Repair Biotechnologies, Inc.
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Developing therapies to degrade free cholesterol

With its first-in-class Cholesterol Degrading Platform (CDP), Repair Biotechnologies is tackling the root cause of many difficult-to-treat age-related diseases.

High cholesterol is linked to many diseases, including age-related conditions, according to Reason, CEO of Repair Biotechnologies. The company is developing first-in-class gene therapies based on its Cholesterol Degrading Platform (CDP), targeting intracellular free-cholesterol, previously considered undruggable. "In animal models our therapy reverses both atherosclerosis and non-alcoholic fatty liver disease (NASH) to a sizeable degree," said Reason. Moving towards its first clinical trials, he sees the potential to treat numerous age-related and other conditions.

Co-founded in 2018 by Reason, a patient advocate, and Bill Cherman, a biotech investor, Repair Biotechnologies springs from the growing longevity movement and aims to tackle one of medicine's fundamental questions: how can we intervene to repair the biological damage of aging and thereby reverse the progression of diseases of aging?

The company's pipeline derives from the work of an innovative academic group, now optimized and backed up by extensive research and development (R&D) led by CSO Mourad Topors, heading a team of scientists in Syracuse, New York. Topors was formerly a faculty member at Harvard Medical School, before moving to Pfizer and subsequently consulting for several pharmaceutical companies.

Degrading excess free cholesterol

Cholesterol is largely manufactured in the liver and transported throughout the body via a system of carrier molecules such as low-density lipoprotein (LDL) particles. Inside cells, cholesterol is esterified to provide protection from the toxicity of free cholesterol. Local excesses can overwhelm this protective mechanism and cells have no internal mechanism for degrading cholesterol (Fig. 1). "When your system of transport breaks down, which happens in obesity and aging, localized excesses of cholesterol form. Our data show that the consequent toxicity is an important cause of downstream damage and disease," explained Reason.

No current therapeutics directly target free cholesterol. While lifestyle changes, statins, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can dramatically reduce LDL cholesterol levels, they do not significantly impact free-cholesterol excess or reverse the damage caused by free cholesterol. "Getting rid of excess free cholesterol was impossible until our approach to effectively target it," said Topors.

In several mouse models, removing excess intracellular free-cholesterol via Repair's gene therapy can reverse damage. "Our CDP produces a fusion protein that degrades excess free cholesterol in vivo, safely and selectively, without affecting cholesterol necessary for cell function," said Reason.

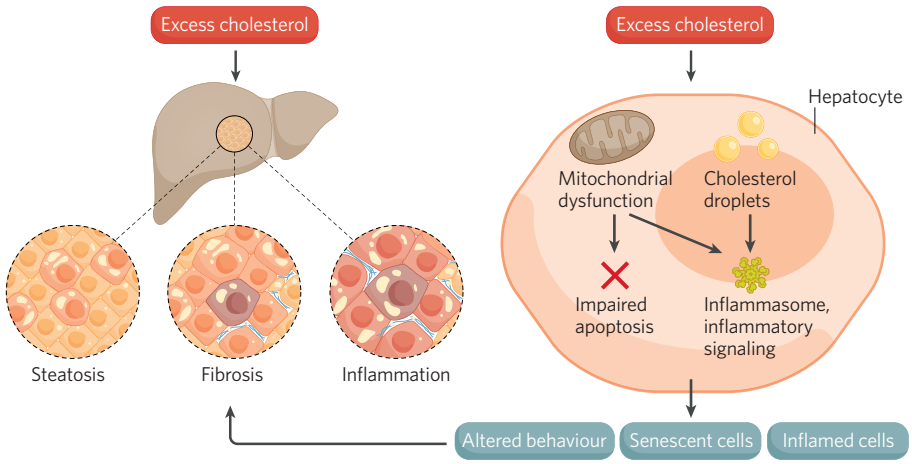

Fig. 1 | Targeting excess cholesterol in the body.

Targeting cholesterol-linked conditions and beyond

The company's initial focus is on conditions linked to cholesterol such as atherosclerosis, the chronic maladaptive inflammatory response leading to cardiovascular disease. Cholesterol-rich plaques form from excess accumulation of cholesterol within the walls of arteries, leading to heart attack and stroke, and cause more than a quarter of all human deaths[1]. Established therapies focused on lowering LDL cholesterol cannot meaningfully remove established plaques, but Repair's animal studies have shown a sizeable reversal of plaques following clearance of free cholesterol. The company is now finalizing its formulation and preclinical studies.

Repair is also developing a therapy for NASH, which affects 3% to 6% of the US population, being more prevalent in patients with metabolic disease and obesity. It progresses from inflammation and fibrosis to cirrhosis in approximately 20% of cases and is associated with increased overall mortality. There is no US Food and Drug Administration (FDA)-approved therapy for NASH, and, like atherosclerosis, its progressive pathology is largely irreversible.

"As with atherosclerosis, the literature suggests that excessive accumulation of free cholesterol is a significant problem in NASH," said Topors. Repair's results confirm this hypothesis. CDP gene therapy reduced liver-tissue free cholesterol in mouse models significantly after only a few days, rapidly reducing key serum markers of liver damage. Moreover, hallmarks of NASH pathology including liver inflammation, insulin resistance and, most importantly, liver fibrosis were all significantly reduced following an 8-week therapy. "Our therapy only removes excess free cholesterol. Sizable benefits emerge quickly, proving the point regarding the role of free cholesterol in NASH," added Reason.

Diverse therapeutic applications

The company expects its platform to be adapted and applied widely in different areas. "NASH and atherosclerosis are the first diseases that we target. We believe that our therapy is promising for numerous other conditions," said Topors. The Repair team expects to develop a long pipeline of therapies for treatable conditions. "Even when looking only at obesity, excess intracellular free-cholesterol may be meaningfully involved in a wide range of associated conditions," said Reason.

Repair is now preparing to file an investigational new drug (IND) application with the FDA for its CDP gene therapy to treat NASH and hopes to complete a pre-IND meeting by early 2024. It then expects to seek institutional funding and pharma partnerships to assist in running phase 1/2 clinical trials. The company has huge ambitions, said Reason: "Our end goal is to prevent the 15 million plus deaths that occur every year from heart attack, stroke, and other consequences of the effects of aging and obesity on cholesterol metabolism. We have a technology that offers that possibility."

1. GBD 2013 Mortality and Causes of Death Collaborators. *Lancet* **385**, 117–171 (2015). https://doi.org/10.1016/S0140-6736(14)61682-2

CONTACT
Reason, CEO & Co-founder
Repair Biotechnologies, Inc.
Syracuse, NY, USA
Email: reason@repairbiotechnologies.com