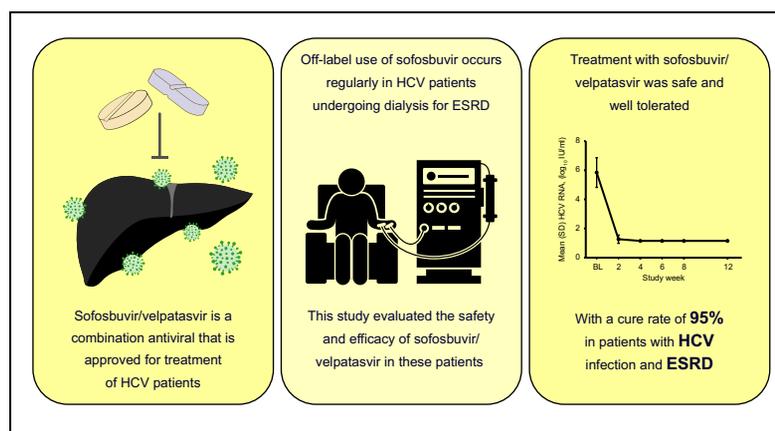


# Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis

## Graphical abstract



## Highlights

- Sofosbuvir/velpatasvir (SOF/VEL) is approved for patients with HCV infection.
- There is no dosing recommendation for SOF-based regimens for HCV-infected patients on dialysis.
- We evaluated SOF/VEL for 12 weeks in HCV-infected patients with end-stage renal disease on dialysis.
- SOF/VEL was safe and well tolerated, with a cure rate of 95% in our study.

## Authors

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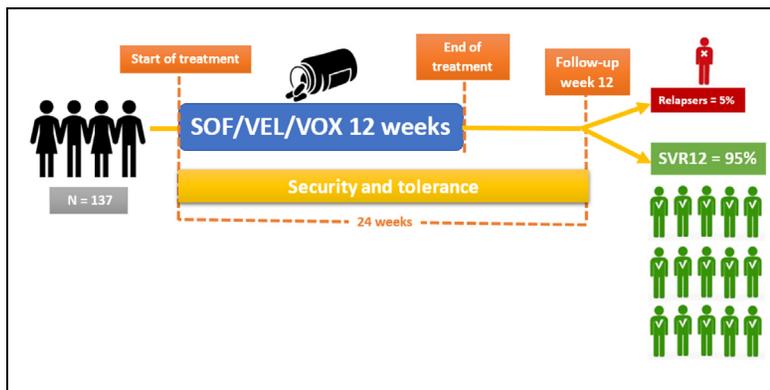
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## Lay summary

Sofosbuvir/velpatasvir is a combination direct-acting antiviral that is approved for treatment of patients with hepatitis C virus (HCV) infection. Despite the lack of dosing recommendations, sofosbuvir-containing regimens (including sofosbuvir/velpatasvir) are frequently used for HCV-infected patients undergoing dialysis. This study evaluated the safety and efficacy of sofosbuvir/velpatasvir for 12 weeks in patients with HCV infection who were undergoing dialysis. Treatment with sofosbuvir/velpatasvir was safe and well tolerated, resulting in a cure rate of 95% in patients with HCV infection and end-stage renal disease.

# Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs

## Graphical abstract



## Highlights

- Patients achieve high SVR12 rates with sofosbuvir/velpatasvir/voxilaprevir after prior DAA failures.
- Sofosbuvir/velpatasvir/voxilaprevir is a very safe and well tolerated combination.
- GT3 cirrhotic patients with previous treatment with NS5A-inhibitors are poor responders.
- GT3 is the only factor that impacts SVR12 rates in retreatment with sofosbuvir/velpatasvir/voxilaprevir.

