# High-dose Niacin is a promising treatment for Non-Alcoholic Fatty Liver Disease

*Non-Alcoholic Fatty Liver Disease (NAFLD) is a common condition worldwide. It can progress to liver failure and death. No drug treatment in the clinic has yet shown sufficient efficacy to receive regulatory approval. Prof Moti Kashyap and co-workers at the University of California, Irvine and Aasta Pharmaceuticals have found that Niacin reversed every stage of NAFLD in preclinical studies. Furthermore, a human clinical trial has shown that high-dose Niacin reduces the build-up of fat in the liver. The research team have discovered that Niacin has unique mechanisms of action, which make it an excellent candidate for combination therapy with drugs in development.*

Non-Alcoholic Fatty Liver Disease (NAFLD) refers to a range of medical conditions for which the patient has too much fat in the liver which has not been caused by excessive alcohol consumption. NAFLD is common worldwide, affecting 20-25% of adults. This disease is more prevalent in the West, affecting 75 million people in the USA.

For 25-30% of patients, NAFLD progresses from steatosis (the build-up of fat in the liver) to non-alcoholic steatohepatitis (often called NASH), and is characterised by inflammation of the liver. For about a fifth of these patients, this disease can further progress to fibrosis (scarring of the liver) and cirrhosis (the scarred liver cannot function correctly), manifesting clinically in stomach haemorrhage, liver failure, liver cancer and, ultimately, death. Indeed, NAFLD is estimated in a few years to become the leading cause of liver transplantation.

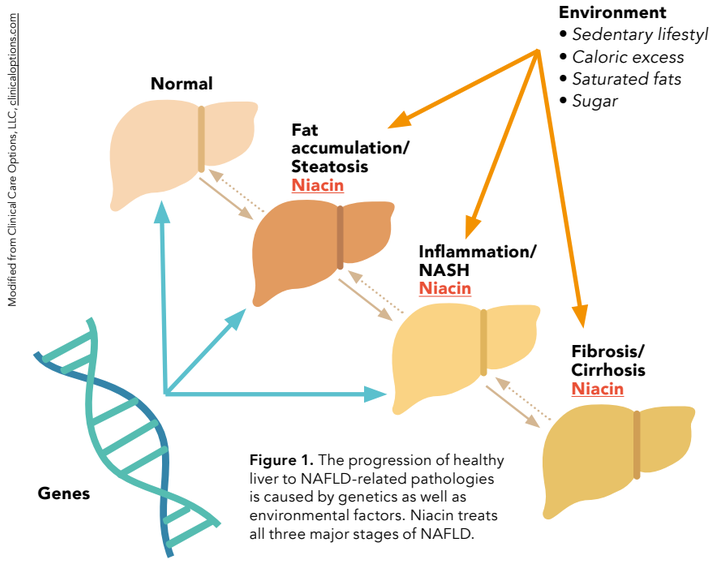
Disease progression is slow; it can take decades for cirrhosis to develop from steatosis. Since the early disease stages (steatosis and steatohepatitis) are asymptomatic, the patient is unaware of this 'ticking time bomb' health risk. This ignorance is unfortunately shared with healthcare professionals who underdiagnose and hence underestimate the prevalence of this disease.

NAFLD is often seen in people who are overweight or obese. Patients may also have high blood pressure, type 2 diabetes and high levels of fat and sugar in their blood. In addition, some people have a higher risk of getting this disease because of their genetic make-up.

Healthcare professionals recommend lifestyle changes, such as exercise, healthy eating and weight loss, to treat NAFLD. However, this approach has not always been sufficiently successful and so drug therapy, ideally in tandem with healthy living, may be necessary for many patients.

In addition, most people with NAFLD die of cardiovascular disease, with NAFLD and atherosclerosis (narrowing of the arteries) often being observed in the same patient. Thus, a drug treatment which prevents the build-up of fat could target both medical conditions.

Over fifty drugs, supported by billions of investment dollars, are currently in development, but not one of them has been approved by the regulatory agencies. The few drugs which have reached advanced clinical trials have shown insufficient efficacy and adverse side effects. Importantly, no drug has yet been shown in the clinic to prevent the fatal consequences which stem from liver cirrhosis. Thus, there is an urgent unmet clinical need.




Modified from Clinical Care Options, LLC, clinicaloptions.com

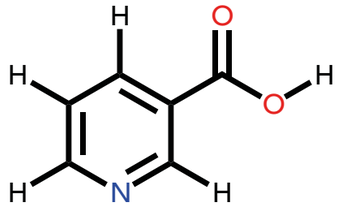
**Figure 1.** The progression of healthy liver to NAFLD-related pathologies is caused by genetics as well as environmental factors. Niacin treats all three major stages of NAFLD.

