4.90 to 5.11, APC = +0.37%), ALD (from 4.67 to 4.81, APC = +0.45%); and NAFLD (1.53 to 1.74, APC = +1.33%) increased.
Analysis of GBD regions suggests that increases (APC) in HBV-, HCV- and NAFLD-related deaths from LC was highest in Central Latin America, while increases in ALD-related death from LC was highest in High-income North American region (Figure). Additionally, increases in HBV-, HCV-, ALD-related deaths from CLD were highest in Caribbean region while increases in NAFLD-related deaths from CLD was highest High-income North American region (Figure).
Conclusion: The burden of CLD and LC are driven by increases in NAFLD and ALD. There are also regional differences in burden and etiology of liver disease.

GS009

Is there a murine model that fully recapitulates human NASH? An unbiased bioinformatics approach to rank pre-clinical models based on proximity to human disease

Michele Vacca[1,2], Ioannis Kamzolas[1,3], Lea Mørch Harder[4], Fiona Oakley[5], Christian Trautwein[6], Maximilian Hatting[6], Trenton Ross[7], Barbara Bernardo[8], Anouk Oldenburger[9], Sara Toftegaard Hjuler[4], Iwona Ksiazek[10], Daniel Linden[11,12], Detlef Schuppan[13], Sergio Rodriguez-Cuenca[1], Maria Manuela Tonini[14], Aimo Kannt[15,16], Tamara Rodriguez-Castaneda[15], Cecília M. P. Rodrigues[17], Simon Cockell[18], Olivier Govaere[19], Ann K. Daly[19], Michael Allison[20], Kristian Honnens de Lichtenberg[4], Yong Ook Kim[13], Anna Lindblom[11], Stephanie Oldham[21], Anne-Christine Andréasson[11], Franklin Schlerman[22], Jonathon Marioneaux[23], Arun Sanyal[24], Marta B. Afonso[17], Anthony Rinaldi[7], Yuichiro Amano[25], Valérie Paradis[26], Alastair Burt[19], Davies Susan[27], Ann Driessen[28], Hiroaki Yashiro[29], M. Julia Brosnan[7], Carla Yunis[7], Pierre Bedossa[30], Dina Tiniakos[31,32], Quentin Anstee[31,33], Evangelia Petsalaki[3], Peter Davidsen[4], Jim Perfield[34], Antonio Vidal-Puig[1]. *[1]University of Cambridge, WT/MRC Institute of Metabolic Science, United Kingdom; [2]University of Bari Aldo Moro, Interdisciplinary Department of Medicine, Bari, Italy; [3]European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, UK, Hinxton, Cambridge, United Kingdom; [4]Novo Nordisk, Research and Early Development, Novo Nordisk A/S, Denmark, Måløv, Copenhagen, Denmark; [5]Newcastle University, Newcastle Fibrosis Research Group, Biosciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, Newcastle, United Kingdom; [6]Aachen University Hospital, Department of Medicine III, Aachen; [7]Pfizer IMRU, Internal Medicine Research Unit, Pfizer Worldwide Research and Development, Cambridge Massachusetts, United States; [8]Pfizer, Internal Medicine, Pfizer Worldwide Research and Development, 558 Eastern Point Road, Groton, CT, 06340, USA, Groton, United States; [9]Boehringer Ingelheim Pharma GmbH and Co. KG, CardioMetabolic Diseases Research, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach a.d. Riss, Germany, Biberach an der Riß, Germany; [10]Novartis Pharma AG, Novartis Institutes for BioMedical Research, Novartis Pharma AG, 4056 Basel, Switzerland, Basel, Switzerland; [11]AstraZeneca, Bioscience Metabolism, Research and Early Development Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals RandD, AstraZeneca, Gothenburg, Sweden, Gothenburg, Sweden; [12]University of Gothenburg, Division of Endocrinology, Department of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden, Gothenburg, Sweden; [13]Institute of Translational Immunology and Research Center for Immunotherapy, Johannes Gutenberg University Medical Center, Mainz, Germany; [14]Integrated Biobank of Luxembourg (IBBL), Luxembourg Institute of Health, Translational Medicine Operations Hub, Luxembourg, Dudelange, Luxembourg; [15]Sanofi-Aventis Deutschland GmbH, RandD Diabetes, Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt, Germany, Frankfurt am Main, Germany; [16]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Theodor-Stern-Kai 7, 60956 Frankfurt, Germany, Frankfurt am Main, Germany; [17]University of Lisbon, Research Insitute for Medicines, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal, Lisbon, Portugal; [18]Newcastle University, Bioinformatics Support Unit, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, Newcastle upon Tyne, United Kingdom; [19]Newcastle University, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, Newcastle upon Tyne, United Kingdom; [20]Cambridge University Hospitals NHS Foundation Trust, Liver Unit, Cambridge NIHR Biomedical Research Centre, Cambridge, United Kingdom; [21]AstraZeneca, Bioscience Metabolism, Research and Early Development Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals RandD, AstraZeneca, Gaithersburg, MD, USA, Gaithersburg, MD, United States; [22]Pfizer, Inflammation and Immunology Research Unit, Pfizer Worldwide Research and Development, Cambridge Massachusetts, Cambridge Massachusetts, United States; [23]Sanyal Biotechnology LLC, Sanyal Biotechnology LLC, Norfolk, Virginia, USA, Virginia, United States; [24]Virginia commonwealth university, Department of Internal Medicine, Virginia commonwealth university, Richmond, VA, United States; [25]Takeda Pharmaceuticals International AG, Takeda Pharmaceuticals International AG, Takeda Pharmaceutical Company Limited, Fujisawa, Japan, Fujisawa, Japan; [26]Université Paris-Diderot, Department of Imaging and Pathology, Hôpital Beaujon, Paris, France; [27]Cambridge University Hospitals NHS Foundation Trust, Department of Cellular Pathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [28]University of Antwerp, Department of Pathology, University of Antwerp, Antwerp, Belgium, Antwerp, Belgium; [29]Takeda Pharmaceuticals International AG, Takeda Pharmaceuticals International AG, Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts, Cambridge, Massachusetts, United States; [30]Newcastle University, LiverPat, Paris, France and Translational and Clinical Research Institute, Newcastle University, UK, France; [31]Newcastle University, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, Newcastle upon Tyne, United Kingdom; [32]National and Kapodistrian University of Athens, Department of Pathology, Aretaieion Hospital, Medical School, National and Kapodistrian University of Athens, Greece, Athens, Greece; [33]Newcastle University, Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom, Newcastle upon Tyne, United Kingdom; [34]Eli Lilly and Company, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, Indianapolis, Indiana, United States*
Email: ajv22@medschl.cam.ac.uk