## Authors

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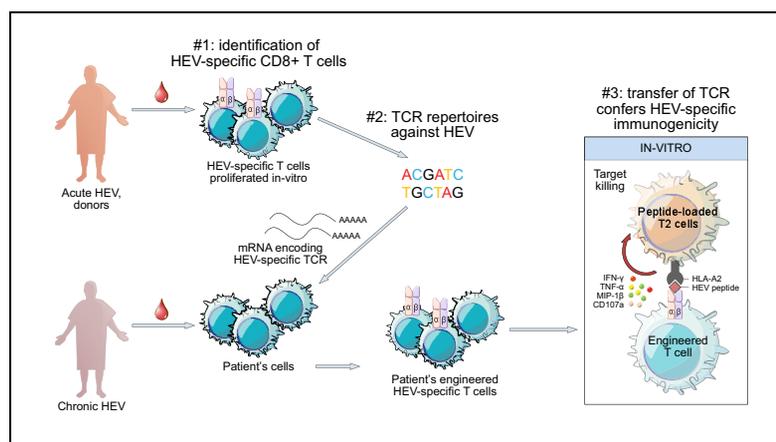
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## Lay summary

Treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 12 weeks is the current recommendation for the 5% of patients infected with HCV who do not achieve eradication of the virus under treatment with direct-acting antivirals. In a Spanish cohort of 137 patients who failed a previous combination of direct-acting antivirals, a cure rate of 95% was achieved with SOF/VEL/VOX. Genotypic characteristics of the virus (genotype 3) and the presence of cirrhosis were factors that decreased the rate of cure. Treatment with SOF/VEL/VOX is an effective and safe rescue therapy due to its high efficacy and very good safety profile.

# Defining virus-specific CD8+ TCR repertoires for therapeutic regeneration of T cells against chronic hepatitis E

## Graphical abstract



## Highlights

- Identified 2 HEV-specific CD8+ T cell epitopes located at the RNA helicase and RNA-dependent RNA polymerase.
- Identified and sequenced T cell receptor (TCR) repertoires against HEV.
- Transfer of engineered TCRs to T cells of chronically infected patients confers HEV-specific immunogenicity and cytotoxicity.

## Authors

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## Correspondence

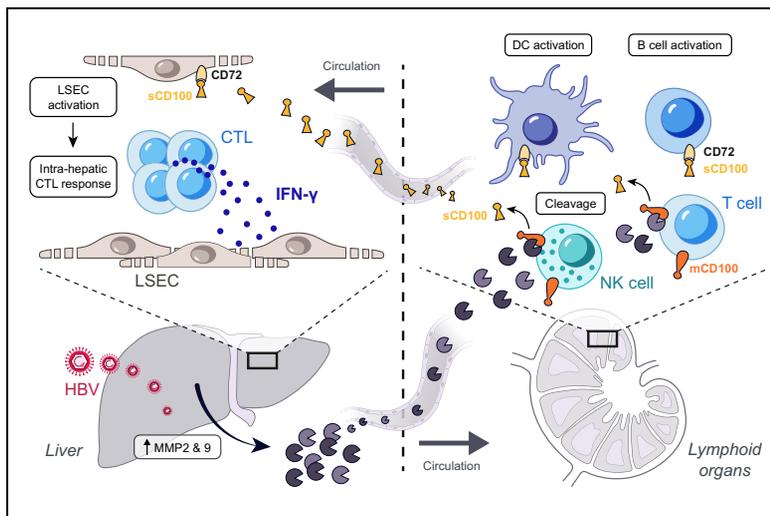
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## Lay summary

Patients who are immunosuppressed are vulnerable to developing chronic liver disease following infection with hepatitis E virus (HEV). To-date, there is no approved therapy for chronic hepatitis E. Interferon- $\alpha$  and ribavirin are off-label treatment options, but their applications are limited by side effects. Thus, immunotherapy, more specifically T cell-based therapy, may be an alternative approach. We designed T cell receptor-engineered T cells that effectively conferred immune cells, taken from patients with chronic hepatitis E, with the ability to recognize virus-specific epitopes and mediate killing of target cells *in vitro*.

# MMP2/MMP9-mediated CD100 shedding is crucial for inducing intrahepatic anti-HBV CD8 T cell responses and HBV clearance

## Graphical abstract



## Highlights

- HBV infection results in altered mCD100 expression and serum sCD100 levels.
- sCD100 can increase anti-HBV CTL response and accelerate HBV clearance.
- mCD100 shedding and sCD100 formation is mediated by MMP2 and MMP9.
- CHB patients show decreased serum MMP2 and sCD100 levels.
- MMP2/9 inhibition suppresses anti-HBV CTL response and delays HBV clearance.