***We believe that investment in a Phase 2 trial, if successful, could generate a valuation of $5-10 billion for the combination therapy.***

## NIACIN IS A PROMISING TREATMENT

Prof Moti Kashyap and co-workers at the University of California, Irvine have discovered that high-dose Niacin (commonly known as vitamin B3), acting as a drug, can reverse all the stages of NAFLD in human liver cells and in rats.

For example, it was observed that giving Niacin to rats with steatosis not only prevented progression to steatohepatitis, but also reduced the fat content of the rat livers. Furthermore, the discovery that Niacin can reverse fibrosis, in cells obtained from patients with this condition, is very promising.



Chemical structure of Niacin.

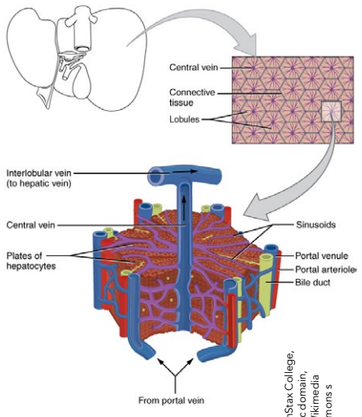
In a small clinical trial, a Niacin oral formulation (a tablet), called Extended-Release Niacin (the tablet dissolves more slowly so that the drug is released into the bloodstream over a prolonged period of time), was found to reduce the liver fat content of 39 patients, who had excess fat in their livers, by 47% after 6 months of treatment.

Prof Kashyap has determined two mechanisms of action for Niacin which are unique to this drug compared to the other treatments currently in the clinic for NAFLD. Firstly, Niacin inhibits an enzyme called DGAT2 (diacylglycerol acyltransferase 2). This means that Niacin prevents the production of triglycerides (fat) in the liver. Secondly, Niacin reduces the amount of oxidation in the cell caused by reactive oxygen species (molecules which can cause oxidation). Now the progression of the disease from fat build-up to inflammation and fibrosis is partially driven by these reactive oxygen species. Thus, Niacin prevents the disease from advancing to more severe stages.

Because Niacin is available without prescription as a vitamin, the level of knowledge that we have about Niacin formulations (the form in which the medicine is given to the patient) has been misunderstood by some people in the industry. For example, none of the 'over-the-counter' formulations for Niacin have been fully tested for safety. And there is a known side-effect for these particular formulations called flushing (warmth, redness, itching and tingling of the skin, especially of the face and neck).

There is a Niacin formulation that was developed for reducing the flushing side effect and tested for safety (approved by the FDA in the USA) that is currently being used by physicians to treat hyperlipidemia (abnormally high levels of fats in the blood) and to prevent heart disease and stroke. This is the Niacin Extended-Release formulation, which was successfully used in a small clinical trial alluded to earlier.

However, no Niacin formulation is currently approved by the FDA for the treatment of NAFLD and its complications of NASH and fibrosis, and so trials are warranted. Yet if the trials are successful, this Niacin formulation could

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Microscopic anatomy of the liver.



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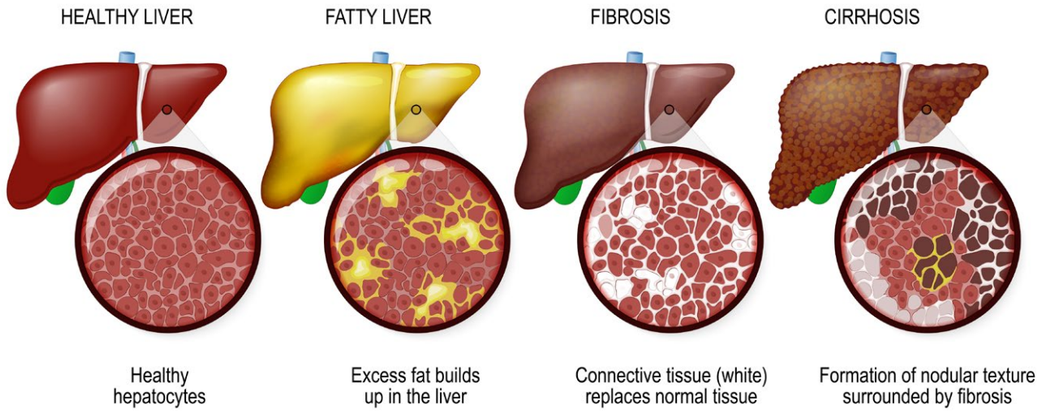


Excess fat in the liver can lead to fibrosis (scarring of the liver) and cirrhosis (the scarred liver cannot function correctly), manifesting clinically in stomach haemorrhage, liver failure, liver cancer and, ultimately, death.

be used to treat multiple conditions, such as heart disease and NAFLD, in the same patient. In addition, Prof Kashyap has noted that there is a strong possibility that the past successful monotherapy trials using Niacin in cardiovascular patients included individuals with undiagnosed steatohepatitis (liver inflammation) or NASH.

