BIOMARKERS FOR LIVER DISEASE

A QUICK OVERVIEW

ORIGENE

The impact of chronic disease on society is rapidly rising.[1] The World Health Organization (WHO) estimates that 46% of global conditions and 59% of mortality are due to chronic diseases. Thirty-five million individuals worldwide die yearly from chronic illness, increasing steadily.[2] Most chronic liver diseases in the developed world include alcoholic liver disease, chronic viral Hepatitis, including hepatitis B and C, nonalcoholic fatty liver disease (NAFLD), and hemochromatosis.[3]

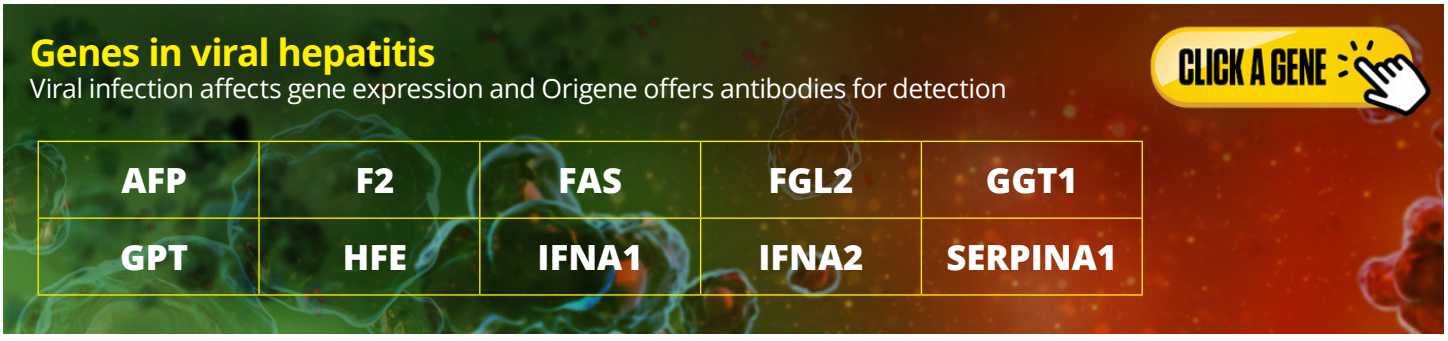
Liver disease refers to any damage or disorder that limits or reduces the function of the liver. It can be genetic (inherited) or acquired (something that arises from an infection, unwholesome habits or actions, or exposure to specific toxins).[4]

The liver disease accounts for approximately 2 million deaths per year worldwide, 1 million due to complications of cirrhosis, and 2 million due to viral hepatitis and hepatocellular carcinoma.[5, 6]

Hepatitis

One of the most widespread infectious diseases in the world is hepatitis B.[7] Over 350 million of the 2 billion people with hepatitis B virus (HBV) infection are chronic carriers, characterized by the persistence of the virus and HBV surface antigen (HBsAg) in blood as well as the generation of viral antigens and HBV DNA in the liver.[8-10] Annual deaths from chronic liver disease linked to HBV exceed a million.[11]

Hepatitis, characterized by liver inflammation, can result from several factors, including excessive alcohol consumption, autoimmune conditions, medicines, or pollutants. Viral Hepatitis, on the other hand, is the most common cause of Hepatitis and results from a viral infection. Most of the time, Hepatitis results from hepatitis viruses A, B, C, D, E, & G.[12]



Pathophysiology: It is triggered by many microorganisms such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Herpes Simplex virus (HSV)[13]

There are two main types of hepatitis therapies available:[14]

Immune modulator drugs: Interferon-type drugs that boost the immune system to help eliminate the hepatitis B virus.[15] *Antiviral drugs*: These are drugs that stop or slow down the hepatitis virus from reproducing, which reduces the inflammation and damage to the liver.[16]

Current treatment approach: First-line oral medication, such as tenofovir disoproxil fumarate (TDF) or entecavir, should be administered to any patient with acute HBV illness (ETV).[17] Direct-acting antivirals (DAAs) are the most common treatment for Hepatitis.

Newer Targets

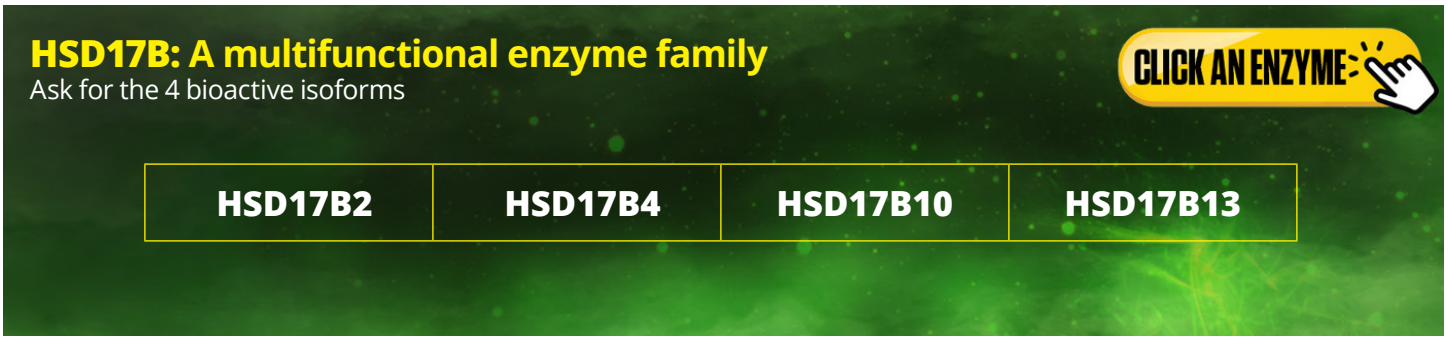
Table 1: New therapy for chronic hepatitis by acting as immunomodulators[19-23, 43-44]

Classification by mechanism	Drug name	Mechanism of action
TLR agonists	Vesatolimod[29]	TLR-7 Agonist
	RO7020531[30]	TLR7 Agonist
	JNJ-4964[31]	TLR7 Agonist
	GS-9688[32]	TLR-8 Agonist
IAP (Inhibitor of Apoptosis Protein) antagonist	APG-1387[28]	Mimicking endogenous SMAC molecules to degrade IAPs
Immune Checkpoint Inhibitors	Envafolimab[27]	Anti-PD-1/PD-L1
Monoclonal Antibodies	GC1102[24]	HBsAg monoclonal antibody
	VIR-3434[26]	RNA gene silencer
Other Immune Approaches	IMC-I109V[25]	Immune mobilizing monoclonal T cell receptors against the virus

B cell: Bursa-dependent lymphocyte; **CHB**: Chronic hepatitis B; **HBcAg**: Hepatitis B core antigen; **HBsAg**: Hepatitis B surface antigen; **HBx**: Hepatitis B virus X protein; **IAPs**: Inhibitor of apoptosis proteins; **IFN-α**: Interferon alfa; **ISGs**: IFN-stimulated genes; **PD-1**: Programmed cell death protein 1; **PD-L1**: Programmed cell death-ligand 1; **SMAC**: Second mitochondria-derived activator of caspase; **T cell**: Thymus-dependent lymphocyte; **TLR**: Toll-like receptor.

Future prospective:

For the treatment of chronic hepatitis B, several antiviral and immunomodulatory drugs have been combined. Alpha interferon and gamma interferon, alpha interferon and acyclovir, prednisone and interferon, and other combinations were some of them.[18]



HSD17B is a multifunctional enzyme has 14 isoforms. HSD17B4 and HSD17B10 are associated with inborn metabolism errors; hence a key target for research. OriGene offers a comprehensive tool box for analyzing HSD17B which includes cDNA clones, antibodies and recombinant proteins in addition to bioactive isoforms.

Alcoholic Hepatitis

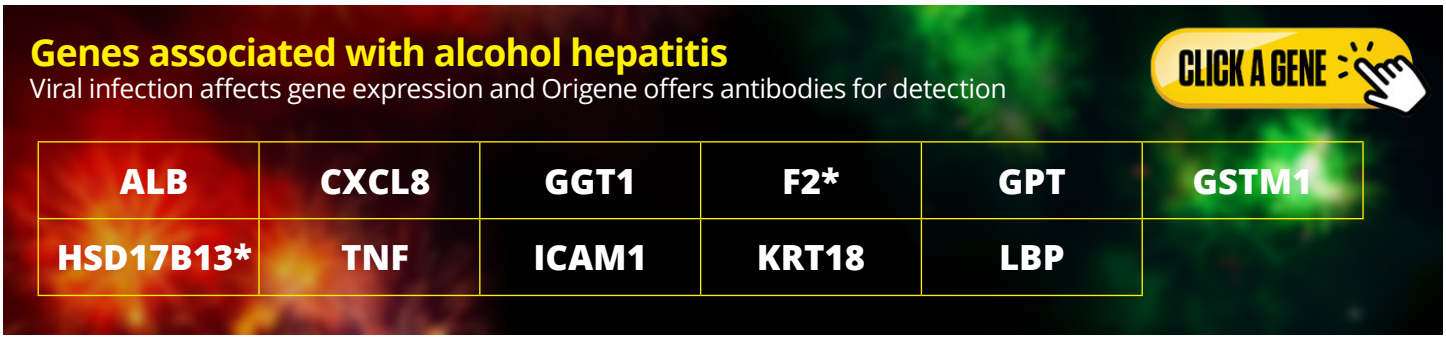
Alcoholism (A.H.), fatty liver disease (steatosis), and, ultimately, cirrhosis can all be caused by excessive alcohol use. A severe form of alcoholic Hepatitis is characterized by the fast onset of jaundice, malaise, painful hepatomegaly, and modest signs of a systemic inflammatory response.[33]

Approximately two-thirds of adults in the United States drink alcohol,[34] while 7.2% suffer from alcohol use disorder (AUD).[35] Excessive alcohol intake is the third leading preventable cause of death in the United States.[36]

In the hepatocytes, alcohol enters an oxidative metabolic route that lowers the nicotinamide adenine dinucleotide (NAD) proportion to NADH. This encourages lipogenesis by preventing the oxidation of triglycerides and fatty acids.[45]

Following the treatment used for the A.H.

