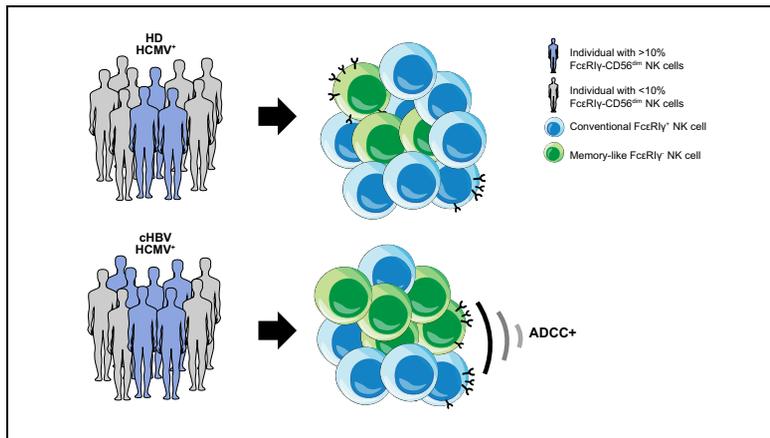


# NK-cell responses are biased towards CD16-mediated effector functions in chronic hepatitis B virus infection

## Graphical abstract



## Highlights

- Frequent HBV/HCMV co-infection is associated with the expansion of memory-like NK cells.
- Memory-like NK cells are largely conserved in chronic hepatitis B virus infection.
- Memory-like NK cells determine the NK-cell response in chronically hepatitis B virus-infected patients.
- Adaptive antibody-dependent NK-cell response is increased in chronic hepatitis B virus infection.

## Authors

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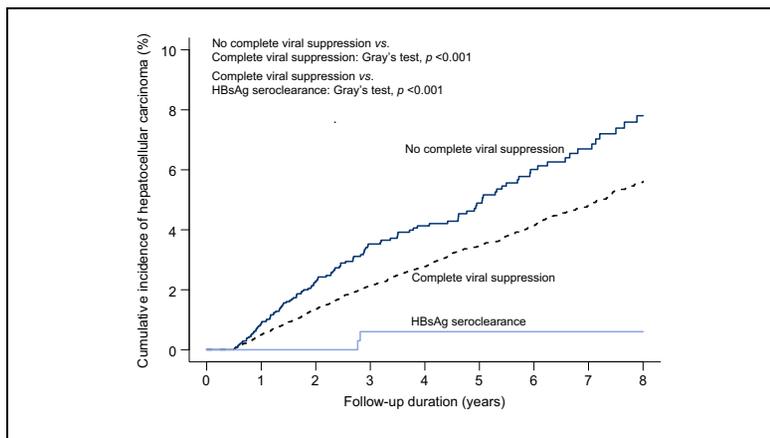
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## Lay summary

In chronic hepatitis B virus infection, NK-cell phenotype and function is altered. In this study, we demonstrate that these changes are linked to the emergence of a distinct NK-cell subset, namely memory-like NK cells. The emergence of these memory-like NK cells is associated with coinfection of HCMV that affects the majority of patients with chronic hepatitis B.

# HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues

## Graphical abstract



## Highlights

- Patients without complete viral suppression have the highest risk of HCC.
- NA-induced HBsAg seroclearance leads to lower HCC risk than complete viral suppression alone.
- Patients with HBsAg seroclearance and complete viral suppression have a similar risk of hepatic events.

## Authors

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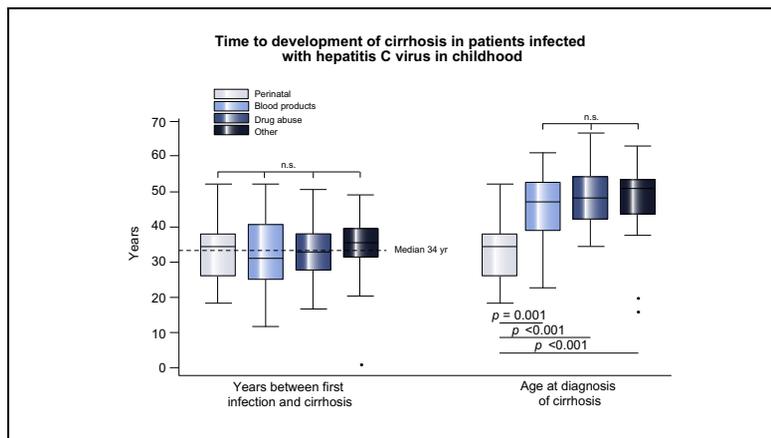
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## Lay summary

