhibitors, such as ursodeoxycholic acid (UDCA) and z-guggulsterone (ZGG), decrease ACE2 levels and reduce viral infection in vitro in primary biliary, intestinal and pulmonary organoids. We interrogated the impact of systemic UDCA administration in human livers perfused ex-situ, demonstrating reduced ACE2 levels and SARS-CoV-2 infection. Furthermore, we showed that commencing UDCA treatment lowers ACE2 levels in primary biliary cholangitis (PBC) patients. Finally, we identified a correlation between UDCA treatment and better clinical outcome in COVID-19 patients, including hospitalisation, ICU admission, mechanical ventilation and death, using registry data.

Conclusion We identified FXR as a novel master regulator of ACE2 expression. Using a bench-to-bedside approach we combined in vitro, ex-vivo and patient data to demonstrate the efficacy of ACE2 downregulation against SARS-CoV-2 infection and identified approved and inexpensive drugs (UDCA, ZGG) which could be repurposed as prophylactic and therapeutic agents against SARS-CoV-2 infection, paving the road for future clinical trials.

008

DIETARY FACTORS UNDERLYING NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND ITS SEVERITY: A LARGE, POPULATION-BASED, CASE-CONTROL STUDY

^{1,2}Amrita Vijay, ^{1,2}Amina Al-Awadi*, ^{1,2}Jane Chalmers, ^{3,4}Leena Balakumaran, ^{1,2}Jane Grove, ^{2,5}Ana Valdes, ⁶Maira Taylor, ⁴Kotacherry Shenoy, ^{1,2}Guruprasad Aithal.
¹Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK; ²NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK; ³Holistic Health and Research Institute, Trivandrum, India; ⁴Population Health and Research Institute, Trivandrum, India; ⁵School of Medicine, University of Nottingham, Nottingham, UK; ⁶School of Life Sciences, University of Nottingham, Nottingham, UK

10.1136/gutjnl-2021-BASL.8

Background Studies investigating dietary factors underlying the development of non-alcoholic fatty liver disease (NAFLD) have focused on either total energy intake or the role of specific macro- or micronutrients. Systematic evaluation of influence of diverse food types on the development of NAFLD and co-morbidity cluster is lacking. Prevalence of NAFLD is higher in Asia (29.6%) than the global average of 25%. We hypothesised that specific food groups, types and cooking methods determine the susceptibility to NAFLD and its severity in this population.

Methods Using a validated food frequency questionnaire (FFQ) involving 361 local recipe compositions, individual dietary intakes and health characteristics were collected from 993 NAFLD patients and 973 healthy controls in Trivandrum (Kerala, India). Each of 2165 individual ingredients were categorised into 3 levels using a food tree-based classification: 'food groups' such as cereals, vegetables, formed tree-level 1; 'food types' such as refined rice, leafy vegetables, formed