- Guselkumab (Anti-IL 23 Monoclonal Antibody)[37]
- Pentoxifylline (phosphodiesterase inhibitor)[38]
- Infliximab (anti-TNF antibody)[39]



Nonalcoholic fatty liver disease (NAFLD)

NAFLD is increasingly recognized as a significant cause of liver-related morbidity and mortality because of its potential to progress to cirrhosis and liver failure. NAFLD is the deposition of fat in the liver of a nonalcoholic subject, a condition that may progress to end-stage liver disease.[40-42, 46]

NAFLD is a prevalent liver disease in the United States (USA),[47] affecting approximately 20% of the adult population.[48] Its prevalence is 10-24% of the general population in different countries. Among obese persons, the prevalence rises to 57-74% and 25-75% among obese diabetics.[49, 50]

Table 2: Potential agents for the treatment of NAFLD[51, 52]

Pharmacological agent	Target
Obeticholic acid	FXR agonist
Semaglutide	GLP-1 receptor agonist
Resmetirom (MGL-3196)	THR-ß agonist
Aramco	SCD1 inhibitor
Lanifbranor	PPAR α, δ, γ agonist
Belapectin (GR-MD-02)	Galectin-3 inhibitor
Pegbelfermin (BMS-986036)	FGF21 analog
MK-3655	Monoclonal antibody agonist of the b-Klotho/FGFR1c receptor complex
TVB-2640	FASN inhibitor
Tirzepatide	Dual GIP and GLP-1 receptor agonist
BI456906	Dual GIP and GLP-1 receptor agonist
BMS-986263	HSP47 siRNA
CC-90001	JNK inhibitor

FXR: farnesoid X receptor; **GLP-1**: glucagon-like peptide-1; **THR**: thyroid hormone receptor; SCD1, stearoyl CoA desaturase 1; **PPAR**: peroxisome proliferative activated receptor; **FGF**: fibroblast growth factor; **FGFR**: FGF receptor; **FASN**: fatty acid synthase; **GIP**: glucose-dependent insulinotropic polypeptide; **HSP**: heat shock protein; **JNK**: Jun N-terminal kinase. This table does not cover all of the trials. In addition to the problems presented in this table, there are ongoing trials of GLP-1 receptor agonists, SGLT2 inhibitors, PPAR agonists, and combinations of various drugs.

HSD17B13, a liver-enriched, hepatocyte-specific, lipid droplet-associated protein, has been reported to be strongly associated with the development and progression of NAFLD/NASH in both mice and humans; hence a potential therapeutic target for NAFLD/NASH.

Tools for analyzing HSD17B13: Bioactive protein, Clones, Antibodies

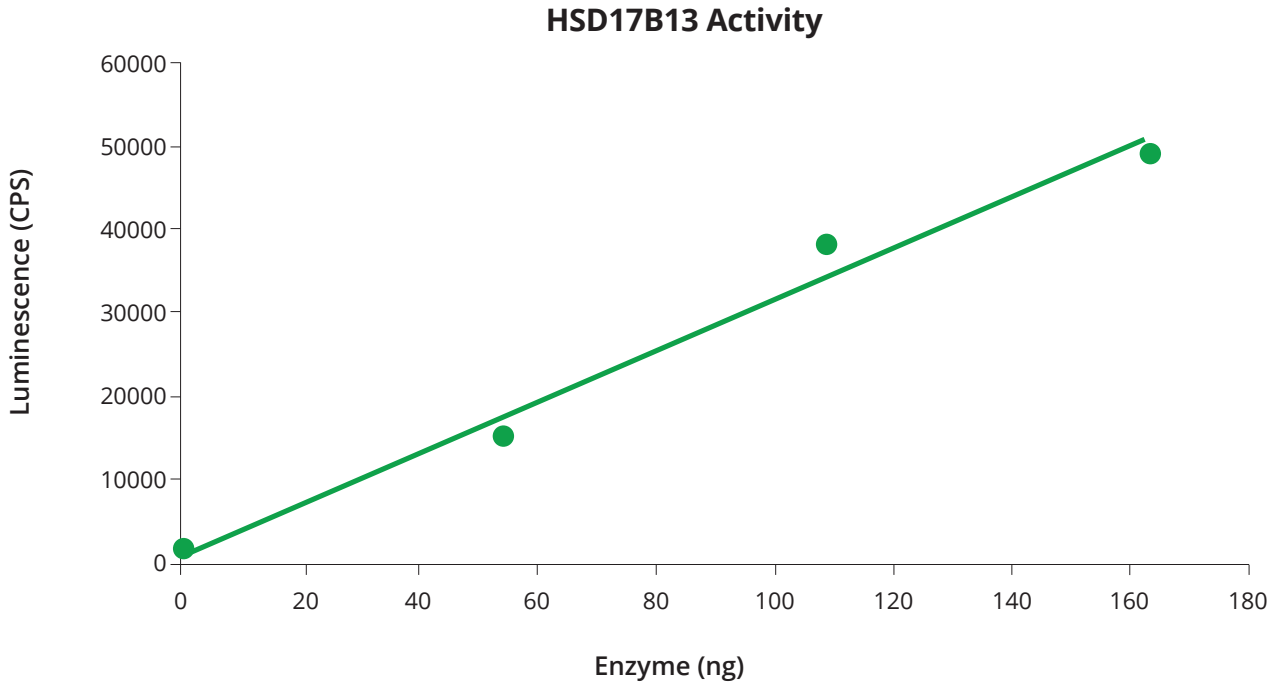
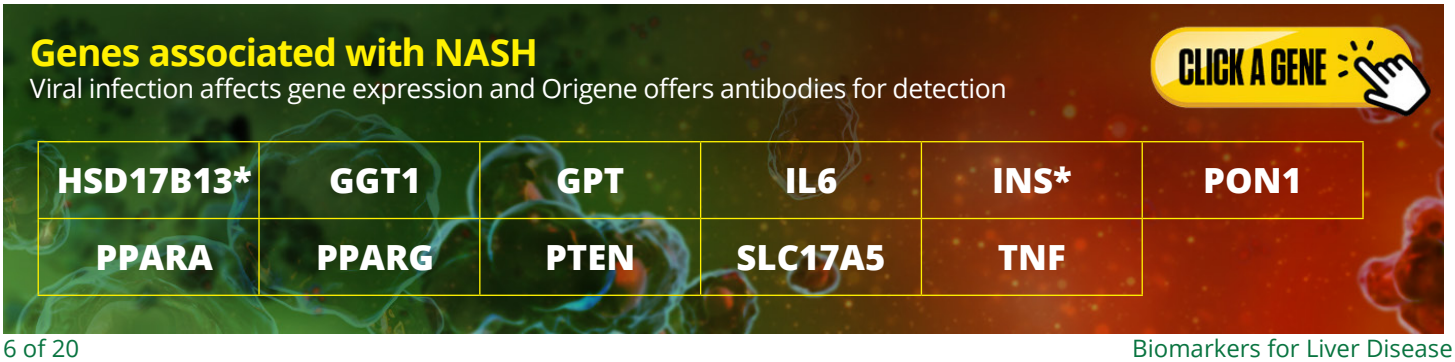


Figure 1: Bioactive HSD17B13 TP300460. Enzymatic activity with 75µM β-estradiol as a substrate, measured by NADH production (indicated by luminescence).

Nonalcoholic Steatohepatitis (NASH)

NASH is characterized as the ectopic buildup of fat in the liver (hepatic steatosis) in the absence of additional sources of secondary liver fat buildup.[53] Fat accumulation in at least 5% of hepatocytes is pathogenic because it can happen in healthy persons in small amounts.[53] NAFLD is one of the most common causes of liver disease in the United States. The majority of people with NAFLD have NAFL. Only a small number of people with NAFLD have NASH. Experts estimate about 24% of U.S. adults have NAFLD, and about 1.5% to 6.5% of U.S. adults have NASH.[54]



Insulin (INS) is one of key genes associated with NASH. Studies have shown that lipotoxicity, insulin resistance (IR) and inflammation are involved in the disease process. Lipotoxicity promotes inflammation and IR, which in turn, increase adipocyte lipolysis and exacerbates lipotoxicity. Furthermore, IR and inflammation form a vicious circle, with each condition promoting the other and accelerating the development of NAFLD in the presence of lipotoxicity.