We investigated 20,263 nucleos(t)ide analogue (NA)-treated patients with chronic hepatitis B. Patients with NA-induced hepatitis B surface antigen seroclearance on top of complete viral suppression have a lower risk of hepatocellular carcinoma but not hepatic events than those only achieving complete viral suppression under prolonged NA treatment.

# Epidemiology and natural history of hepatitis C virus infection among children and young people

## Graphical abstract



## Highlights

- In UK children, HCV infection is transmitted by IV drug use in 53%, blood products in 24% and perinatally in 11%.
- Cirrhosis occurs in 32% of patients, a median of 33 years after infection, irrespective of infection route.
- Treatment impact on disease progression better if started before cirrhosis.
- Anti-HCV therapy should be available in childhood to prevent long-term liver disease.

## Authors

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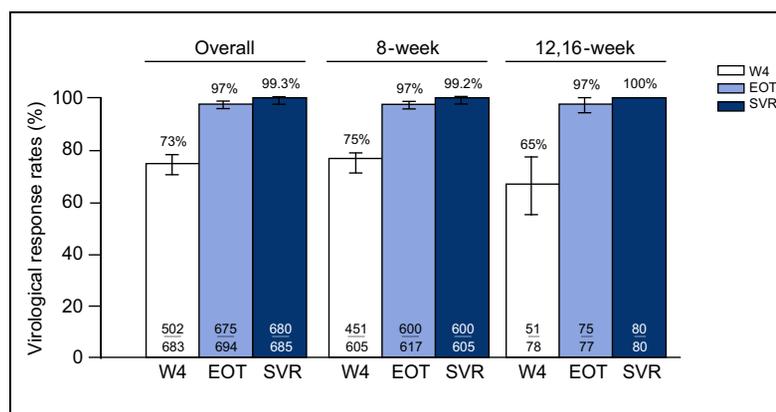
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## Lay summary

Chronic hepatitis C virus (HCV) infection is a global health problem, which can now be treated with potent direct-acting antiviral drugs. This study demonstrates that HCV infection in childhood causes serious liver disease in 32% of patients, a median of 33 years after infection, irrespective of age, mode and route of infection. Disease outcomes were better in patients treated before the development of advanced liver disease. Antiviral therapy should be made available in childhood to prevent long-term liver disease and the spread of HCV.

# Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C

## Graphical abstract



## Highlights

- Glecaprevir/pibrentasvir combination has demonstrated excellent SVR rates (99.2%) in this real-world study in Italy.
- Male gender (0.022) and HCV genotype 3 (0.046) were associated with the lowest rates of SVR after 8-week G/P treatment.
- 8.3% of the patients reported mild adverse events and 0.7% of them prematurely withdrew antiviral treatment.

## Authors

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## Correspondence

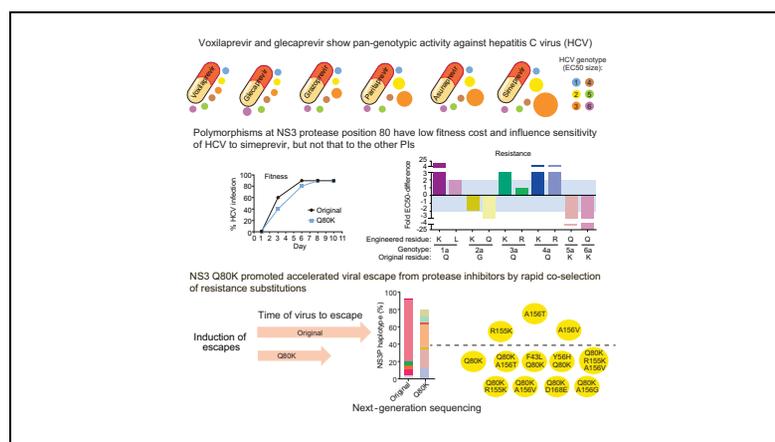
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## Lay summary

A large number of patients with hepatitis C virus have been treated with glecaprevir/pibrentasvir (G/P) within the NAVIGATORE-Lombardia Network, in Italy. This is the first real-world study evaluating effectiveness and safety of G/P in patients with hepatitis C virus treated according to international recommendations. This study demonstrated excellent effectiveness (with sustained virological response rates of 99.3%) and safety profiles.

