# Therapeutic cocktails – the drink that protects against liver disease

**Dr Sam W French**, a distinguished pathologist from UCLA at Harbor-UCLA Medical Center, is investigating how liver disease in alcoholic patients can be prevented by targeting the proteins and genes that play a key role in the causation processes.

## Q&A

***Why is the liver so difficult to treat?***
The liver is difficult to treat because chronic disease is irreversible: the fibrosis that results from chronic liver disease permanently alters the blood supply and replaces the liver cells with scar tissue. Only a liver transplant using a normal liver restores the normal functions. Also, the liver cells are permanently unable to multiply and regenerate new liver cells with normal function. This is called liver/cell senescence.

***How does cell cycle arrest impact liver regeneration?***
Cell cycle arrest permanently prevents liver cell regeneration. The only treatment that will allow liver cell regeneration is injecting granulocytic-colony stimulating factor. This stimulates the bone marrow to generate a supply of liver cell progenitor cells which multiply and regenerate the liver parenchyma and replace the senescent liver cells.

***If betaine is added to alcoholic drinks to prevent liver disease from developing, could this encourage alcohol abuse?***
No, the alcoholic is addicted and doesn't modify his/her drinking behaviour because of additives to the alcoholic beverage.

***Other than methyl donors such as betaine, do you believe that there are other compounds that could be used to prevent alcoholic liver disease?***
Many different treatments for alcoholic liver disease have been tried after the disease is established by chronic alcoholic abuse. So far, no treatment has been found other than by stopping the alcohol abuse. No treatment to prevent alcoholic liver disease has ever been proposed other than abstinence.

***Where do you see your research focus in five years' time?***
A clinical trial treating alcoholic liver disease in patients by injecting granulocytic-colony stimulating factor will be my focus. Two studies have already been done in India which changed the death rate due to alcoholic hepatitis from 80% to 20% over a period of six months.

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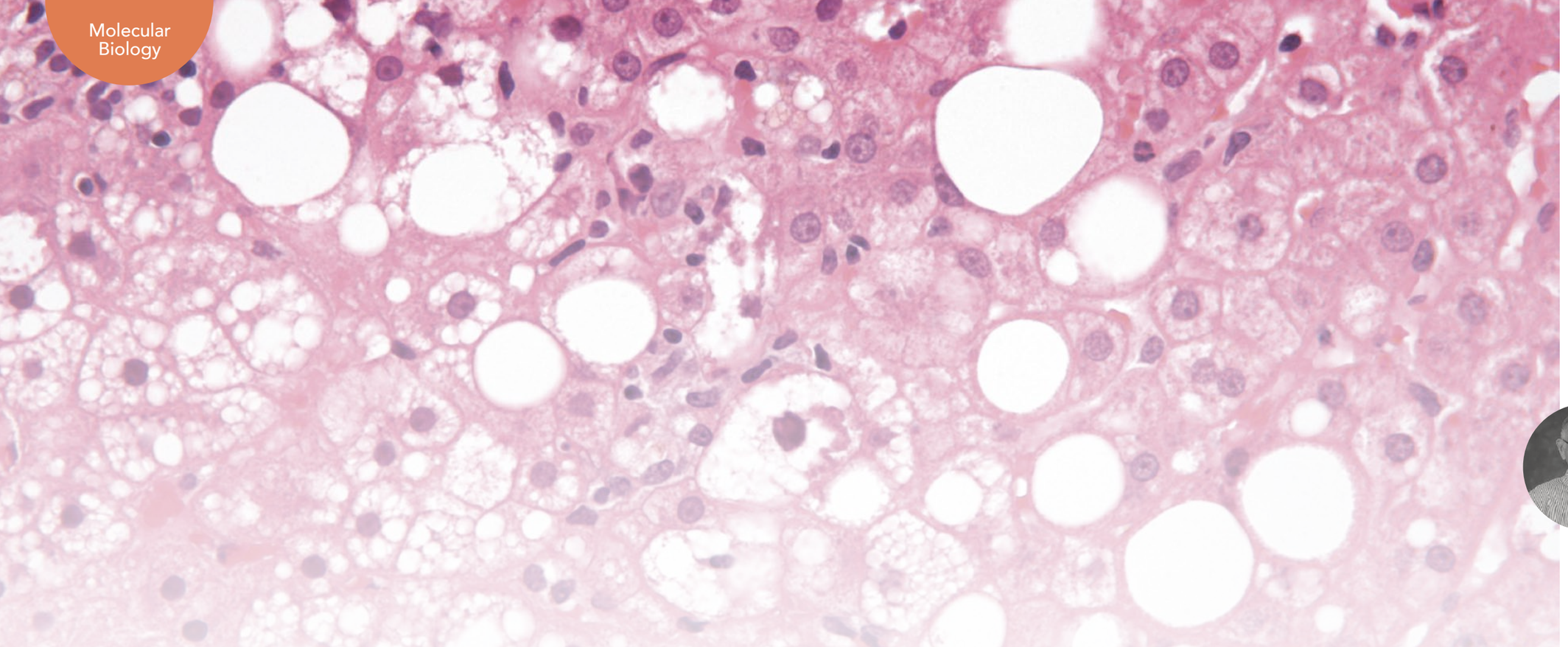
The liver is a remarkable organ. As the body's natural filter, hepatocytes (liver cells) degrade metabolic waste and detoxify harmful blood compounds, maintaining a homeostatic balance. Amazingly, the human liver is also capable of regenerating following extensive tissue trauma, even from just 25% of the original healthy tissue.