Find the tools for analyzing INS: **Here**

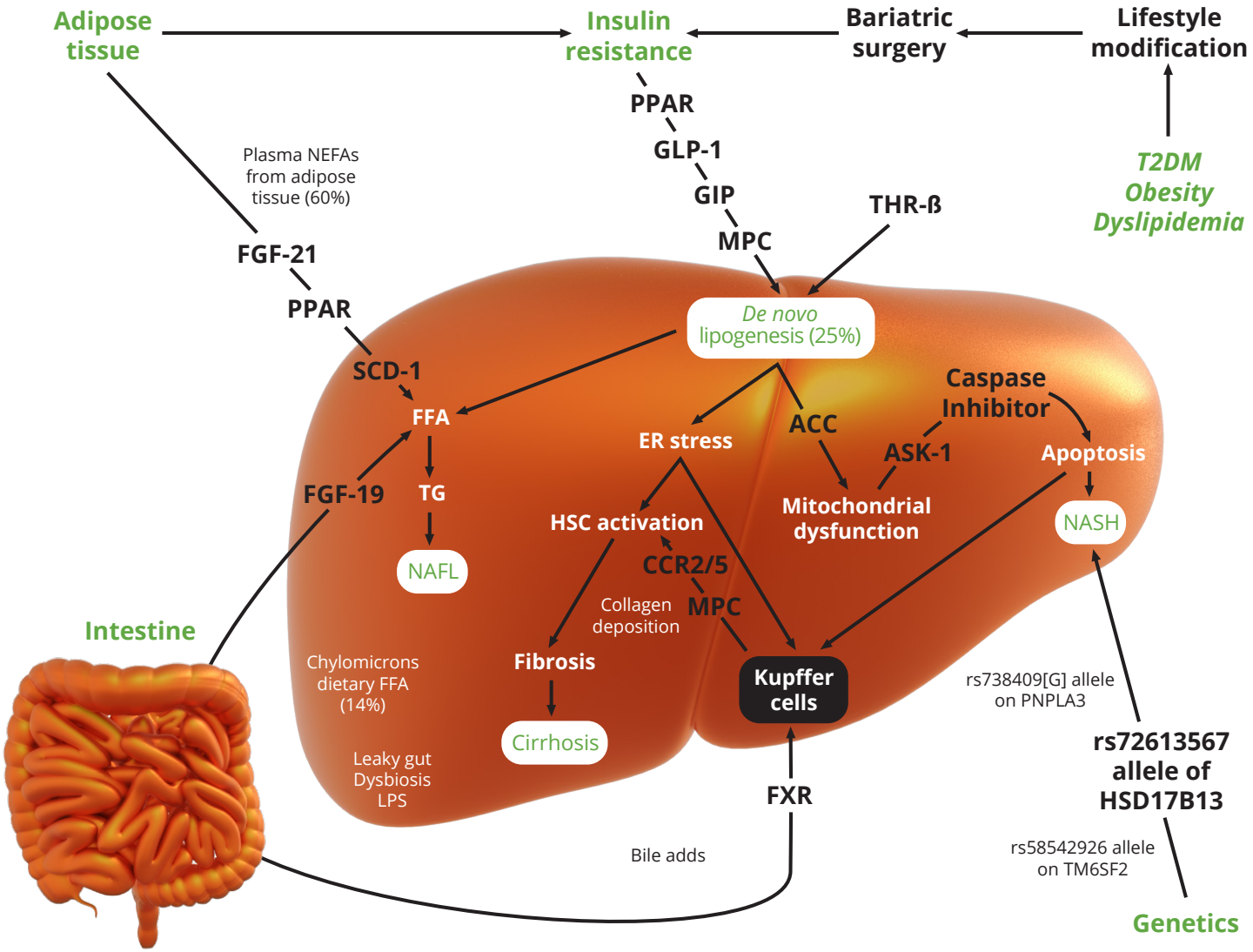


Figure 2: Pathogenetic pathways & pharmacological targets for therapy of NASH
Multiple pathogenetic pathways have been studied as possible pharmacological targets for the treatment of NASH[55]

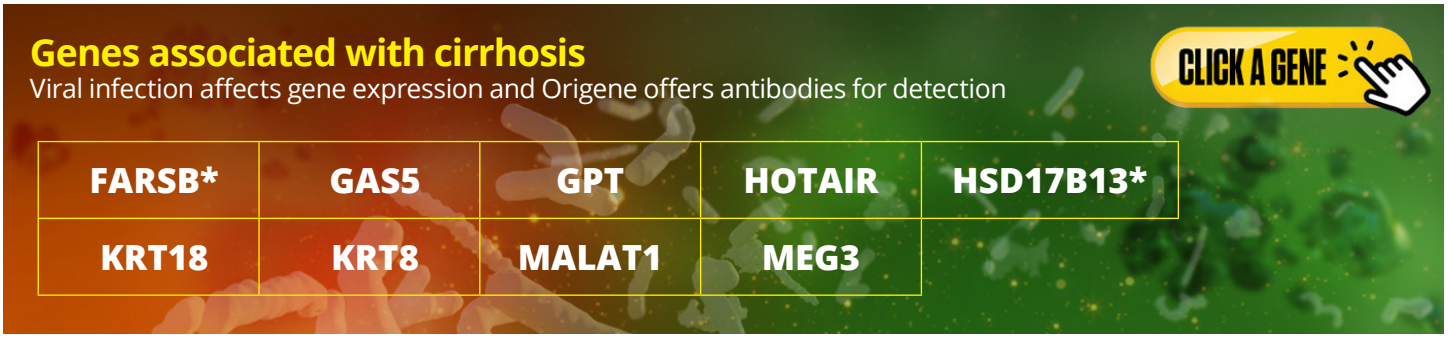
Table 3: Drugs and their mechanisms of action

Drug name	Mechanism of action
Aramchol, PF-06865571 & PF-05221304[56]	SCD1 inhibition and ABCA1 stimulation
Lanifibranor[57, 58]	PPARs agonist
Obeticholic Acid[59]	FXR agonist
Resmetirom[60]	Highly selective agonist of THR-ß
Semaglutide[61, 62]	GLP-1 agonist
Oltipraz[63]	AMPK-S6k1 and LXRg-SREBP-1c inhibition
Secukinumab[64]	Anti-Interleukin 17 A

Liver Cirrhosis

In response to chronic liver injury, cirrhosis is defined as the histological formation of regenerating nodules surrounded by fibrous bands, which results in portal hypertension and end-stage liver disease.[65]

Researchers estimate that about 1 in 400 adults in the United States have cirrhosis. Cirrhosis is more common in adults ages 45 to 54. About 1 in 200 adults ages 45 to 54 in the United States has cirrhosis.[66]



Two key genes associated with liver cirrhosis are **FARSB** and **HSD17B13**. FARSB belongs to the aminoacyl-tRNA synthetase class Iic subfamily.