# HCV genotype 1-6 NS3 residue 80 substitutions impact protease inhibitor activity and promote viral escape

## Graphical abstract



## Highlights

- Pan-genotypic activity of voxilaprevir and glecaprevir in cell culture infectious HCV.
- High fitness of engineered HCV genotype 1-6 protease position-80-variants.
- Position-80-variants showed altered sensitivity to simeprevir but not to other PIs.
- Q80K promoted accelerated HCV escape from PIs in long-term treatment.
- Escape was mediated by rapid co-selection of additional resistance substitutions.

## Authors

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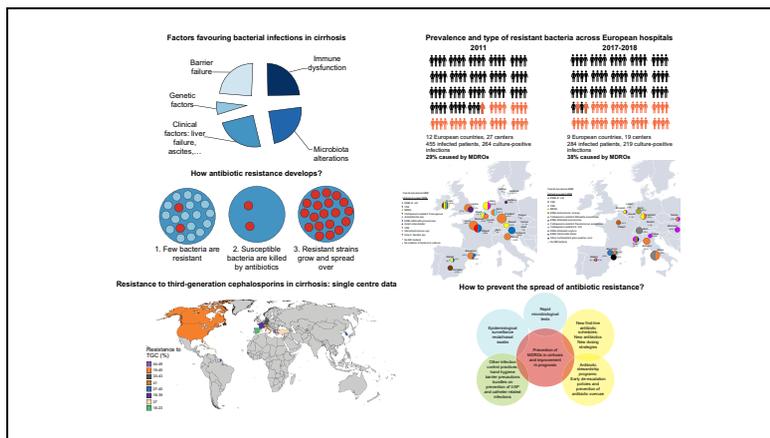
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## Lay summary

Among all clinically relevant hepatitis C virus protease inhibitors, voxilaprevir and glecaprevir showed the highest and most uniform activity against cell culture infectious hepatitis C virus with genotype 1-6 proteases. Naturally occurring amino acid changes at protease position 80 had low fitness cost and influenced sensitivity to simeprevir, but not to other protease inhibitors in short-term treatment assays. Nevertheless, the pre-existing change Q80K had the potential to promote viral escape from protease inhibitors during long-term treatment by rapid co-selection of additional resistance changes, detected by next generation sequencing.

# Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe

## Graphical abstract



## Authors

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## Lay summary

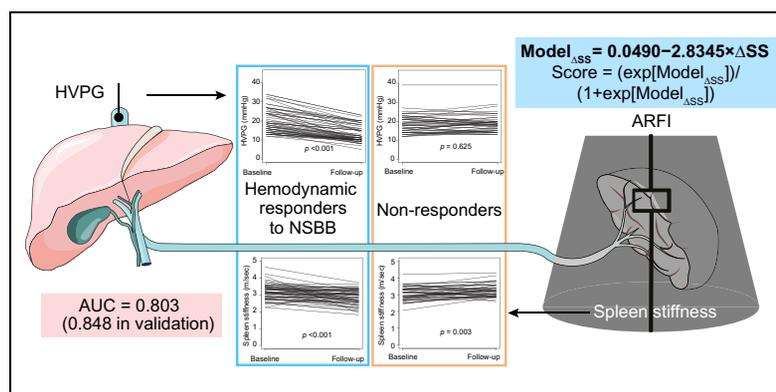
Infections caused by bacteria resistant to the main antibiotic families are prevalent in patients with cirrhosis. This study demonstrates that this healthcare problem is increasing and extends through all European regions. Infections caused by these difficult to treat bacteria resolve less frequently and often cause the death of the patient. The type of resistant bacteria varies markedly among different hospitals.