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is recognized as a dysmetabolic state encompassing a wide range of liver diseases, including simple steatosis, steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. The majority of preclinical NASH research is performed in rodents; nevertheless, the appropriate model recapitulating human disease is yet uncertain. To address this major unmet need, the LITMUS group did a wide-ranging retrospective review of commonly used murine models, comparing them to human NASH.
Method: We collated data/samples from 42 murine genetic/dietary NAFLD models (617 animals) and developed a complex bioinformatics pipeline providing an unbiassed ranking system (NASH Human Proximity Score, NHPS) that incorporates 1) metabolic phenotype; 2) centralized liver histology; 3) liver transcriptome benchmarked against human NASH (Accession: E-MTAB-9815; GSE130970; GSE135251). NHPS ranked the models based either on their metabolic significance (Fig. A) or ability to induce NASH-fibrosis (Fig. B), both considering a strong (phenotypic/histologic/transcriptomic) relevance to human NASH.
Results: In wild-type (WT) mice, the NHPS found that Western Diets (WD; high in cholesterol, refined carbohydrates, and fat), with/

without sugars in the drinking water, were the most similar to human NASH in terms of metabolic significance (induction of obesity and dyslipidaemia; Fig. A), and ability to induce histologically significant fibrosis (without compromising metabolic relevance; Fig. B). A plethora of choline-deficient (CD) models with varying nutrient (fat, cholesterol, methionine) compositions quickly induced NASH-fibrosis; however, body weight, metabolic profiling and transcriptomic data suggest relatively poor translatability to human NASH (especially in WT mice); these models should be used with caution only for specific purposes (e.g. to test anti-inflammatory or anti-fibrotic compounds). Across the diets investigated, WT rats and genetically altered (GA) models of obesity (e.g. ob/ob, MC4r KO) or hypercholesterolemia (e.g. LDLR KO) had the added benefit of aggravating liver damage and accelerating fibrosis progression while preserving metabolic traits.

