Bristol Myers Squibb™

# PRO-C3 as a NASH Biomarker

Biomarkers in NASH

Biomarkers can function as diagnostic tools, predict disease progression for individual patients and/or identify those patients who are more likely to respond to a particular treatment.

Consequently, biomarkers have the potential to accurately inform treatment decisions and improve disease outcomes.

The prevalence of nonalcoholic steatohepatitis (NASH) has rapidly increased in recent years due to the rise in obesity.[1] The current NASH diagnosis is achieved through a liver biopsy. Validated biomarkers are needed to assess disease activity and response to interventions in patients with NASH.

NASH

NASH is a progressive liver disease characterized by fat deposits, inflammation and tissue damage.[2] NASH occurs in patient populations who drink little to no alcohol.[2] As the disease progresses, the liver undergoes scarring - or fibrosis - which ultimately leads to cirrhosis and permanent organ damage. NASH with significant fibrosis is associated with higher rates of morbidity and death, and is expected to soon become the 11 leading cause for liver transplants.[3]

| Healthy liver | Fat accumulation | NASH | Cirrhosis |
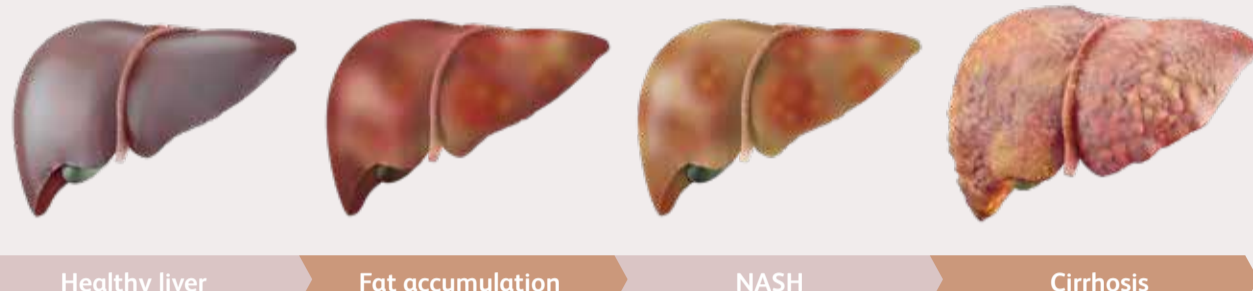
Fibrosis and Biomarkers

Fibrosis is a stage of liver scarring characterized by the accumulation of a protein called collagen.

During fibrosis, small fragments of collagen, called pro-peptides, are released. These pro-peptides may be useful as biomarkers as they reflect the formation of collagen and therefore, the formation of fibrotic tissue.

Type lll collagen is one of the most abundant proteins in fibrotic tissue and a reliable biomarker for liver fibrosis.[4] PRO-C3, the pro-peptide of type lll collagen, may be an accurate biomarker for the formation of fibrotic tissue in the liver.

Type lll Collagen Biomarkers

N-terminal pro-collagen

Mature collagen

PRO-C3

Formation peptides

Degradation peptides
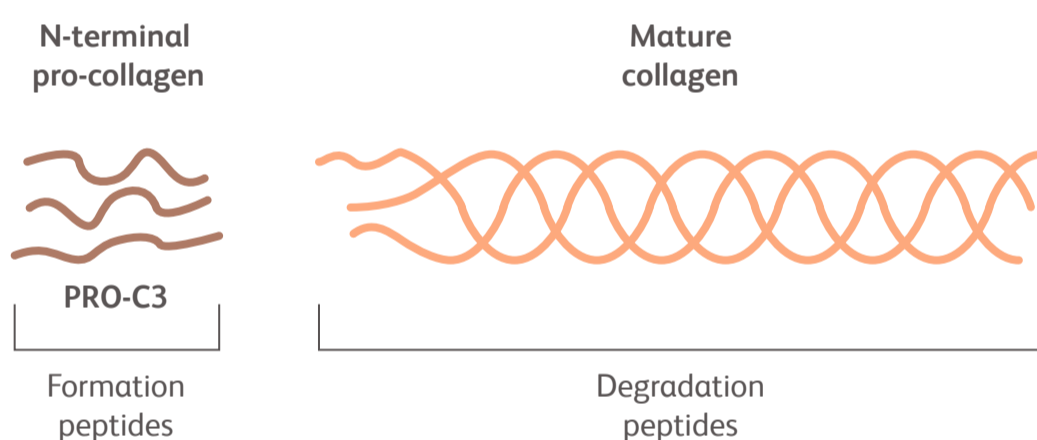
Collagen breaking down to pro-collagen at the N-terminus

Clinical Implications

The potential of PRO-C3 as a biomarker of fibrosis disease activity is being investigated to understand if it may:

• Identify patients more likely to benefit from and respond to treatment for liver fibrosis

• Reflect changes in fibrosis disease severity while undergoing treatment

PRO-C3 as a Biomarker

PRO-C3 is a biomarker that detects the formation of type lll collagen and can be measured with a blood test.

Other collagen biomarkers detect a specific type of collagen but do not distinguish between newly formed and older collagen. PRO-C3 detects the synthesis of type lll collagen which is anticipated to reflect the formation of new fibrotic tissue.

At present, there are no biomarkers for fibrosis available that can predict or determine a response to therapy. PRO-C3 has potential as both a prognostic marker for disease activity and outcome, and may also be able to identify patients with active disease.

PRO-C3 is one of many biomarkers under investigation at Bristol Myers Squibb and is being studied in collaboration with Nordic Bioscience who discovered this biomarker.

Learn more about our work in fibrosis by visiting:
www.bms.com/researchers-and-partners/areas-of-focus.html

1. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013 Nov; 10(11):686-690.
2. National Institute of Diabetes, Digestive and Kidney Diseases (Updated: May 2014)
https://www.niddk.nih.gov/health-information/health-topics/liver-disease/nonalcoholic-steatohepatitis/Pages/facts.aspx
3. Wong R et al. Gastroenterology 2015;148:547-555.
4. Frei A, Zimmermann A, Weigand K. The N-terminal propeptide of collagen type III in serum reflects activity and degree of fibrosis in patients with chronic liver disease. Hepatology. 1984;4:830–134