OriGene offers a range of tools for analyzing FARSB: **Here**

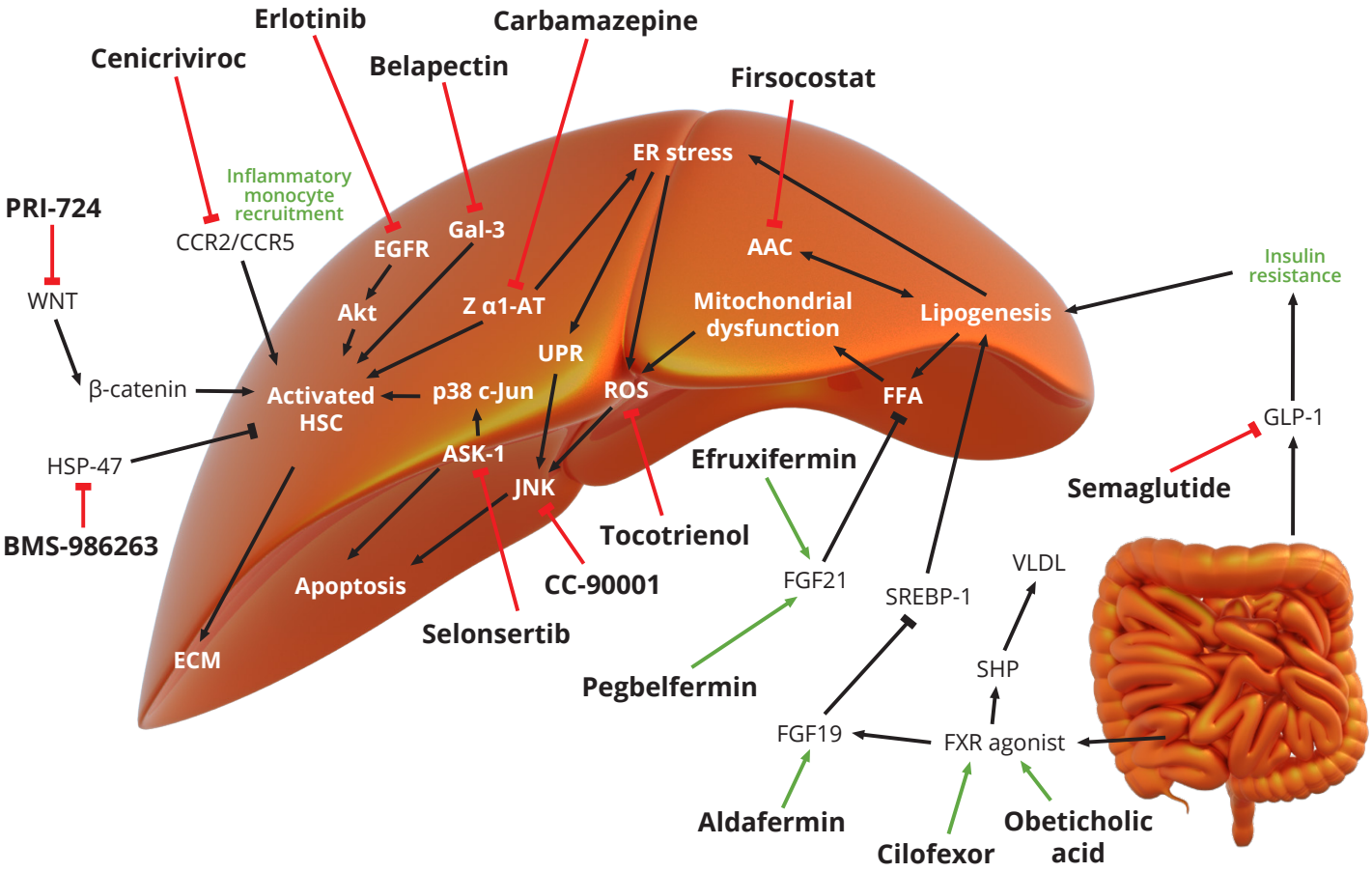


Figure 3: Summary of emerging drugs for the treatment of cirrhosis[67]

Table 4: Summary of medicines for the treatment of cirrhosis[67]

Compound	Indication	Mechanism of action
Obeticholic acid (INT-747)	Compensated NASH cirrhosis (Reverse)	Lipogenesis/oxidative stress (Steroidal FXR agonist)
Belapectin (GR MD 02)	NASH cirrhosis with portal hypertension	Macrophage activation/ fibrogenesis (Galectin-3 inhibitor)
Cenicriviroc (TAK-652;TBR-652)	NASH cirrhosis (and a liver-related clinical outcome in Aurora)	Inflammation/immune activation (CCR2/CCR5 dual antagonist)
Pegbelfermin (BMS-986,036; ARX-618)	Compensated NASH	Lipogenesis/oxidative stress (FGF21 analog)
Efruxifermin (AKR-001)	NASH and fibrosis stage F1-F4	Lipogenesis/oxidative stress (FGF21 analog)
Aldafermin (NGM282)	Compensated NASH cirrhosis (Alpine 4)	Lipogenesis/oxidative stress (FGF19 analog)
BMS-986,263 (ND-L02-s0201)	Compensated NASH cirrhosis	Collagen synthesis (HSP47 inhibitor)
CC-90,001	NASH with bridging fibrosis (F3) or compensated cirrhosis (F4)	Apoptosis/inflammasome (JNK inhibitor)
Semaglutide	Compensated NASH cirrhosis	Insulin resistance (GLP-1 agonist)
Firsocostat (ND-630; GS-0976)	Compensated NASH cirrhosis	Lipogenesis/oxidative stress (ACC inhibitor)
Cilofexor (GS-9674)	Compensated NASH cirrhosis	Lipogenesis/oxidative stress (non-steroidal FXR agonist)
Selonsertibf	Compensated NASH cirrhosis (combination regimen only)	Apoptosis/inflammasome (ASK-1 inhibitor)
Tocotrienol	End-stage liver disease related to NASH	Oxidative stress/inflammation (an isomer of Vitamin E)
PRI-724	HBV/HCV cirrhosis (Child-Pugh A/B)	HSC activation (Wnt/β-catenin inhibitor)
Carbamazepine	Severe liver disease due to Alpha-1 Antitrypsin Deficiency (clinically significant portal hypertension)	Mutant ATZ (autophagy enhancer)
Erlotinib hydrochloride	Liver fibrosis or cirrhosis (Child-Pugh ≤6)	HSC activation (EGFR inhibitor)

Hepatocellular Carcinoma (HCC)

The most frequent primary liver cancer is hepatocellular carcinoma (HCC), which also has a high mortality rate from cancer. HCC is the ninth most common cancer that leads to mortality in the United States.[68, 69]

Each year, the American Cancer Society estimates the number of new cancer cases and deaths in the United States. It compiles the most recent data on population-based cancer occurrence and outcomes. In 2022, 1,918,030 new cancer cases and 609,360 cancer deaths are projected to occur in the United States.[70]

Treatment options for HCC depend on the disease's stage (Figure 4). These include surgery (including curative resection and liver transplantation), radiofrequency ablation, stereotactic ablative radiotherapy/stereotactic body radiation therapy, transarterial chemoembolization (TACE), transarterial radioembolization, and systemic targeted therapies, including Atezolizumab/Bevacizumab (immune checkpoint inhibitors [ICIs] that are now the established standard of care for advanced HCC) and Sorafenib/Lenvatinib (multi-targeted tyrosine kinase inhibitors that were previously the standard of care for advanced HCC).[71]

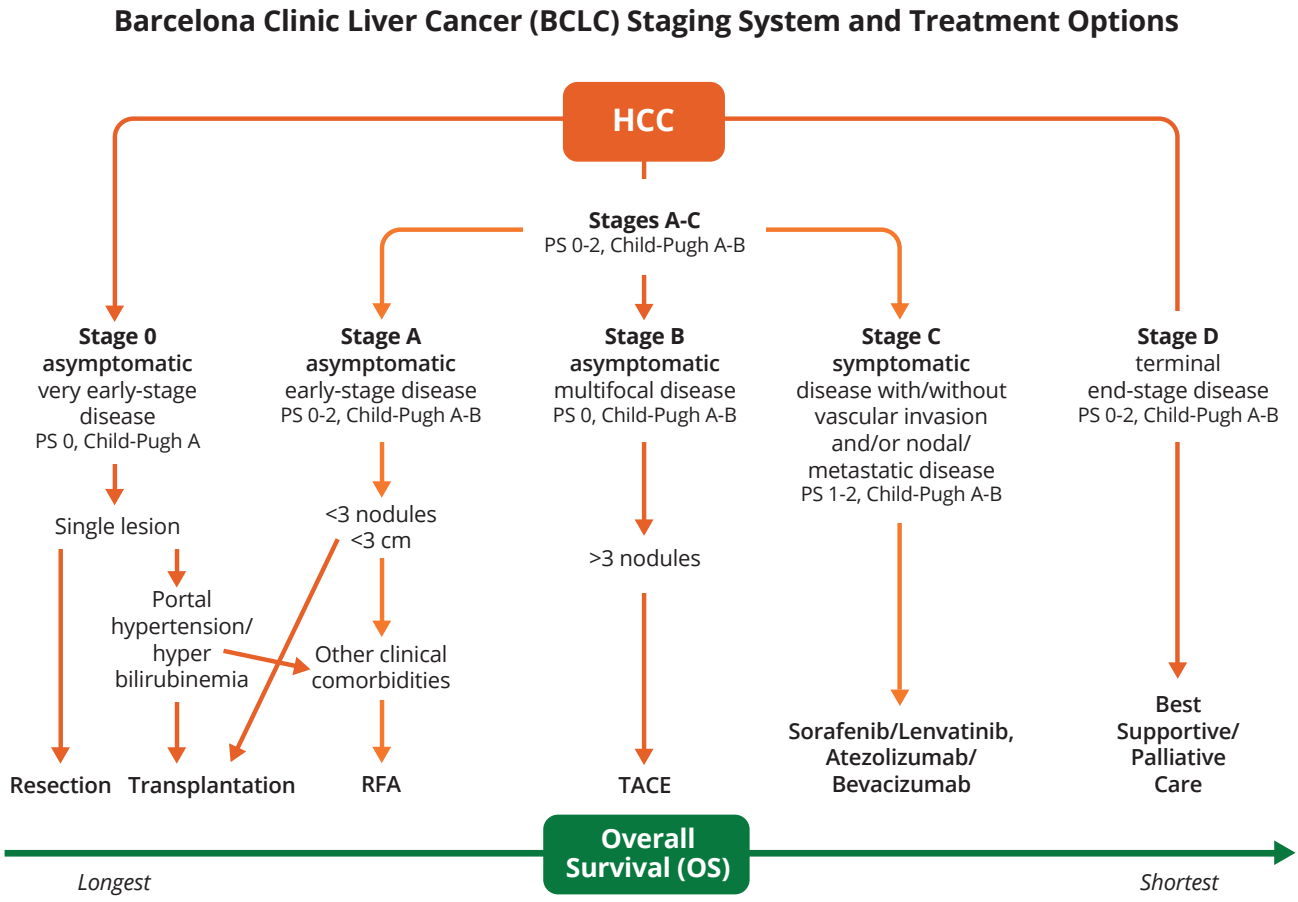


Figure 4: Treatment options for hepatocellular carcinoma (HCC) according to the Barcelona Clinic Liver Cancer (BCLC) staging system