## Authors

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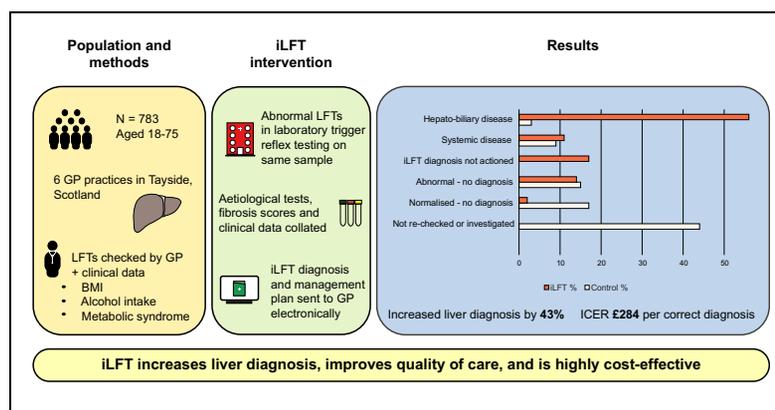
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## Lay summary

Chronic hepatitis B virus (HBV) infection is a major public health problem worldwide. The clearance of HBV relies largely on an effective T cell immune response, which usually becomes dysregulated in chronic HBV infection. Our study provides a new mechanism to elucidate HBV persistence and a new target for developing immunotherapy strategies in patients chronically infected with HBV.

# Intelligent liver function testing (iLFT): A trial of automated diagnosis and staging of liver disease in primary care

## Graphical abstract



## Authors

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## Lay summary

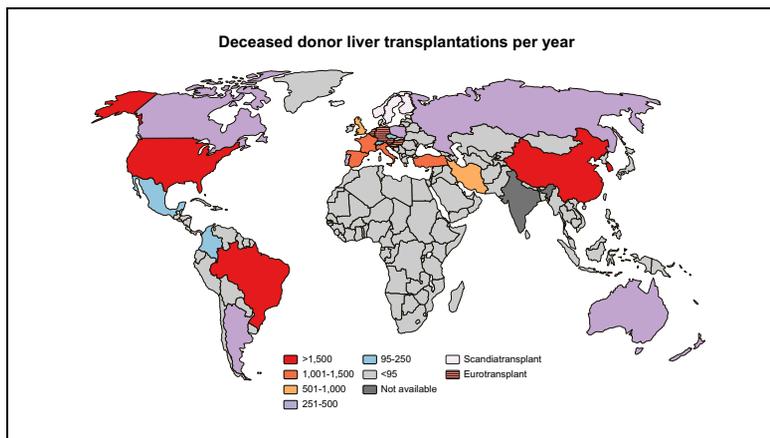
There is a growing epidemic of advanced liver disease, this could be offset by early detection and management. Checking liver blood tests (LFTs) should be an opportunity to diagnose liver problems, but abnormal results are often incompletely investigated. In this study we were able to substantially increase the diagnostic yield of the abnormal LFTs using the automated intelligent LFT system. With the addition of referral recommendations and management plans, this strategy provides optimum investigation and management of LFTs and is cost saving to the NHS.

## Highlights

- Intelligent liver function testing utilises the smarter application of existing knowledge and technology.
- Intelligent liver function testing increases diagnosis of liver disease by 43%, with diagnostic accuracy over 90%.
- Intelligent liver function testing enables earlier identification of treatable liver disease.

# Allocation of liver grafts worldwide – Is there a best system?

## Graphical abstract



## Highlights

- An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity.
- Large differences exist between centers and countries for ethical and legislative reasons.
- A future globally applicable strategy should combine donor and recipient factors.
- This strategy must predict probability of death on the waiting list, post-transplant survival and morbidity, and costs.

## Authors

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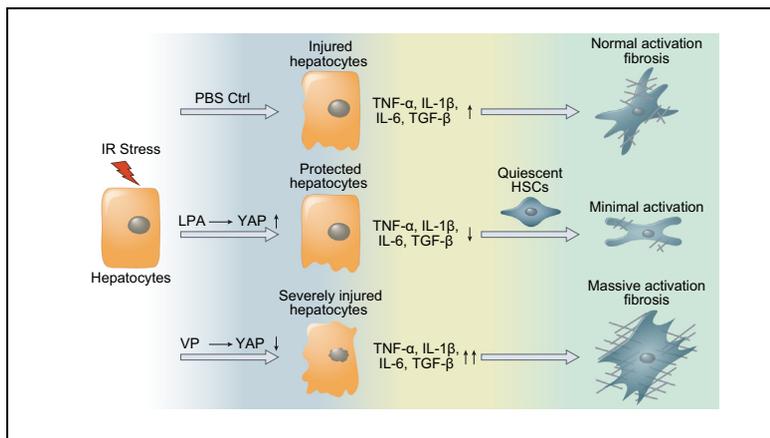
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## Lay summary

An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity. While the model for end-stage liver disease is currently the standard for this model, many adjustments were implemented in most countries. A future globally applicable strategy should combine donor and recipient factors predicting probability of death on the waiting list, post-transplant survival and morbidity, and perhaps costs.

