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FXR ANTAGONISTS AS NEW AGENTS FOR COVID19

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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.

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

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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

tree-level 2; and 'cooking methods' such as boiling, frying, formed tree-level 3. The associations between particular food intakes and health outcomes (presence of NAFLD and significant fibrosis, diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular events) were determined by logistic regression.

Results Individuals with NAFLD consumed significantly higher amount of cereals (as refined rice), fat and edible oils (as animal fat), meat (as red meat), sugar (as refined sugar) and fried foods, and lower amount of vegetables, pulses, nuts, seeds, and milk compared to controls (all $P < 0.05$). Consumption of meat (as red meat), fats (as animal fat), nuts and refined rice was positively associated with both the presence of NAFLD and its severity (significant fibrosis), whereas, consumption of vegetables (as leafy vegetables), fruits, oily seeds, spices, and dried pulses was negatively associated with NAFLD. Fried and boiled food consumption were positively and negatively associated with NAFLD, respectively. Increased consumption of animal fats was associated with diabetes, hypertension, and cardiovascular outcomes, whereas consumption of wholegrain rice was negatively associated with these health-related outcomes.

Conclusions Comprehensive evaluation of food intakes using validated FFQ and tree-based approach in a large, well-characterised population-based cases and controls has enabled the identification of specific dietary indicators associated with NAFLD, its severity and the co-morbidity cluster. These findings provide a basis for culturally sensitive advice to prevent the development of NAFLD as well as the design of individualised intervention in those with NAFLD.

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A DOUBLE BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY TO ASSESS SAFETY AND TOLERABILITY OF ORAL ENTEROSORBENT CARBALIVE (YAQ-001) IN CIRRHOTIC PATIENTS

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Background Yaq-001 is a non-absorbable, synthetic carbon with high adsorptive capacity for bacterial products including lipopolysaccharide (LPS) and pro-inflammatory cytokines. Studies in cirrhotic rats showed reduced endotoxemia, improvements in end-organ dysfunction and reduced sensitisation to LPS. The aims of this study were to evaluate the safety and tolerability of Yaq-001 in decompensated cirrhotic (DC) patients and characterise immunological and metabolic effects. **Methods** This EU-funded H2020 study (CARBALIVE:634579) recruited patients with diuretic-responsive cirrhotic ascites. 28-

Abstract 009 Figure 1 Effect of Yaq-001 treatment on indices of systemic (A) and gut (B) inflammation and (C) gut permeability (SD+SEM). HC and Decomp values from PMID: 32838247