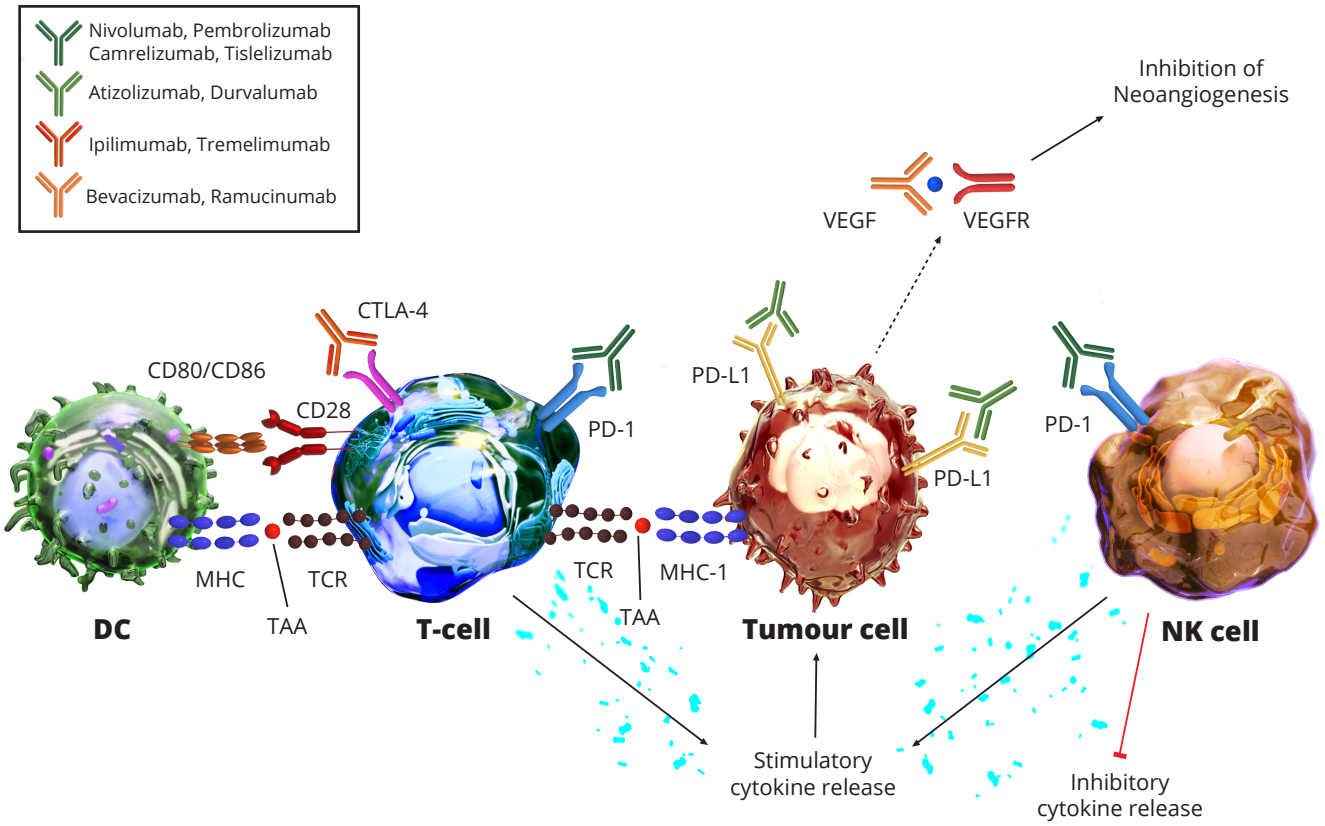


Figure 5: Recently used Immune checkpoint inhibitors agents with the mechanism of action. PD-1, PD-L1, and CTLA-4-targeting monoclonal antibodies that have been or are being developed as ICIs for the treatment of HCC are listed below.[72, 73]

Table 5: Monoclonal antibody comparison

Monoclonal antibody	Ligand target	Antibody class
Nivolumab	PD-1	IgG4
Pembrolizumab	PD-1	IgG4
Camrelizumab	PD-1	IgG4
Tislelizumab	PD-1	IgG4
Atezolizumab	PD-L1	IgG1
Durvalumab	PD-L1	IgG1
Ipilimumab	CTLA-4	IgG1
Tremelimumab	CTLA-4	IgG2

Autoimmune Hepatitis (AIH)

liver characterized by circulating autoantibodies and elevated serum globulin levels. It can present in acute or chronic forms. In autoimmune diseases, AIH is associated with non-organ-specific antibodies in the context of hepatic autoimmunity.[75]

Autoimmune Hepatitis is more common in females than males, with a ratio of 3.6:1. However, it is reported that 100,000 to 200,000 individuals are affected yearly. The current proposition for pathogenesis is thought to be secondary to a failure of immune tolerance in a genetically susceptible individual leading to a T-cell-mediated inflammation caused by various environmental triggers. Common triggers include infections, medications, and toxins. Specific human leukocyte antigen (HLA) haplotypes are more susceptible to the development of autoimmune Hepatitis.[76]

Therefore, future immunotherapies should aim to restore self-tolerance to hepatic autoantigens, nullifying the need for long-term immunosuppression.

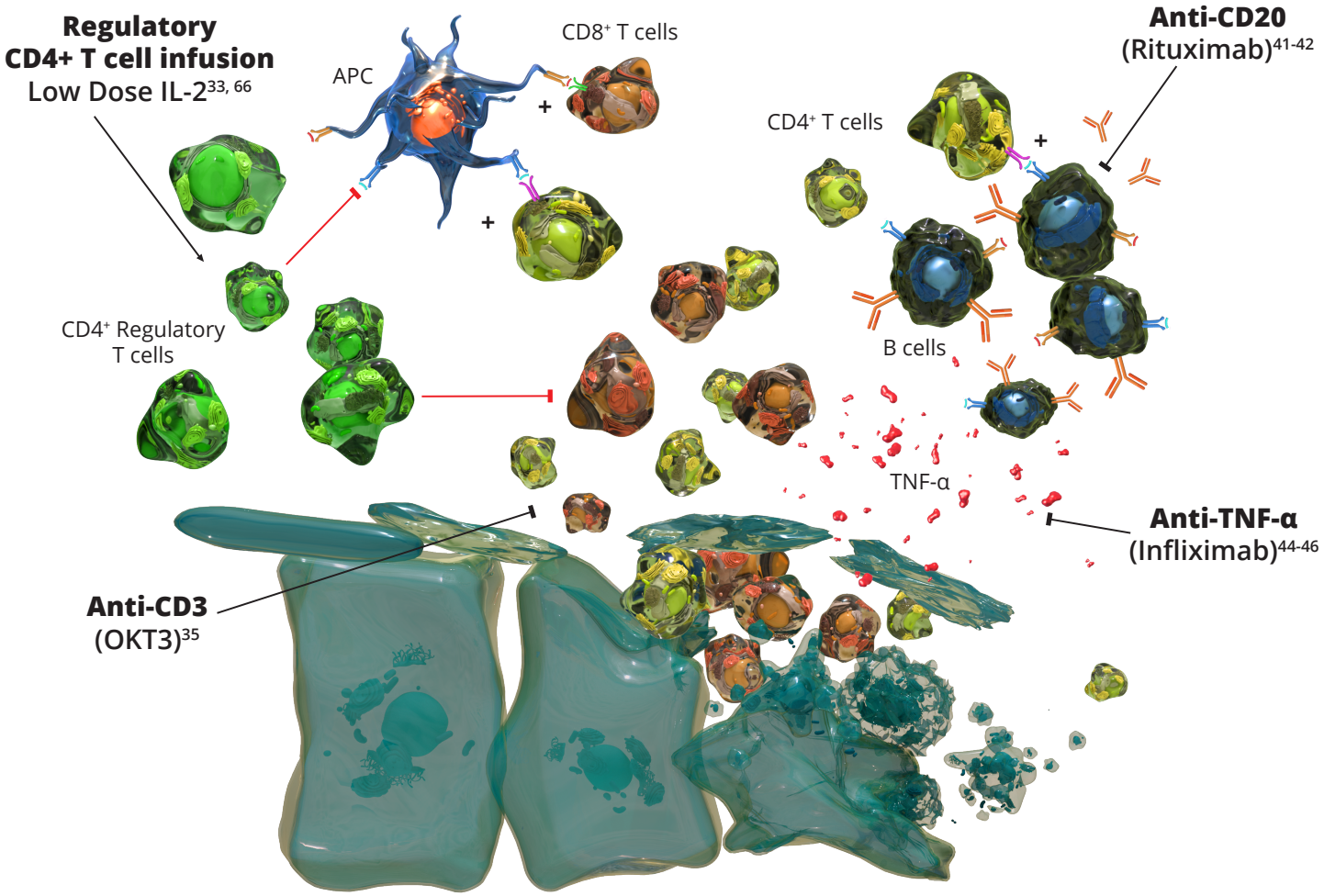


Figure 6: Putative mechanisms of liver damage and new immunotherapies for autoimmune Hepatitis[77]