Conclusion: Our findings give us a clear picture of how well the phenotype, liver histology, and liver transcriptome of common NAFLD models mimic human illness, and rank the proximity of their phenotype to human NASH. Overall, WD models rank best from a metabolic/transcriptomic standpoint; however, only a few models show substantial fibrosis (F2+), necessitating extended induction durations unless combined with GA backgrounds. The reverse translational value of human biomarkers of NASH progression is being investigated in prospective studies.

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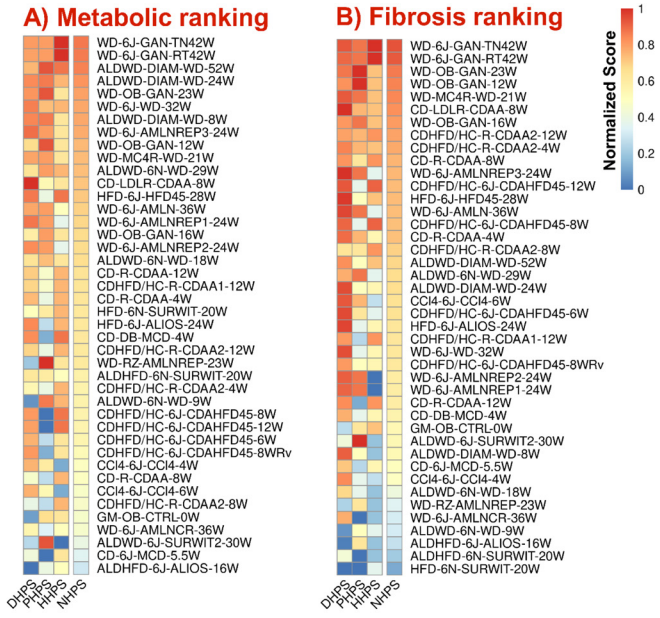

NHPS: Weighted sum (1/3 each) of DHPS (DSEA Human Proximity Score – Sequencing data), PHPS (Phenotype Human Proximity Score), HHPS (Histology Human Proximity Score).

Abbreviations: *ALDHFD, American Lifestyle Diets (High Fat Diet supplemented with refined sugars in the drinking water); ALDWD, American Lifestyle Diets (WD supplemented with refined sugars in the drinking water); ALIOS, American Lifestyle-Induced Obesity Syndrome diet (high in trans-fats and sugar); AMLN, (Trans-fat containing) Amylin Liver NASH diet; AMLNCR, AMLN diet with caloric restriction; AMLNREP, Replacement diets for AMLN (without trans-fat); CCL4, Carbon tetrachloride (Positive controls for fibrosis); CD, Choline Deficient diets; CDAA, Choline Deficient amino acid defined diet; CDAA1, CDAA supplemented with 1% cholesterol; CDAA2, CDAA supplemented with 2% cholesterol; CDAHFD45, CD-HFD 45% Fat; CDHFD/HC, Choline Deficient diets, supplemented with Fat and/or Cholesterol; CTRL, Control/chow diet; DB, db/db mice; DIAM, DIAMOND mice; GAN, Gubra Amylin NASH diet; GM, Genetically Manipulated animals; HFD, High Fat Diets; LDLR, LDLR-KO mice; MCD, Methionine-Choline Deficient Diet; MC4R, MC4rKO mice; OB, ob/ob mice; R, Rat (Janvier RjHan:Wi); RT42W, Room Temperature (42 weeks); RZ, Rat (ZSF1); SURWIT, Surwit diet; SURWIT2, Surwit Diet (2% Cholesterol); TN42W, Thermoneutral conditions (42 weeks); WD, Western Diets (high in cholesterol, refined carbohydrates, and fat); 6J, C57BL/6J mice; 6N, C57BL/6N mice; 8WRv, 8-week diet followed by a 4-week reversal to chow.*

Figure: NASH Human Proximity Score (NHPS).