## Highlights

- MDR bacterial infections are a prevalent, growing and complex healthcare problem in decompensated cirrhosis and ACLF.
- Prevalence increased from 29% to 38% in culture-positive infections from 2011 to 2017-2018.
- Antibiotic resistance negatively impacts prognosis and is associated with higher mortality rates.
- Nosocomial infection, ICU admission and recent hospitalization are independent risk factors of MDR infection.
- Strategies aimed at preventing the spread of antibiotic resistance in cirrhosis should be urgently evaluated.

# Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices

## Graphical abstract



## Authors

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## Lay summary

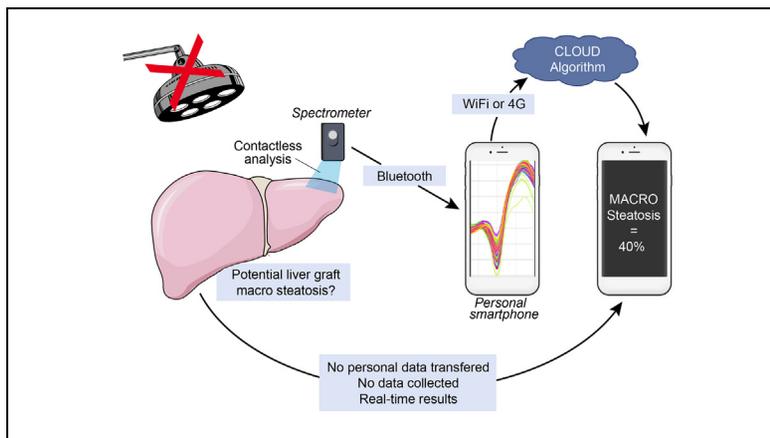
Non-selective beta-blockers are the mainstay of primary prophylaxis to prevent variceal bleeding in patients with cirrhosis and high-risk esophageal varices. This prospective study showed that a prediction model based on changes in spleen stiffness before vs. after dose titration might be a non-invasive marker for response to prophylactic non-selective beta-blocker (carvedilol) therapy in patients with cirrhosis and high-risk esophageal varices.

## Highlights

- ARFI-measured  $\Delta\text{SS}$  predicted hemodynamic response to prophylactic carvedilol.
- Prediction model =  $0.0490 - 2.8345 \times \Delta\text{SS}$ ; score =  $\frac{\exp[\text{Model}\Delta\text{SS}]}{1 + \exp[\text{Model}\Delta\text{SS}]}$ .
- Using 0.530 as the threshold value, AUC was 0.803 (in validation, AUC = 0.848).
- $\Delta\text{SS}$  may predict carvedilol response non-invasively, obviating HVPG measurement.

# Evaluation of a micro-spectrometer for the real-time assessment of liver graft with mild-to-moderate macrosteatosis: A proof of concept study

## Graphical abstract



## Highlights

- Liver macrosteatosis is a major prognostic factor after liver transplantation.
- Visual estimation is inaccurate and frozen sections are rarely available during procurement.
- We developed an algorithm to assess macrosteatosis through a portable spectrometer.
- This algorithm was calibrated and validated on human livers.
- This affordable non-invasive tool may help surgeons with clinical decision-making.