Current standard treatment with azathioprine and prednisolone induces remission in most patients. However, for those patients not responding to standard therapy or not tolerating these drugs, few alternatives can be used, and their effectiveness might be limited.[78]

Anti-CD20 antibodies (rituximab): that deplete B cells and have demonstrated efficacy in other autoimmune conditions.[79, 80]

Anti-CD3 monoclonal antibodies (OKT3): are used in treating severe acute rejection after solid organ transplantation.[81]

TNF-α blockade with monoclonal antibodies (infliximab)

Cholestasis

A significant function of the liver is the production and secretion of bile. Any disturbance in the complex sequence of cellular events that ultimately result in the entry of bile fluid into the duodenum impairs the bile secretory process and therefore invokes a condition descriptively called Cholestasis.[82]

Epidemiology: Cholestasis is observed across all age groups. However, the pediatric and adolescent age group is more susceptible to Cholestasis owing to the immaturity of the liver.[83]

Pathophysiology: Water enters the canaliculi by a chemical and osmotic gradient created by the trafficked protein that carries the bile content there. Understanding the mechanisms behind some disorders, such as benign recurrent intrahepatic Cholestasis (F1C1 locus gene) and progressive familial intrahepatic Cholestasis, has been made possible by identifying anomalies within some of these transporter proteins (F1C2 locus gene). Bile salts that aren't appropriately transported build up in the liver. The bile salts' potent detergent-like activity damages membranes and impairs their ability to function. The physical restriction of bile flow at the level of extrahepatic biliary ducts is another mechanism of Cholestasis. Hepatotoxicity can also bring on by retained bile.[83, 84]

Current treatment approaches for Cholestasis

- Ursodeoxycholic Acid (UDCA)
- Obeticholic Acid (OCA) Tropifexor

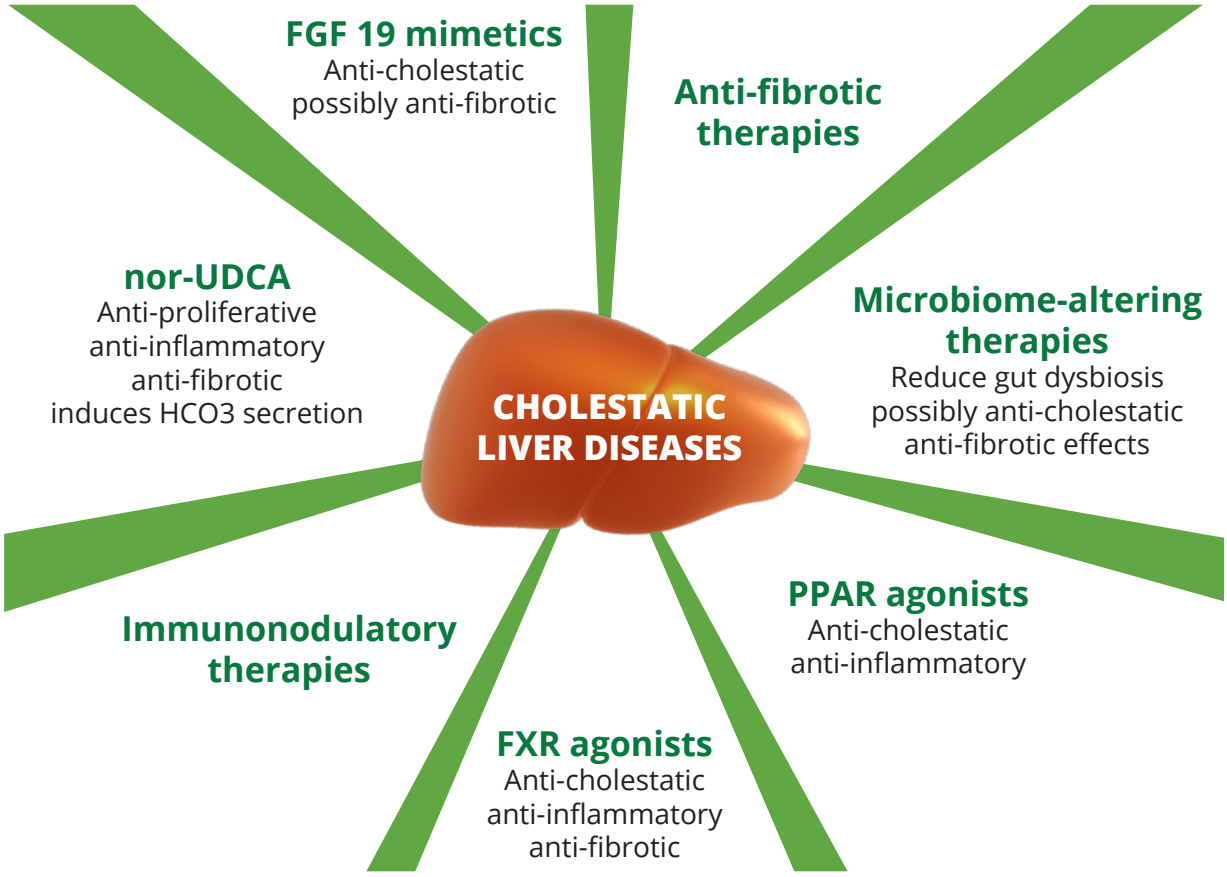


Figure 7: Novel classes of therapies for cholestatic liver diseases[85]

Monoclonal Antibodies

Using monoclonal antibodies (MoAbs) is one of the most promising ways of improving patient outcomes. Following the treatment approach for Cholestasis:

Table 6: Novel classes of drugs for cholestatic liver diseases[86, 87]

Drug	Mechanism of Action
Rituximab	Monoclonal antibody against CD20; B-cell depletion
Ustekinumab	Monoclonal antibodies against IL-12 and IL-23
Abatacep	Monoclonal antibody that targets CD80 and CD86 on antigen-presenting cells and interferes with T-cell activation
Infliximab	Monoclonal antibody against TNF-α
Simtuzumab	Humanized IgG4 monoclonal antibody against LOXL
CM-101	anti-ccl24 monoclonal antibody reduces cholangiocytes proliferation
Baricitinib	Inhibitors of Janus kinase (JAK) 1 and 2

Future prospective:

Many research organizations worldwide strive to identify and characterize new mAb targets for Cholestasis. Furthermore, advanced molecular engineering has enabled the development of superior mAb alterations and formulations that address several technical issues, such as optimal immune effector mechanism stimulation, stability, and half-life.

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References

1. Jana A, Chattopadhyay A. Prevalence and potential determinants of chronic disease among elderly in India: Rural-urban perspectives. PloS one. 2022 Mar 11;17(3):e0264937.
2. World Health Organization. Global status report on blood safety and availability 2021.
3. Sharma A, Nagalli S. Chronic Liver Disease. [Updated 2021 Nov 25]. In: StatPearls [Internet]. Treasure Island (F.L.): Stat Pearls Publishing; 2022.
4. merican liver association guidelines. Available on https://liverfoundation.org/for-patients/about-the-liver/the-progression-of-liver-disease/
5. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. Journal of Hepatology. 2019 Jan 1;70(1):151-71.
6. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. Clin Liver Dis (Hoboken). 2021 Jun 4;17(5):365-370. DOI: 10.1002/cld.1061. PMID: 34136143; PMCID: PMC8177826.
7. Maddrey WC. Hepatitis B: a significant public health issue. Journal of medical virology. 2000 Jul;61(3):362-6.
8. Hou J, Liu Z, Gu F. Epidemiology and Prevention of Hepatitis B Virus Infection. Int J Med Sci. 2005;2(1):50-57. doi: 10.7150/ijms.2.50. Epub 2005 Jan 5. PMID: 15968340; PMCID: PMC1142225.
9. Wright TL. Introduction to chronic hepatitis B infection. Official journal of the American College of Gastroenterology| ACG. 2006 Jan 1;101:S1-6.
10. World Health Organization. Hepatitis B. World Health Organization Fact Sheet No. 2004. Available at: http://who.int/mediacentre/factsheets/fs204/en (accessed June 5, 2005).
11. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology. 2020 Nov;72(5):1605-16.
12. Mehta P, Reddivari AKR. Hepatitis. [Updated 2021 Dec 31]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554549/
13. McCance KL, Huether SE, Brashers VL, Rote NS, editors. Pathophysiology: The biological basis for disease in adults and children. Elsevier; 2019.
14. Akbar SM, Al-Mahtab M, Khan MS, Raihan R, Shrestha A. Immune therapy for hepatitis B. Ann Transl Med. 2016 Sep;4(18):335. doi: 10.21037/atm.2016.08.48. PMID: 27761439; PMCID: PMC5066052.