# Activation of YAP attenuates hepatic damage and fibrosis in liver ischemia-reperfusion injury

## Graphical abstract



## Authors

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## Lay summary

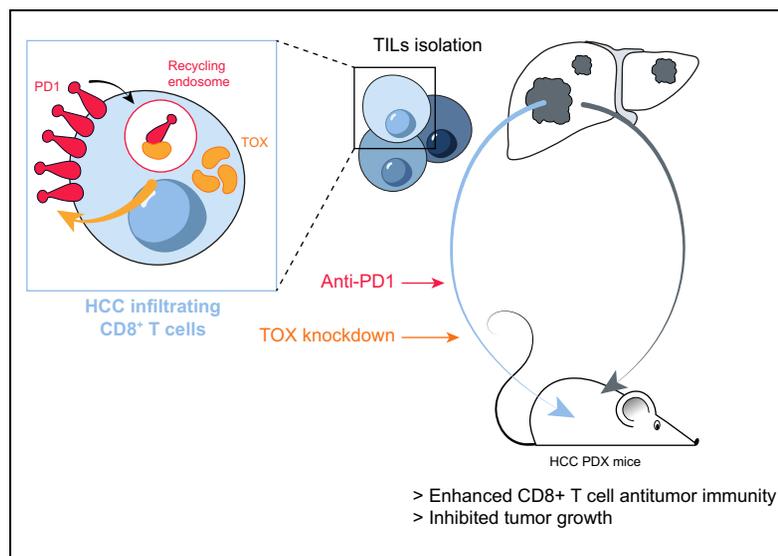
In the clinical arm, graft YAP expression negatively correlated with liver function and tissue damage after human liver transplantation. YAP activation attenuated hepatocellular oxidative stress and diminished the innate immune response in mouse livers following ischemia-reperfusion injury. In the mouse model, YAP inhibited hepatic stellate cell activation, and abolished injury-mediated fibrogenesis up to 7 days after the ischemic insult.

## Highlights

- High graft YAP expression was correlated with well-preserved histology and improved hepatocellular function in human OLT.
- YAP activation promoted downstream regenerative/anti-oxidative gene induction.
- YAP activation diminished oxidative stress, necrosis/apoptosis, and suppressed the innate inflammatory response.
- YAP activation suppressed extracellular matrix synthesis and hepatic stellate cell activation, and stopped fibrogenesis.
- YAP activation failed to protect *Nrf2*-deficient mouse livers against IR-mediated tissue damage.

# TOX promotes the exhaustion of antitumor CD8<sup>+</sup> T cells by preventing PD1 degradation in hepatocellular carcinoma

## Graphical abstract



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## Lay summary

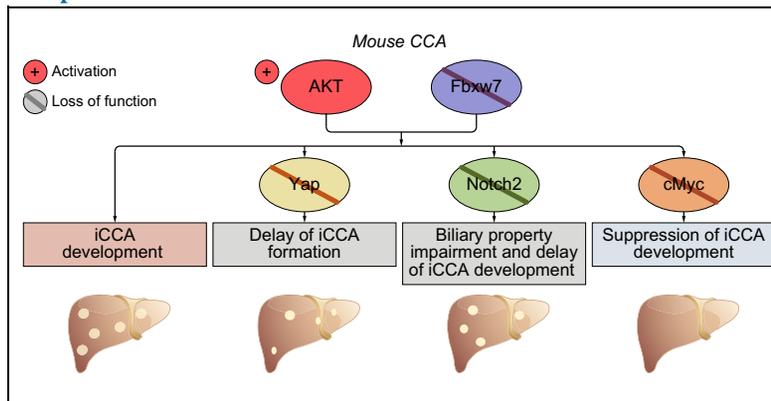
Abundant TOX expression in CD8<sup>+</sup> T cells impairs their antitumor function in hepatocellular carcinoma. Mechanically, TOX reduces PD1 degradation and promotes PD1 translocation to the cell surface in CD8<sup>+</sup> T cells, thus maintaining high PD1 expression at the cell surface. Downregulating TOX expression improves the antitumor function of CD8<sup>+</sup> T cells, which shows the synergetic role of anti-PD1 therapy, highlighting a promising strategy for enhancement of cancer immunotherapy.