GS010

Efficacy and safety of finite 48-week treatment with the siRNA JNJ-3989 and the capsid assembly modulator (CAM-N) JNJ-6379 in HBeAg negative virologically suppressed (VS) chronic hepatitis B (CHB) patients: results from REEF-2 study

Kosh Agarwal[1], Maria Buti[2], Florian van Bömmel[3], Pietro Lampertico[4], Ewa Janczewska[5], Marc Bourliere[6], Thomas Vanwolleghem[7,8], Oliver Lenz[9], Thierry Verbinnen[9], Thomas Kakuda[9], Cristina Mayer[9], John Jerzorwski[9], Maria Beumont-Mauviel[9], Ronald Kalmeijer[9], Michael Biermer[9], Isabelle Lonjon-Domanec[9]. *[1]Institute of Liver Studies, King's College Hospital; [2]Hospital Universitario Valle de Hebrón; [3]University Hospital Leipzig; [4]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan; [5]Medical University of Silesia; [6]Hôpital Saint Joseph; [7]Antwerp University Hospital (UZA); [8]Viral Hepatitis Research Group, Laboratory of Experimental Medicine and Pediatrics, University of Antwerp; [9]Janssen Research and Development*
Email: kosh.agarwal@nhs.net

Background and aims: JNJ-3989 is an siRNA designed to target all hepatitis B virus (HBV) RNAs, thus reducing synthesis of all HBV proteins. JNJ-6379 is a CAM-N that inhibits viral replication by inducing the formation of empty viral particles. The REEF-2 study assessed the efficacy and safety of JNJ-3989 200 mg SC Q4W, JNJ-6379 250 mg PO QD, and nucleos(t)ide analog (NA) PO QD in patients with HBeAg negative CHB.

Method: In this Phase 2b, double-blind, multicenter (EU only), placebo (PBO)-controlled study, non-cirrhotic HBeAg negative CHB patients with HBsAg >100 IU/ml and NA treatment for ≥2 years were randomized (2:1) to receive add-on JNJ-3989 + JNJ-6379 or PBO. All treatment including NA was discontinued after 48 weeks. The primary end point was the proportion of patients achieving HBsAg <0.05 IU/ml at follow-up week 24 without restarting NA treatment. Here, we report interim data at week 48 (end of treatment; EOT).

Results: 130 patients (67% male, 20% Asian, mean age 46 [23–65] years) were analyzed (85 active, 45 control). In the active and control arm at baseline (BL), 80% and 76% of patients had HBsAg levels ≥1,000 IU/ml (mean 3.4 [2.0–4.6] and 3.5 [2.0–4.8] $\log_{10}$ IU/ml) and mean duration of prior NA use was 8.4 (2.2–20.7) and 8.1 (2.2–17.4) years. At EOT, mean (SE) reductions in HBsAg from BL were −1.89 (0.060) $\log_{10}$ IU/ml in the active arm and −0.06 (0.012) $\log_{10}$ IU/ml in the control arm. In Asian (n = 15) and non-Asian patients (n = 61) in the active arm, HBsAg reductions were −2.05 (0.52) $\log_{10}$ IU/ml and −1.85 (0.52) $\log_{10}$ IU/ml, respectively. At EOT, the proportion of patients achieving HBsAg <100, <10, <1 IU/ml was 71.1%, 19.7%, and 2.6% in the active arm; and 2.4%, 0%, and 0% in the control arm; no patient in either arm achieved HBsAg seroclearance. Adverse events (AEs) were reported in 81.2% and 71.1% of patients in the active and control arms (grade 3/4 AEs were 15.3% and 4.4%). 7.1% of patients in the active arm had grade 3 eGFR events. After treatment initiation, eGFR reductions were seen in the active arm without further progression on continued treatment. Serious AEs were reported in 2 patients in the active arm and 1 patient in the control arm; none were considered related to study drug. Treatment discontinuation rates were 3.5% and 2.2% in the active and control arms; no AEs led to death.

Conclusion: JNJ-3989 + JNJ-6379 + NA showed greater reduction in HBsAg levels over 48 weeks compared to PBO + NA and was generally well tolerated and safe.