15. Treatment Options for Hepatitis B. Available https://www.hepb.org/treatment-and-management/treatment/
16. Chen LP, Zhao J, Du Y, Han YF, Su T, Zhang HW, Cao GW. Antiviral treatment to prevent chronic hepatitis B or C-related hepatocellular carcinoma. World J Virol. 2012 Dec 12;1(6):174-83. doi: 10.5501/wjv.v1.i6.174. PMID: 24175223; PMCID: PMC3782279.
17. Ahn J.C., Ahn J. Hepatitis B: Standard and Novel Treatment Options. Clin Liver Dis (Hoboken). 2018 Aug 22;12(1):19-23. doi: 10.1002/cld.719. PMID: 30988904; PMCID: PMC6385900.
18. Di Bisceglie AM. Combination therapy for hepatitis B. Gut. 2002 Apr;50(4):443-5. doi: 10.1136/gut.50.4.443. PMID: 11889057; PMCID: PMC1773159.
19. Kayesh MEH, Kohara M, Tsukiyama-Kohara K. Toll-Like Receptor Response to Hepatitis B Virus Infection and Potential of TLR Agonists as Immunomodulators for Treating Chronic Hepatitis B: An Overview. Int J Mol Sci. 2021 Sep 28;22(19):10462. doi: 10.3390/ijms221910462. PMID: 34638802; PMCID: PMC8508807.
20. Tang Y, Liang H, Zeng G, Shen S, Sun J. Advances in new antivirals for chronic Hepatitis B. Chin Med J (Engl). 2022 Feb 2;135(5):571-583. doi: 10.1097/CM9.0000000000001994. PMID: 35120358; PMCID: PMC8920451.
21. Ebert G, Allison C, Preston S, Cooney J, Toe JG, Stutz MD, Ojaimi S, Baschuk N, Nachbur U, Torresi J, Silke J. Eliminating hepatitis B by antagonizing cellular inhibitors of apoptosis. Proceedings of the National Academy of Sciences. 2015 May 5;112(18):5803-8.
22. Clark MP, Huynh T, Rao S, Mackiewicz L, Mason H, Romal S, Stutz MD, Ahn SH, Earnest L, Sozzi V, Littlejohn M. Clinical stage drugs targeting inhibitor of apoptosis proteins purge episomal Hepatitis B viral genome in preclinical models. Cell death & disease. 2021 Jun 23;12(7):1-1.
23. Li S, Li N, Yang S, Deng H, Li Y, Wang Y, Yang J, Lv J, Dong L, Yu G, Hou X. The study of immune checkpoint inhibitors in chronic hepatitis B virus infection. International Immunopharmacology. 2022 Aug 1;109:108842.
24. Kim SH. HBV neutralizing human monoclonal antibody (GC1102) for liver transplantation & chronic hepatitis B treatment. 2009 Nov:91
25. Mak LY, Seto WK, Yuen MF. Novel antivirals in clinical development for chronic hepatitis B infection. Viruses. 2021 Jun 18;13(6):1169.
26. Tang Y, Liang H, Zeng G, Shen S, Sun J. Advances in new antivirals for chronic hepatitis B. Chinese Medical Journal. 2022 Mar 5;135(05):571-83.
27. Li S, Li N, Yang S, Deng H, Li Y, Wang Y, Yang J, Lv J, Dong L, Yu G, Hou X. The study of immune checkpoint inhibitors in chronic hepatitis B virus infection. International Immunopharmacology. 2022 Aug 1;109:108842.
28. Liu H, Hou J, Zhang X. Targeting cIAPs, a New Option for Functional Cure of Chronic Hepatitis B Infection. Virologica Sinica. 2018 Oct;33(5):459-61.
29. Janssen HL, Brunetto MR, Kim YJ, Ferrari C, Massetto B, Nguyen AH, Joshi A, Woo J, Lau AH, Gaggar A, Subramanian GM. Safety, efficacy, and pharmacodynamics of vesatolimod (GS-9620) in virally suppressed patients with chronic hepatitis B. Journal of Hepatology. 2018 Mar 1;68(3):431-40.
30. Luk A, Jiang Q, Glavini K, Triyatni M, Zhao N, Racek T, Zhu Y, Grippo JF. A single and multiple ascending dose study of toll-like receptor 7 agonists (RO7020531) in healthy Chinese volunteers. Clinical and translational science. 2020 Sep;13(5):985-93.
31. Tang Y, Liang H, Zeng G, Shen S, Sun J. Advances in new antivirals for chronic hepatitis B. Chinese Medical Journal. 2022 Mar 5;135(05):571-83.
32. Mackman RL, Mish M, Chin G, Perry JK, Appleby T, Aktoudianakis V, Metabo S, Pyun P, Niu C, Daffis S, Yu H. Discovery of GS-9688 (Selgantolimod) as a potent and selective oral toll-like receptor 8 agonists for the treatment of chronic hepatitis B. Journal of Medicinal Chemistry. 2020 May 14;63(18):10188-203.
33. Shah NJ, Royer A, John S. Alcoholic Hepatitis. [Updated 2022 Mar 2]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470217/
34. Olson S, Gerstein DR. Alcohol in America: Taking Action to Prevent Abuse. Washington (D.C.): National Academies Press (U.S.); 1985. 1, Drinking in America. Available from: https://www.ncbi.nlm.nih.gov/books/NBK217463/
35. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. 2018 Aug 28;320(8):815-824. doi: 10.1001/jama.2018.11406. PMID: 30167705; PMCID: PMC7391072.
36. Stahre M, Roeber J, Kanny D, Brewer RD, Zhang X. Peer reviewed: contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. Preventing chronic disease. 2014;11.
37. Guselkumab (Anti-IL 23 Monoclonal Antibody) for Alcohol Associated Liver Disease. ClinicalTrials.gov Identifier: NCT04736966. Available on https://clinicaltrials.gov/ct2/show/NCT04736966
38. Parker R, Armstrong MJ, Corbett C, Rowe IA, Houlihan DD. Systematic review: pentoxifylline for the treatment of severe alcoholic Hepatitis. Alimentary pharmacology & therapeutics. 2013 May;37(9):845-54.
39. Sharma P, Kumar A, Sharma BC, Sarin SK. Infliximab monotherapy for severe alcoholic Hepatitis and predictors of survival: an open-label trial. Journal of Hepatology. 2009 Mar 1;50(3):584-91.
40. Benedict M, Zhang X. Nonalcoholic fatty liver disease: An expanded review. World J Hepatol. 2017 Jun 8;9(16):715-732. doi: 10.4254/with.v9.i16.715. PMID: 28652891; PMCID: PMC5468341.