## Authors

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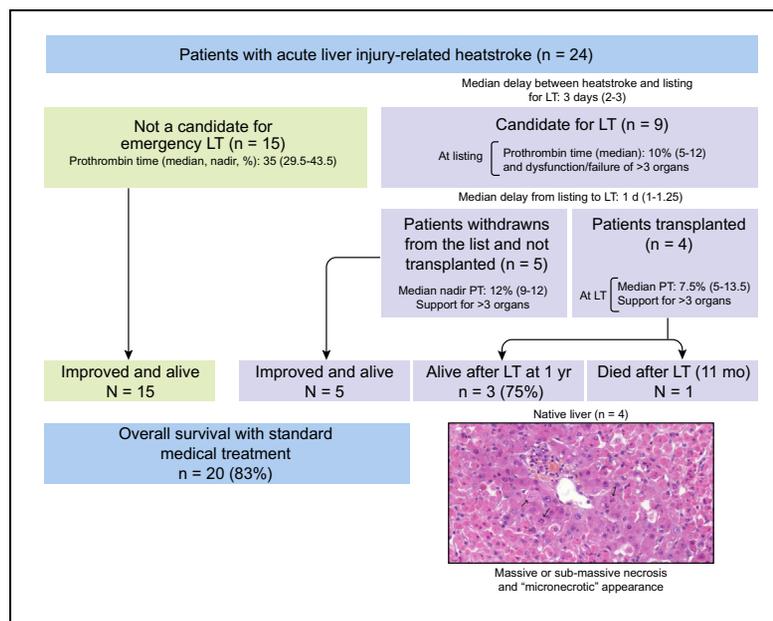
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## Lay summary

Macro-vacuolar liver steatosis is a major prognostic factor for outcomes after liver transplantation. However, it is often difficult for logistical reasons to get this estimation during procurement. Therefore, we developed an algorithm for a commercial, portable and affordable spectrometer to accurately estimate this content in a real-time fashion. This device could be of great interest for clinical decision-making to accept or discard a potential human liver graft.

# Liver transplantation in patients with liver failure related to exertional heatstroke

## Graphical abstract



## Authors

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## Lay summary

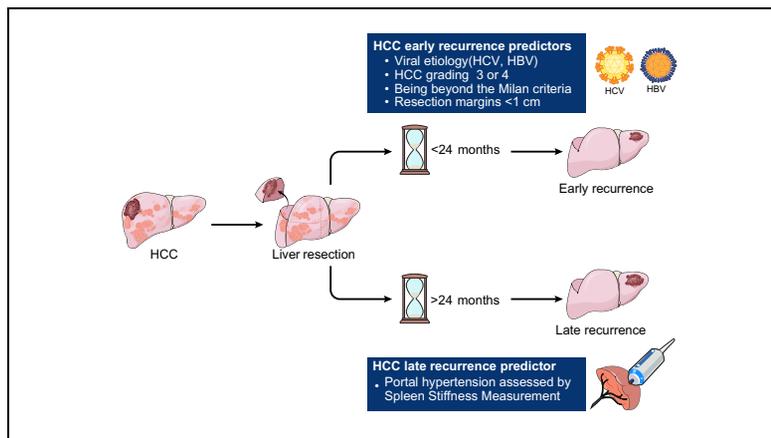
Acute liver injury due to heatstroke can progress to acute liver failure with organ dysfunction despite medical treatment; in such situations, liver transplantation (LT) may offer a therapeutic option. The classic criteria for LT appear to be poorly adapted to heatstroke-related acute liver failure. We confirmed that medication is the first-line therapy acute liver injury caused by heatstroke, with LT only rarely necessary. A decision to perform LT should not be made hastily. Fluctuations in prothrombin time and the patient's clinical status should be considered even in the event of severe liver failure.

## Highlights

- The first-line treatment for heatstroke that causes severe liver injury is medical.
- Liver transplantation (LT) is a rare alternative that achieves good survival rates.
- The decision to transplant must consider the kinetics of PT and patients' clinical status.
- All explanted livers were characterised by a "mitonecrotic appearance on histology."

# Role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection

## Graphical abstract



## Highlights

- Predictive factors for early and late recurrence of HCC are different.
- Early recurrence of HCC is associated with underlying primary HCC and surgical techniques and strategies.
- Late recurrence is associated with the degree of portal hypertension assessed by spleen stiffness measurement.