## Highlights

- TOX promotes CD8<sup>+</sup> T cell exhaustion in hepatocellular carcinoma.
- TOX impairs CD8<sup>+</sup> T cell antitumor function and response to anti-PD1 therapy.
- TOX increases surface PD1 level of tumor-infiltrating CD8<sup>+</sup> T cells.
- TOX in peripheral CD8<sup>+</sup> T cells is an unfavorable prognostic factor for hepatocellular carcinoma.

# Loss of Fbxw7 synergizes with activated Akt signaling to promote c-Myc dependent cholangiocarcinogenesis

## Graphical abstract



## Highlights

- Downregulation of the FBXW7 tumor suppressor gene was identified as a universal feature of human intrahepatic cholangiocarcinoma (iCCA).
- Hydrodynamic transfection of inactivated Fbxw7 synergized with an activated form of AKT to induce rapid iCCA in mice.
- Cholangiocarcinogenesis was prevented by c-Myc suppression, while being delayed by either *Yap* or *Notch 2* depletion in these mice.
- Inhibition of c-MYC might represent an innovative therapeutic strategy for the treatment of human iCCA with low FBXW7.

## Authors

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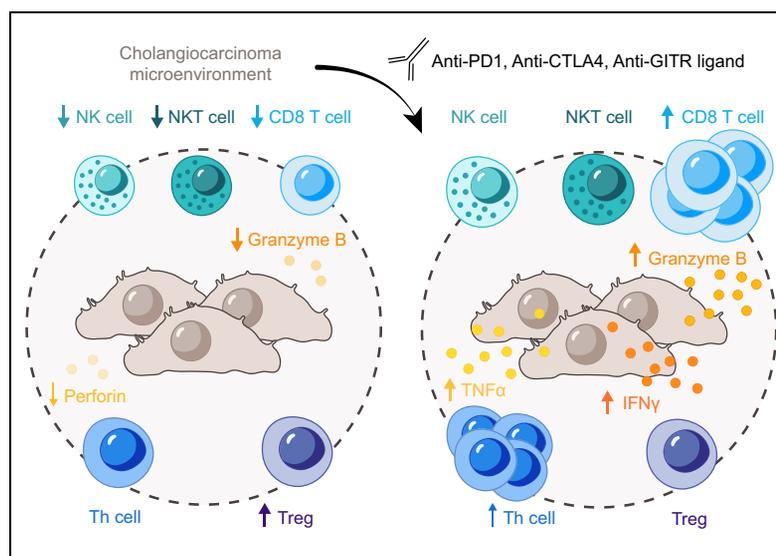
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## Lay summary

There is mounting evidence that FBXW7 functions as a tumor suppressor in many cancer types, including intrahepatic cholangiocarcinoma, through its ability to promote the degradation of numerous oncoproteins. Herein, we have shown that the low expression of FBXW7 is ubiquitous in human cholangiocarcinoma specimens. This low expression is correlated with increased c-MYC activity, leading to tumorigenesis. Our findings suggest that targeting c-MYC might be an effective treatment for intrahepatic cholangiocarcinoma.

# Reduction of immunosuppressive tumor microenvironment in cholangiocarcinoma by *ex vivo* targeting immune checkpoint molecules

## Graphical abstract



## Highlights

- NK cells and cytotoxic T cells infiltrate poorly into cholangiocarcinoma.
- Regulatory T cells accumulate in cholangiocarcinoma.
- PD1, CTLA4 and GITR are over-expressed on tumor-infiltrating T cells in cholangiocarcinoma.
- Blocking PD1 or CTLA4 or stimulating GITR enhances effector functions of tumor-infiltrating T cells in cholangiocarcinoma.