***The commercial value lies in combining a Niacin formulation with another patented drug in development. That would create an immensely powerful drug for the treatment of 20-30 million patients in the US alone.***

**A POWERFUL POTENTIAL DRUG FOR THE TREATMENT OF MILLIONS OF PATIENTS**

Prof Kashyap and Dr Vijay Kamanna are founders, and Dr Naresh Nakra is the CEO of Aasta Pharmaceuticals LLC. Together, they developed Niacin as a treatment for NAFLD. They have been issued with a patent by the US Patent Office for the treatment and reversal of fatty liver disease by Niacin. This patent not only covers Niacin but also derivatives and analogues. Thus, there is ample scope to develop an even more effective drug in the future.

Aasta Pharmaceuticals are actively seeking partners, including pharmaceutical companies and financial institutions, to invest in their research and to share in their anticipated lucrative outcome. They have stated, "We believe that a relatively small investment in a Phase 2 trial program of a few million dollars could generate a valuation of $5-10 billion for the combination therapy (discussed in the next paragraph) if successful, based on industry norms."

**COMBINING NIACIN WITH A SECOND DRUG**

Though Niacin has demonstrated effectiveness at every stage of NAFLD, Aasta Pharmaceuticals first want to conduct clinical trials to investigate the ability of high-dose Niacin to treat NASH and fibrosis.

They consider the unique mechanisms of action of Niacin to be important because combining Niacin with another drug ('Drug X') with a different mechanism can result in enhanced efficacy. Indeed, Prof Kashyap has said, "The commercial value lies in combining a Niacin formulation with another patented drug in development. That would be more effective than either drug alone. A combination product would be a powerful drug for the treatment of 20-30 million patients in the US alone that are suffering from NASH."

Aasta Pharmaceuticals would like to partner with other companies who also have NAFLD / NASH drugs in development for the purposes of conducting phase 2 combination drug therapy trials.

If your pharmaceutical organisation were to supply a drug candidate, Drug X, then Aasta Pharmaceuticals would assess interactions between your Drug X and Niacin in a pharmacokinetics study (a study which evaluates what happens to the drugs that are administered to an animal or a person). The purpose of this study would be to find out if giving both drugs together resulted in either of the drugs not working as well as expected.

If the pharmacokinetics study is successful, a 12-month Phase 2 trial will be initiated. The patients will be divided into four groups:
1. Patients taking the placebo.
2. Patients taking Niacin.
3. Patients taking Drug X.
4. Patients taking Niacin and Drug X.

For each patient, the amount of fat in the liver, the degree of liver inflammation and the extent of liver scarring will be measured at regular intervals.

If your company would like to partner and/or invest in this opportunity, please get in touch with Aasta Pharmaceuticals using the contact details given on their company website: www.aastapharma.com



# Behind the Research

## Moti L. Kashyap

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## Research Objectives

Prof Kashyap and his team discovered that Niacin reduces oxidative stress and inhibits a critical enzyme in liver fat formation, making it a key component for the treatment and reversal of fatty liver disease and its complications.

## Detail

**Bio**

Moti Kashyap is Professor of Medicine Emeritus, University of California, Irvine. He is a physician-scientist and Co-Founder of Aasta Pharmaceuticals. He was trained in Internal Medicine, and Lipid Metabolism at McGill University and Cardiovascular Research Institute, San Francisco. Kashyap has published extensively especially on niacin research, clinical and basic, and is Fellow of several professional bodies.

**Funding**

- Southern California Institute for Research and Education
- Department of Veterans Affairs Healthcare System, Long Beach

**Collaborators**

- Vaijinath Kamanna, PhD
- Shobha Ganji, PhD
- Naresh Nakra, PhD

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## Personal Response

***Will a partner organisation be able to influence the design of the Phase 2 clinical trial?***

"Yes. The partner and our team would jointly develop a detailed protocol to address safety and efficacy. The final design will have to be discussed and approved by the FDA in the USA."

***What inspired you to conduct this research?***

"I was inspired by certain observations during my over 25 years of research on Niacin. The unique mechanisms of action of niacin discovered by our team led me to conceive the idea that Niacin could be a potential therapy for Fatty Liver Disease for which there is no approved pharmacologic treatment. Subsequent testing of this idea confirmed this in preclinical and preliminary clinical trial data, warranting a phase 2 trial program especially with another patented drug in development to enhance efficacy."