Despite its resilience, the liver is not invincible and is especially vulnerable to alcohol abuse. Excessive binge drinking reduces the liver's ability to regenerate, leading to life-threatening diseases such as liver cancer and alcoholic hepatitis, ultimately resulting in cirrhosis (scarring of the liver). In fact, in 2010, 47.9% of all cirrhosis deaths were due to alcohol abuse. Alcoholic liver disease is incredibly difficult to treat – liver transplants often being the only late-stage option. However, a lack of available organs, coupled with a high incidence of immune rejection, limits success. By studying alcoholic hepatitis



liver biopsies, Dr French and his team are elucidating the mechanisms behind alcohol-induced liver damage and evaluating potential preventative therapies.

**CAUSES OF ALCOHOL-INDUCED LIVER DISEASE**

By administering rats with ethanol to mimic the effects of binge drinking, Dr French, in collaboration with a French colleague, has discovered that one of the most significant effects of alcohol abuse on the liver is the inhibition of 26s proteasome. This organelle degrades unwanted or dangerous proteins and has a key regulatory role in many other processes that occur in the liver; its disruption greatly enhances the risk of developing liver disease.

One effect of 26s proteasome inhibition is increased levels of oxidative stress. This is due to an accumulation of unfolded proteins, which are normally degraded by 26s proteasome.

**CELL CYCLE ARREST**

In order to avoid the undesirable replication of oxidised DNA, the cell cycle is arrested, preventing liver regeneration, as no new hepatocytes are being produced. Dr French used RNA sequencing to analyse the abundance of certain proteins in diseased livers and discovered that cell cycle arrest is the result of over-production of five genes: *p15*, *p21*, *p27*, *ATM* and *TGFB*.

Essentially, the cell cycle is the process whereby a cell divides to produce two genetically identical copies (via mitosis) replacing damaged cells. Prior to mitosis, the cell is in 'interphase' – it is preparing to divide by replicating the DNA. The genes *p15* and *p21* inhibit the transition to DNA replication, meaning that mitosis cannot occur and the cell cycle is arrested.

By comparing liver biopsies of healthy and diseased livers, Dr French was able to show over-production of *p15* and *p21*.

Interestingly, Dr French and his team have shown that more than 600 genes are over-expressed and 100 genes are under-expressed in alcoholic hepatitis.

> **Dr French has suggested that in the future betaine methyl donors could potentially be added to alcoholic beverages, preventing the development of alcoholic liver diseases**

**MALLORY-DENK BODY (MDB) PRODUCTION**

Using electron microscopy, Dr French detected an increase in hepatocyte MDBs, due to a lack of 26s proteasome activity. MDBs are aggregations of misfolded, damaged protein. MDBs are particularly associated with alcoholic hepatitis – affecting 70–75% of patients. The development of MDBs indicates that the main mechanism involved in alcoholic hepatitis is the loss of protein quality control.

**ALCOHOL-ASSOCIATED LIVER DISEASE PREVENTION**

Following research into the molecular basis of alcohol-induced liver disease, Dr French then conducted studies that focused on manipulating these processes, to actually prevent liver disease from occurring. As an example, cell cycle arrest can be overcome by giving patients a compound to stimulate stem cells (from the bone marrow) to differentiate into new hepatocytes, which leads to liver cell regeneration.

Perhaps, however, the most exciting discovery is that a powerful antioxidant (betaine) can be used to prevent liver damage from alcohol. Dr French has shown that rats administered alcohol containing betaine methyl donors have reduced blood alcohol levels to 100–200mg/% blood alcohol, compared to an anticipated 500mg/% blood alcohol (equivalent of binge drinking). Furthermore, Dr French found that oxidative stress and MDB formation were significantly reduced in ethanol-subjected hepatocytes when treated with betaine in rats and tissue culture of human hepatocytes.

This is because betaine indirectly increases alcohol dehydrogenase activity – an enzyme that breaks down alcohol. Betaine is a methyl donor and methyl groups are needed for the enzymatic conversion of norepinephrine (noradrenaline) to epinephrine (adrenaline). These hormones are involved in the 'fight or flight' response. Epinephrine in particular is the 'stress hormone' and is very effective at increasing metabolic rate and increasing NAD+ generation. In turn, NAD+ is a molecule that is vital for the functioning of alcohol dehydrogenase, which reduces blood alcohol levels.

However, once the disease becomes established in humans, SAMe (a methyl donor like betaine) is ineffective. Patients with chronic liver disease were administered 20g of SAMe per day for 6 months and there was no change in their liver histology.

**THE FUTURE OF LIVER DISEASE PREVENTION**

Dr French has suggested that in the future betaine methyl donors could potentially be added to alcoholic beverages, preventing the development of alcoholic liver diseases. Fortunately, betaine is colourless, odourless, tasteless, soluble, cheap and extremely effective and can reduce high blood alcohol levels by up to 60%. It seems that this is the ideal preventative measure. However, much testing needs to be performed before betaine can be used commercially in alcoholic drinks. Further research is also needed to further our understanding of how alcohol abuse impacts the liver. Only then can effective preventative measures be developed, saving countless lives.

## Detail

**RESEARCH OBJECTIVES**

Alcoholic hepatitis has a very poor prognosis and, so far, liver transplant is the only available late-stage treatment. Dr French's work focuses on understanding the effects of alcohol abuse on the liver and how this can be prevented rather than treated.

**FUNDING**

National Institutes of Health (NIH)

**BIO**

Graduating from the University of California Medical School, Dr Sam W French specialised in Pathology. He has worked in the field for over 60 years and is now Distinguished Professor of Pathology at UCLA, California. Dr French sits on multiple editorial boards and has authored or co-authored over 800 publications which have been cited more than 19,400 times. He was awarded a Life Achievement Award by the LA Pathology Society in 2011 and the Gold Headed Cane Award given by the American Society of Investigative Pathology in 2014.

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