## Authors

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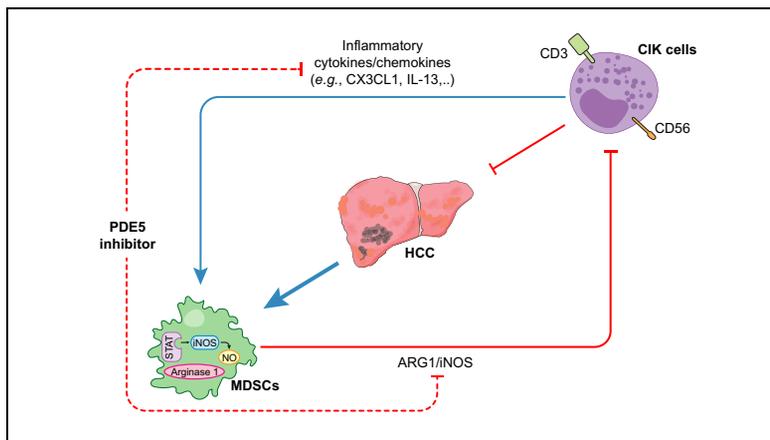
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## Lay summary

The main result of this study is that spleen stiffness measurement, evaluated by transient elastography, seems to be the only predictor of the late recurrence of hepatocellular carcinoma, defined as recurrence after 24 months from liver resection. Indeed, spleen stiffness measurement is directly correlated with the degree of liver disease and portal hypertension, which are both involved in carcinogenesis.

# Targeting the crosstalk between cytokine-induced killer cells and myeloid-derived suppressor cells in hepatocellular carcinoma

## Graphical abstract



## Highlights

- CIK therapy recruits MDSCs in tumor tissues through inflammatory cytokines.
- MDSCs inhibit CIK tumor lytic function in an ARG1 and iNOS dependent manner.
- Tadalafil, an FDA approved PDE5 inhibitor, suppressed the number and function of MDSCs.
- Tadalafil enhances antitumor efficacy of CIK cells in *in vivo* murine HCC models.
- Human MDSCs inhibit human CIK cell cytotoxicity.

## Authors

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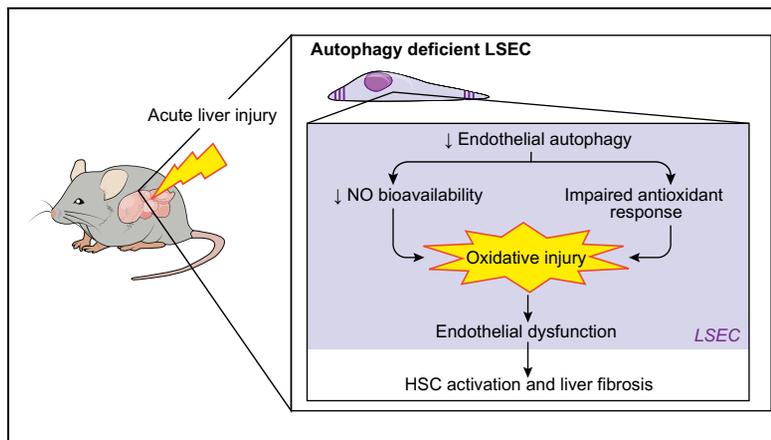
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## Lay summary

Cytokine-induced killer cells are a mixture of immune cells given to eliminate cancer cells. However, not all patients respond to this treatment. Herein, we show in 2 different liver cancer models that myeloid-derived suppressor cells are increased in response to cytokine-induced killer cell therapy. Targeting these myeloid-derived suppressor cells may provide an additional therapeutic benefit alongside cytokine-induced killer cell therapy.

# Impaired endothelial autophagy promotes liver fibrosis by aggravating the oxidative stress response during acute liver injury

## Graphical abstract



## Highlights

- Autophagy maintains liver endothelial cell homeostasis.
- Autophagy deficiency in LSEC increases oxidative stress.
- Autophagy regulates nitric oxide bioavailability and maintains LSEC phenotype.
- Impairment of endothelial autophagy enhances endothelial dysfunction and exacerbates fibrosis.