## Authors

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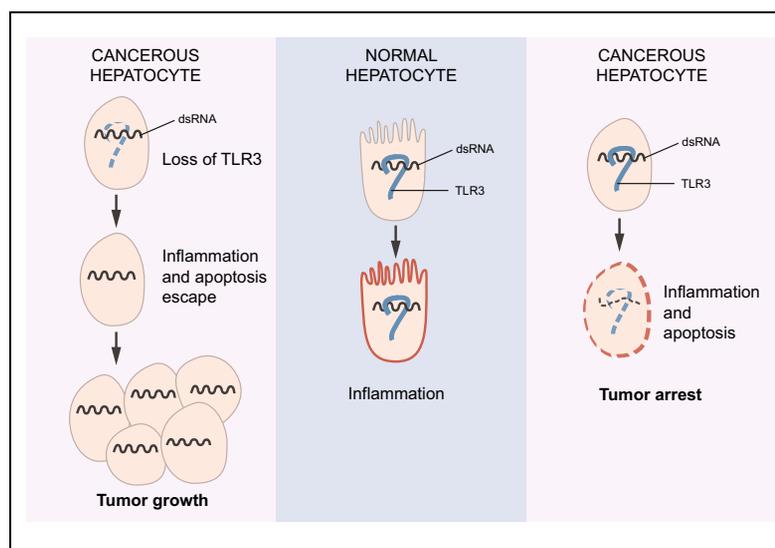
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## Lay summary

The defense functions of immune cells are suppressed in cholangiocarcinoma tumors. Stimulating or blocking “immune checkpoint molecules expressed on tumor-infiltrating T cells can enhance the defense functions of these cells. Therefore, these molecules may be promising targets for therapeutic stimulation of immune cells to eradicate the tumors and prevent cancer recurrence in patients with cholangiocarcinoma.

# Toll-like receptor 3 downregulation is an escape mechanism from apoptosis during hepatocarcinogenesis

## Graphical abstract



## Highlights

- Downregulation of TLR3 in HCC is associated with poor prognosis and with resistance to TLR3-triggered apoptosis.
- Downregulation of TLR3 is an escape mechanism for HCC cells which prevents their apoptosis and enhances tumor progression.
- The effect of TLR3 on apoptosis, which limits tumor progression, is independent of the immune response.
- TLR3 ligands may represent an effective treatment option for HCC expressing TLR3.

## Authors

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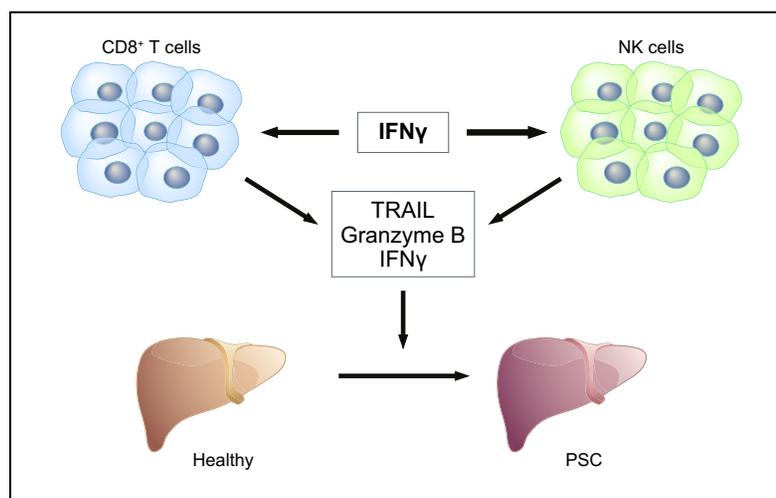
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## Lay summary

Hepatocellular carcinoma (HCC) is a heterogeneous disease associated with a poor prognosis. In patients with HCC, TLR3 downregulation is associated with reduced survival. Herein, we show that the absence of TLR3 is associated with a lower rate of apoptosis, and subsequently more rapid hepatocarcinogenesis, without any change to the immune infiltrate in the liver. Therefore, the poor prognosis associated with low TLR3 expression in HCC is likely linked to tumors ability to escape apoptosis. TLR3 may become a promising therapeutic target in TLR3-positive HCC.