41. Pouwels, S., Sakran, N., Graham, Y., Leal, A., Pintar, T., Yang, W., Kassir, R., Singhal, R., Mahawar, K., & Ramnarain, D. (2022). Nonalcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management, and effects of weight loss. BMC endocrine disorders, 22(1), 63.
42. Benedict M, Zhang X. Nonalcoholic fatty liver disease: An expanded review. World J Hepatol. 2017 Jun 8;9(16):715-732. doi: 10.4254/wjh.v9.i16.715. PMID: 28652891; PMCID: PMC5468341.
43. Tang Y, Liang H, Zeng G, Shen S, Sun J. Advances in new antivirals for chronic Hepatitis B. Chin Med J (Engl). 2022 Feb 2;135(5):571-583. doi: 10.1097/CM9.0000000000001994. PMID: 35120358; PMCID: PMC8920451.
44. Tang Y, Liang H, Zeng G, Shen S, Sun J. Advances in new antivirals for chronic Hepatitis B. Chin Med J (Engl). 2022 Feb 2;135(5):571-583. doi: 10.1097/CM9.0000000000001994. PMID: 35120358; PMCID: PMC8920451.
45. Sharma A, Nagalli S. Chronic Liver Disease. [Updated 2021 Nov 25]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554597/
46. Falck–Ytter Y, Younossi Z M, Marchesini G, Mc Cullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis 2001;21:17-26.
47. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology. 2002 Dec;36(6):1349-54.
48. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of nonalcoholic fatty liver disease. Digestive diseases. 2010;28(1):155-61.
49. Patell R, Dosi R, Joshi H, Sheth S, Shah P, Jasdanwala S. Non-Alcoholic Fatty Liver Disease (NAFLD) in Obesity. J Clin Diagn Res. 2014 Jan;8(1):62-6. doi: 10.7860/JCDR/2014/6691.3953. Epub 2013 Jan 12. PMID: 24596725; PMCID: PMC3939589.
50. Paschos P, Paletas K. Nonalcoholic fatty liver disease and metabolic syndrome. Hippokratia. 2009 Jan;13(1):9-19. PMID: 19240815; PMCID: PMC2633261.
51. Mantovani A, Dalbeni A. Treatments for NAFLD: state of the art. International journal of molecular sciences. 2021 Feb 26;22(5):2350.
52. Fallowfield JA, Jimenez-Ramos M, Robertson A. Emerging synthetic drugs for the treatment of liver cirrhosis. Expert opinion on emerging drugs. 2021 Apr 3;26(2):149-63.
53. Sharma B, John S. Nonalcoholic Steatohepatitis (NASH) [Updated 2021 Sep 21]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470243/
54. The National Institute of Diabetes and Digestive and Kidney Diseases is part of the United States National Institutes of Health, which in turn is part of the Department of Health and Human Services. NIDDK is approximately the fifth-largest of the 27 NIH institutes. Available on https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts#:~:text=NAFLD%20is%20one%20of%20the,of%20U.S.%20adults%20have%20NASH.
55. Sinakos E, Liava C, Loomba R. Emerging advances in the pharmacologic treatment of nonalcoholic steatohepatitis and related cirrhosis. Ann Gastroenterol. 2022 May-Jun;35(3):213-225. doi: 10.20524/aog.2022.0704. Epub 2022 Apr 7. PMID: 35599922; PMCID: PMC9062842.
56. Dufour JF, Caussy C, Loomba R. Combination therapy for nonalcoholic steatohepatitis: rationale, opportunities, and challenges. Gut. 2020 Oct;69(10):1877-1884. doi: 10.1136/gutjnl-2019-319104. Epub 2020 May 7. PMID: 32381514; PMCID: PMC7497577.
57. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, Loomba R, Harrison SA, Balabanska R, Mateva L, Lanthier N. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. New England Journal of Medicine. 2021 Oct 21;385(17):1547-58.
58. Boeckmans J, Natale A, Rombaut M, Buyl K, Rogiers V, De Kock J, Vanhaecke T, M Rodrigues R. Anti-NASH Drug Development Hitches a Lift on PPAR Agonism. Cells. 2019 Dec 21;9(1):37. doi: 10.3390/cells9010037. PMID: 31877771; PMCID: PMC7016963.
59. Ratziu V. Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis. Clin Liver Dis (Hoboken). 2021 Aug 5;17(6):398-400. doi: 10.1002/cld.1076. PMID: 34386202; PMCID: PMC8340357.
60. Harrison SA, Bashir M, Moussa SE, McCarty K, Pablo Frias J, Taub R, Alkhouri N. Effects of Resmetirom on Noninvasive Endpoints in a 36-Week Phase 2 Active Treatment Extension Study in Patients With NASH. Hepatol Commun. 2021 Jan 4;5(4):573-588. Doi: 10.1002/hep4.1657. PMID: 33860116; PMCID: PMC8034581.
61. Liava C, Sinakos E. Semaglutide for nonalcoholic steatohepatitis: closer to a solution? Hepatobiliary Surg Nutr. 2021 Aug;10(4):541-544. doi: 10.21037/hbsn-21-231. PMID: 34430539; PMCID: PMC8351017.
62. Dickson I. Semaglutide is safe and efficacious for NASH resolution. Nature Reviews Gastroenterology & Hepatology. 2021 Jan;18(1)
63. Pallayova M, Taheri S. Nonalcoholic fatty liver disease in obese adults: clinical aspects and current management strategies. Clinical Obesity. 2014 Oct;4(5):243-53.
64. Carrascosa JM, Bonanad C, Dauden E, Botella R, Olveira-Martín A, Systemic Inflammation in Psoriasis Working Group. Psoriasis and nonalcoholic fatty liver disease. Actas Dermo-Sifiliográficas (English Edition). 2017 Jul 1;108(6):506-14.

65. Constance Mobley, Ali Zarrinpar, Chapter 3 - Molecular and Cellular Basis of Liver Failure, Editor(s): Ronald W. Busuttil, Göran B.G. Klintmalm, Transplantation of the Liver (Third Edition), W.B. Saunders, 2015, Pages 40-57, ISBN 9781455702688,
66. Definition & Facts for Cirrhosis. Available on https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis/definition- facts#:~:text=Researchers%20estimate%20that%20about%201,with%20cirrhosis%20are%20not%20diagnosed.
67. Fallowfield JA, Jimenez-Ramos M, Robertson A. Emerging synthetic drugs for the treatment of liver cirrhosis. Expert opinion on emerging drugs. 2021 Apr 3;26(2):149-63.
68. Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D. Hepatocellular carcinoma (HCC): Epidemiology, etiology and molecular classification. Adv Cancer Res. 2021;149:1-61. doi: 10.1016/bs.acr.2020.10.001. Epub 2020 Nov 28. PMID: 33579421; PMCID: PMC8796122.
69. Asafo-Agyei KO, Samant H. Hepatocellular Carcinoma. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559177/
70. Rebecca L Siegel et al. Cancer statistics, 2022 2022 Jan;72(1):7-33. doi: 10.3322/caac.21708. Epub 2022 Jan 12.
71. Liu JKH, Irvine AF, Jones RL, Samson A. Immunotherapies for hepatocellular carcinoma. Cancer Med. 2022 Feb;11(3):571-591. doi: 10.1002/cam4.4468. Epub 2021 Dec 24. PMID: 34953051; PMCID: PMC8817091.
72. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. Front Oncol. 2018 Mar 28;8:86. doi: 10.3389/fonc.2018.00086. PMID: 29644214; PMCID: PMC5883082.
73. Liu HT, Jiang MJ, Deng ZJ, Li L, Huang JL, Liu ZX, Li LQ, Zhong JH. Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: Current Progresses and Challenges. Front Oncol. 2021 Oct 22;11:737497. doi: 10.3389/fonc.2021.737497. PMID: 34745958; PMCID: PMC8570111.
74. Makol A, Watt KD, Chowdhary V.R. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepat Res Treat. 2011;2011:390916. doi: 10.1155/2011/390916. Epub 2011 May 15. PMID: 21760995; PMCID: PMC3132488.
75. Overview of autoimmune Hepatitis. Available on https://www.uptodate.com/contents/overview-of-autoimmune-hepatitis#:~:text=Autoimmune%20hepatitis%20is%20a%20chronic,chronic%20liver%20disease%20and%20cirrhosis.
76. Linzay CD, Sharma B, Pandit S. Autoimmune Hepatitis. [Updated 2021 Aug 27]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459186/
77. Cassim S, Bilodeau M, Vincent C, Lapierre P. Novel immunotherapies for autoimmune Hepatitis. Frontiers in Pediatrics. 2017 Jan 26;5:8.
78. Weiler-Normann C, Schramm C, Quaas A, Wiegard C, Glaubke C, Pannicke N, Möller S, Lohse AW. Infliximab as a rescue treatment in difficult-to-treat autoimmune Hepatitis. Journal of Hepatology. 2013 Mar 1;58(3):529-34.
79. Du FH, Mills EA, Mao-Draayer Y. Next-generation anti-CD20 monoclonal antibodies in autoimmune disease treatment. Auto Immun Highlights. 2017 Nov 16;8(1):12. doi: 10.1007/s13317-017-0100-y. PMID: 29143151; PMCID: PMC5688039.
80. Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, Grau R, Gerdes C, Nopora A, van Puijenbroek E, Ferrara C, Sondermann P, Jäger C, Strein P, Fertig G, Friess T, Schüll C, Bauer S, Dal Porto J, Del Nagro C, Dabbagh K, Dyer MJ, Poppema S, Klein C, Umaña P. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood. 2010 Jun 3;115(22):4393-402. doi: 10.1182/blood-2009-06-225979. Epub 2010 Mar 1. PMID: 20194898; PMCID: PMC2881503.
81. Cassim S, Bilodeau M, Vincent C, Lapierre P. Novel Immunotherapies for Autoimmune Hepatitis. Front Pediatr. 2017 Jan 26;5:8. doi: 10.3389/fped.2017.00008. PMID: 28184367; PMCID: PMC5266689.
82. Gerd A. Kullak-Ublick, Peter J. Meier, MECHANISMS OF CHOLESTASIS, Clinics in Liver Disease, Volume 4, Issue 2, 2000, Pages 357-385, ISSN 1089-3261, https://doi.org/10.1016/S1089-3261(05)70114-8.
83. Shah R, John S. Cholestatic Jaundice. [Updated 2021 Jul 19]. In: StatPearls [Internet]. Treasure Island (F.L.): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482279/
84. Hofmann AF, F. Hofmann A. Cholestatic liver disease: pathophysiology and therapeutic options. Liver. 2002 Apr;22:14-9.
85. Santiago P, Scheinberg AR, Levy C. Cholestatic liver diseases: new targets, new therapies. Therapeutic advances in gastroenterology. 2018 Aug;11:1756284818787400.
86. Goldstein J, Levy C. Novel and emerging therapies for cholestatic liver diseases. Liver International. 2018 Sep;38(9):1520-35.
87. Levy C. Novel Therapies for Cholestatic Liver Disease. Gastroenterol Hepatol (N Y). 2019 Sep;15(9):493-496. PMID: 31787858; PMCID: PMC6875878.

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