## Authors

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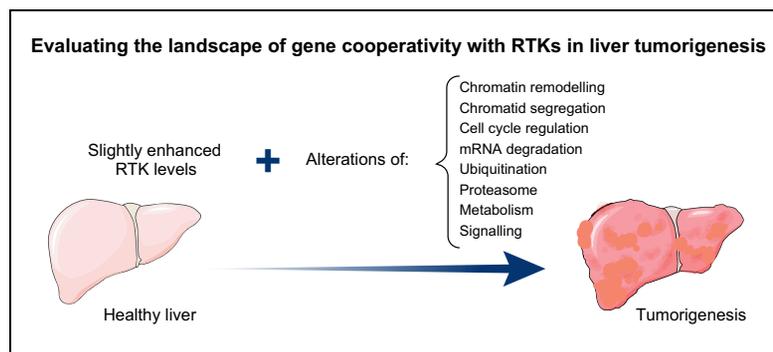
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## Lay summary

Liver endothelial cells are the first liver cell type affected after any kind of liver injury. The loss of their unique phenotype during injury amplifies liver damage by orchestrating the response of the liver microenvironment. Autophagy is a mechanism involved in the regulation of this initial response and its manipulation can modify the progression of liver damage.

# Evaluating the landscape of gene cooperativity with receptor tyrosine kinases in liver tumorigenesis using transposon-mediated mutagenesis

## Graphical abstract



## Highlights

- A transposon genetic screen uncovered 275 putative receptor tyrosine kinase cooperators for liver cancer.
- Most identified genes are also altered in patients with HCC.
- Receptor tyrosine kinase cooperators are regulators of a large spectrum of cellular functions.
- Enhanced receptor tyrosine kinase levels allow a broad range of mechanisms to initiate liver cancer.

## Authors

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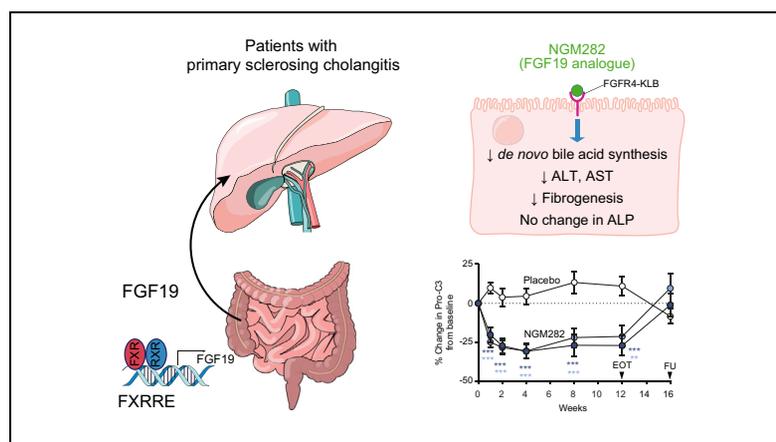
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## Lay summary

Receptor tyrosine kinases (RTKs) are among signals frequently deregulated in patients with hepatocellular carcinoma and their deregulation confers essential biological properties to cancer cells. We have applied a genetic method to randomly mutate large numbers of genes in the context of a mouse model with increased RTK levels, predisposed to develop liver cancer. We identified mechanisms that accelerate tumour formation in cooperation with enhanced RTK levels. The wide array of cellular functions among these cooperators illustrates an extraordinary capability of RTKs to render the liver more vulnerable to additional alterations, by priming cells for tumour initiation.

# Effect of NGM282, an FGF19 analogue, in primary sclerosing cholangitis: A multicenter, randomized, double-blind, placebo-controlled phase II trial

## Graphical abstract



## Highlights

- NGM282 is a first-in-class, engineered analogue of the endocrine hormone FGF19.
- NGM282 did not significantly affect alkaline phosphatase levels in patients with primary sclerosing cholangitis.
- However, NGM282 significantly inhibited bile acid synthesis and improved serum markers of fibrogenesis and liver injury.
- These findings challenge the dogma about what the appropriate endpoints should be for trials in PSC.

## Authors

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## Correspondence

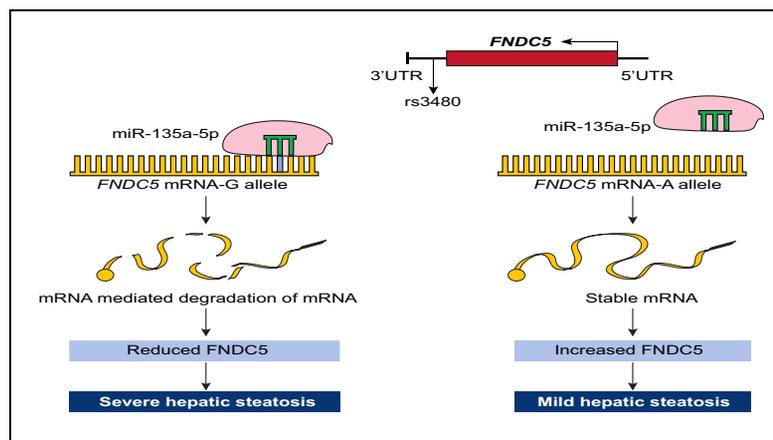
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## Lay summary