# Interferon- $\gamma$ -dependent immune responses contribute to the pathogenesis of sclerosing cholangitis in mice

## Graphical abstract



## Authors

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## Lay summary

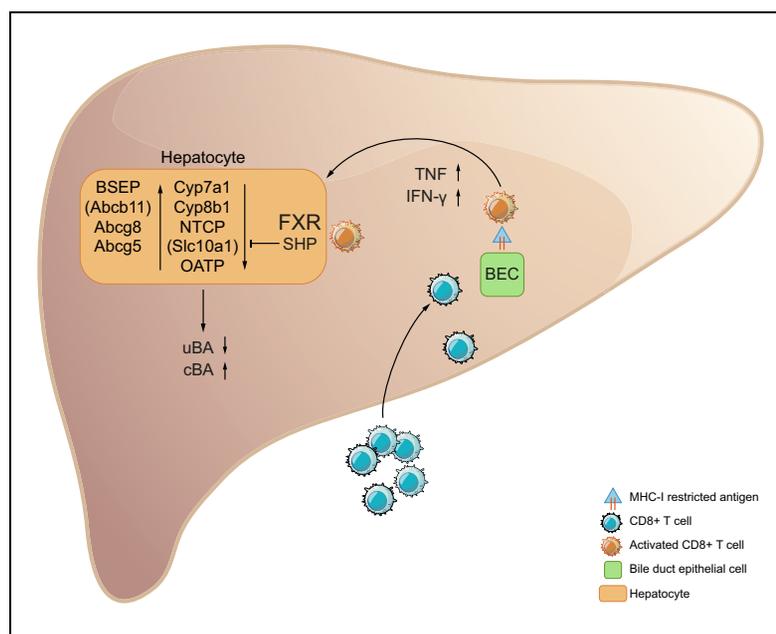
Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by biliary inflammation and fibrosis, whose current medical treatment is hardly effective. We observed an increased interferon (IFN)- $\gamma$  response in patients with PSC and in a mouse model of sclerosing cholangitis. IFN $\gamma$  changed the phenotype of hepatic CD8<sup>+</sup> T lymphocytes and NK cells towards increased cytotoxicity, and its absence decreased liver cell death, reduced frequencies of inflammatory macrophages in the liver and attenuated liver fibrosis. Therefore, IFN $\gamma$ -dependent immune responses may disclose checkpoints for future therapeutic intervention strategies in sclerosing cholangitis.

## Highlights

- Patients with PSC showed increased IFN $\gamma$  serum concentrations and elevated frequencies of hepatic CD56<sup>bright</sup> NK cells.
- Less hepatic NK cells and CD8<sup>+</sup> T cells expressing cytotoxic effector molecules after deletion of IFN $\gamma$  in *Mdr2*<sup>-/-</sup> mice.
- Less inflammatory macrophages and more restorative macrophages after genetic deletion of IFN $\gamma$ .
- Genetic deletion and blockage of IFN $\gamma$  in *Mdr2*<sup>-/-</sup> mice attenuated liver fibrosis.

# Liver infiltrating T cells regulate bile acid metabolism in experimental cholangitis

## Graphical abstract



## Highlights

- Antigen-specific CD8+ T cells can control bile acid metabolism in a murine model of cholangitis.
- The effect of T cells on bile acid metabolism partly depends on TNF and IFN- $\gamma$ , and on T cell contact with hepatocytes.
- Understanding the effect of lymphocytes on bile acid metabolism may help in the design of combined treatment strategies.

## Authors

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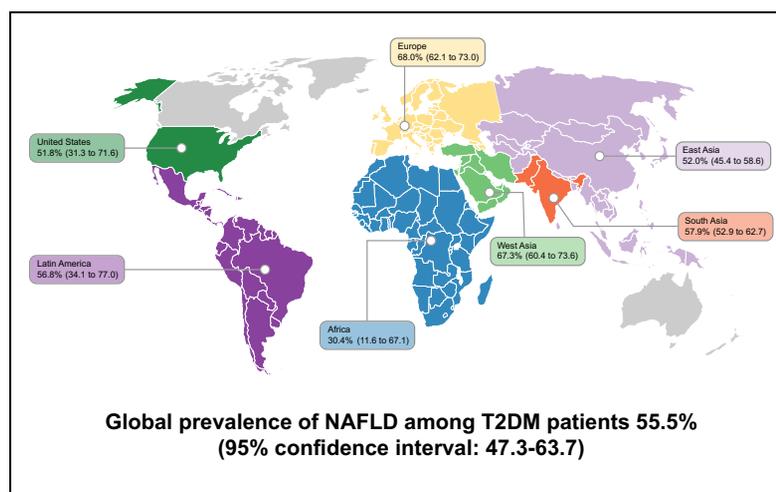
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## Lay summary

