IN BRIEF

NAFLD

NAFLD and risk of cardiovascular disease

Nonalcoholic fatty liver disease (NAFLD) has been thought to be associated with cardiovascular outcomes. A matched cohort study, including >18 million European adults, investigated the risk of acute myocardial infarction (AMI) or stroke in adults with NAFLD or nonalcoholic steatohepatitis (NASH). A diagnosis of NAFLD in routine care does not seem to be associated with risk of AMI or stroke after adjustment for established cardiovascular risk factors. The authors conclude that risk of cardiovascular disease should be assessed in the standard way in these patients, and that NAFLD should not be considered as a risk enhancer.

ORIGINAL ARTICLE Alexander, M. et al. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. *BMJ* **367**, l5367 (2019)

REGENERATIVE MEDICINE

Modelling hepato-biliary-pancreatic organogenesis

Koike et al. modelled human hepato-biliary-pancreatic (HBP) organogenesis from a culture of pluripotent stem cells. The HBP anlage (primordium) is first specified at the boundary between the foregut and the midgut. A 3D differentiation approach was used to specify gut spheroids with distinct regional identities comprising mesoderm and endoderm. Anteroposterior interactions between these spheroids recapitulated the foregut and midgut boundary in vitro and led to the development of structurally and functionally integrated HBP organoids.

ORIGINAL ARTICLE Koike, H. et al. Modelling human hepato-biliary-pancreatic organogenesis from the foregut–midgut boundary. *Nature* **574**, 112–116 (2019)

COLORECTAL CANCER

Treatment regimen for metastatic colorectal cancer

Metastatic colorectal cancer with the *BRAF* V600E mutation has a poor prognosis. An open-label, phase III trial enrolled 665 patients who had disease progression after previous regimens. Patients were randomly assigned to receive encorafenib, binimetinib and cetuximab (triple therapy), encorafenib and cetuximab (double therapy) or cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil and irinotecan) (control group). Median overall survival was 9.0 months in the triple-therapy group, 8.4 months in the double-therapy group and 5.4 months in the control group. Response rate was 26% in the triple-therapy group and 2% in the control group.

ORIGINAL ARTICLE Kopetz, S. et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1908075 (2019)

OESOPHAGEAL CANCER

PD-1 inhibitors for oesophageal cancer

The antitumour activity of PD-1 inhibitors has been reported in several types of squamous cell cancers. In a multicentre, randomized, open-label, phase III trial, patients with previously treated, unresectable advanced or recurrent oesophageal squamous cell carcinoma were randomly assigned to receive nivolumab (a PD-1 inhibitor) or investigator's choice of chemotherapy. Nivolumab was associated with a significant improvement in overall survival ($P = 0.019$) and a favourable safety profile compared with chemotherapy and might represent a new standard second-line treatment option for these patients.

ORIGINAL ARTICLE Kato, K. et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(19)30626-6 (2019)

GUT MICROBIOTA

Bacteroides compete for fibre-derived glycans

Improving health through dietary-induced changes to the gut microbiota requires an understanding of how gut bacterial species interact with dietary components and with each other. In a new study, Patnode et al. describe an approach using forward genetic screens and artificial food particles to study how human gut microorganisms compete for and metabolize fibre-derived nutrients.

First, the authors colonized germ-free mice with a defined selection of human gut microbiota-derived bacterial strains, fed them a high-fat, low-fibre diet with differing combinations of 34 additional fibres, and measured the effects on the abundance of several *Bacteroides* species. Proteomics and forward genetic screens were used to pinpoint the bacterial genes and bioactive components of the fibres that could account for increased abundance of several *Bacteroides* species.

"We identified genes encoding glycan-degrading enzymes that were required for the expansion of target organisms during the administration of fibres containing glycans specific for those enzymes," says Jeffrey Gordon, the corresponding author of the study. "This information is important, since it demonstrates direct metabolism of fibre-derived polysaccharides by the expanding species."

Next, strain omission experiments in mice colonized with different communities of *Bacteroides* species were used to test for interactions between different organisms. For example, the abundance of *Bacteroides vulgatus* increased upon omission of *Bacteroides cellulosilyticus*, with the data suggesting competition between these species for fibre-derived glycans. On the other hand, *Bacteroides ovatus* adjusted to

PANCREATIC CANCER

Fungi promote pancreatic cancer

A new study in mice and humans demonstrates that fungi migrating from the gut to the pancreas might have a role in the progression of pancreatic ductal adenocarcinoma (PDAC). Furthermore, the authors suggest that a fungal genus abundant in PDAC tumours promotes cancer progression via activation of the C3 complement cascade.

"We and others recently discovered that pancreatic tumours contain a robust bacterial microbiome that is important in mediating immune suppression in pancreatic cancer," say George Miller and Deepak Saxena, both corresponding authors of the study. "That spurred us on to look for fungi too."

DNA sequencing of tumours from patients with PDAC and from mouse models of the disease revealed a ~3,000-fold increase in fungi in cancerous tissue compared with normal pancreatic tissue. In a mouse model of PDAC development, pancreatic tumours had a markedly greater prevalence of the fungal genus *Malassezia* than the gut. Samples from patients with PDAC also showed that *Malassezia* spp. were enriched in tumours compared with the gut. In addition, use of green fluorescent protein-labelled fungi demonstrated that fungi can migrate from the gut to the pancreas via the pancreatic duct in mice.

Next, the investigators showed that ablation of the mycobiome in several PDAC mouse models using the antifungal amphotericin B protected against tumour progression. Repopulating these mice with a *Malassezia* species accelerated the growth of PDAC tumours, unlike repopulation with non-*Malassezia* commensal species.

Finally, The Cancer Genome Atlas was used to identify an association between poor survival in PDAC and mannose-binding lectin (MBL), which activates the C3 complement cascade