We present for the first time, the clinical and laboratory effects of a first-in-class, engineered analogue of the endocrine hormone FGF19 in patients with primary sclerosing cholangitis (PSC). By incorporating non-invasive markers of fibrosis, beyond standard liver injury markers, we show that NGM282 impacted on fibrosis turnover and hepatic inflammation without changing alkaline phosphatase. Our findings demonstrate the complexities of using highly potent rational agents in PSC, and furthermore challenge the dogma about what the appropriate endpoints should be for trials in PSC.

# A polymorphism in the Irisin-encoding gene (*FNDC5*) associates with hepatic steatosis by differential miRNA binding to the 3'UTR

## Graphical abstract



## Highlights

- Irisin, the cleaved extra-cellular fragment of *FNDC5* is a myokine thought to have favorable metabolic activity.
- The role of variants in the *FNDC5* gene in NAFLD is not defined.
- Genetic variants in *FNDC5* confer risk of human severe hepatic steatosis.
- Functional studies reveal that this variant mediates this effect via a miRNA-mediated control of *FNDC5* mRNA stability.
- Irisin is likely to have a favourable metabolic impact on NAFLD.

## Authors

Mayada Metwally, Ali Bayoumi, Manuel Romero-Gomez, ..., Liang Qiao, Jacob George, Mohammed Eslam

## Correspondence

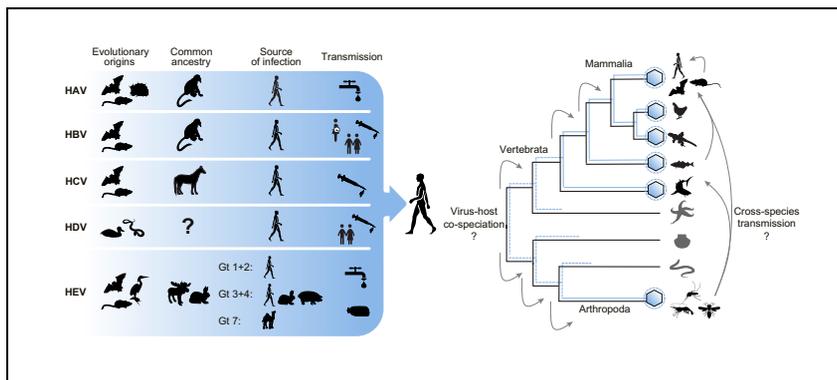
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## Lay summary

Irisin is a novel protein produced mainly by muscle, which is known to be released into the circulation, with an unclear role in liver fat deposition. This study demonstrates that genetic variants in the gene encoding the irisin protein modulate the risk of liver fat in patients with fatty liver disease. Interestingly, these effects are independent of, but additive to those of other recently described genetic variants that contribute to liver fat. In functional studies, we have deciphered the detailed molecular mechanisms by which this genetic variant mediates its effects.

# Evolutionary biology of human hepatitis viruses

## Graphical abstract



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## Summary

Hepatitis viruses are major threats to human health. During the last decade, highly diverse viruses related to human hepatitis viruses were found in animals other than primates. Herein, we describe both surprising conservation and striking differences of the unique biological properties and infection patterns of human hepatitis viruses and their animal homologues, including transmission routes, liver tropism, oncogenesis, chronicity, pathogenesis and envelopment. We discuss the potential for translation of newly discovered hepatitis viruses into preclinical animal models for drug testing, studies on pathogenesis and vaccine development. Finally, we re-evaluate the evolutionary origins of human hepatitis viruses and discuss the past and present zoonotic potential of their animal homologues.