Dysregulation of bile acid metabolism and T cells can contribute to the development of cholangiopathies. Before targeting T cells for the treatment of cholangiopathies, it should be determined whether they exert protective effects on bile acid metabolism. Herein, we demonstrate that T cell-induced cholangitis resulted in decreased levels of harmful unconjugated bile acids. T cells were able to directly control synthesis and metabolism of bile acids, a process which was dependent on the proinflammatory cytokines TNF and IFN- $\gamma$ . Understanding the effect of lymphocytes on bile acid metabolism will help in the design of combined treatment strategies for cholestatic liver diseases.

# The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis

## Graphical abstract



## Highlights

- Prevalence of NAFLD in patients with type 2 diabetes mellitus is more than 2-fold higher than in the general population.
- The overall prevalence of NAFLD among patients with type 2 diabetes mellitus is 55.5%.
- The global prevalence of non-alcoholic steatohepatitis among patients with type 2 diabetes is 37.3%.
- Of the patients with NAFLD and type 2 diabetes mellitus who undergo liver biopsy, 17% have advanced fibrosis.

## Authors

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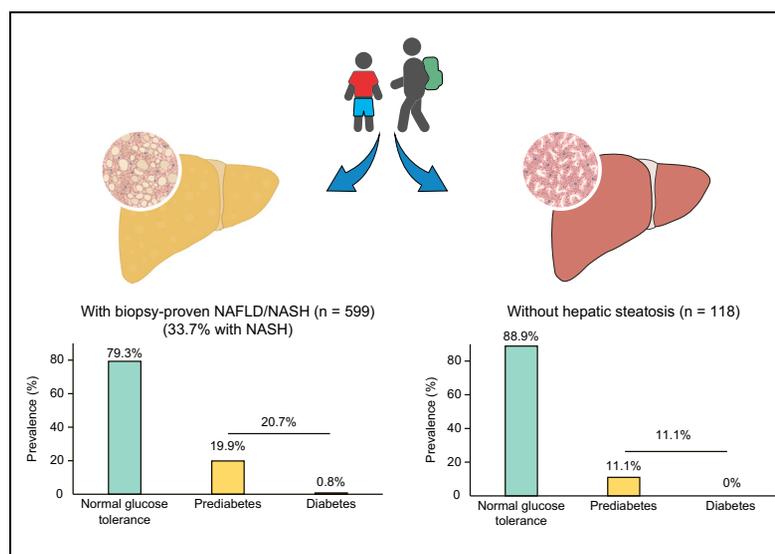
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## Lay summary

Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most prevalent chronic liver disease worldwide. Type 2 diabetes mellitus (T2DM) is an important risk factor for NAFLD. Additionally, T2DM seems to accelerate the progression of liver disease in NAFLD. Despite the high prevalence and serious clinical implications of NAFLD in patients with T2DM, it is usually overlooked in clinical practice. This meta-analysis provides evidence of the high prevalence of NAFLD and NASH in patients with T2DM. In this context, increasing awareness about the importance of NAFLD in patients with T2DM among all important stakeholders (primary care physicians, specialists, and health policy makers) must be prioritized.

# Prevalence of prediabetes and diabetes in children and adolescents with biopsy-proven non-alcoholic fatty liver disease

## Graphical abstract



## Highlights

- The prevalence of abnormal glucose tolerance is uncertain in children with biopsy-proven NAFLD.
- Children with NAFLD have a higher prevalence of abnormal glucose tolerance than those without NAFLD.
- Children with NAFLD and abnormal glucose tolerance have a higher prevalence of NASH than those with normal glucose tolerance.
- Central adiposity is the factor that is most strongly associated with NASH.

## Authors

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## Lay summary

Children with biopsy-proven non-alcoholic fatty liver disease (NAFLD) have a higher prevalence of abnormal glucose tolerance (prediabetes or type 2 diabetes) than children without NAFLD. Children with biopsy-proven NAFLD and abnormal glucose tolerance also have a higher prevalence of the progressive form of disease, non-alcoholic steatohepatitis, than those with normal glucose tolerance, though central adiposity is the factor that is most strongly associated with non-alcoholic steatohepatitis.