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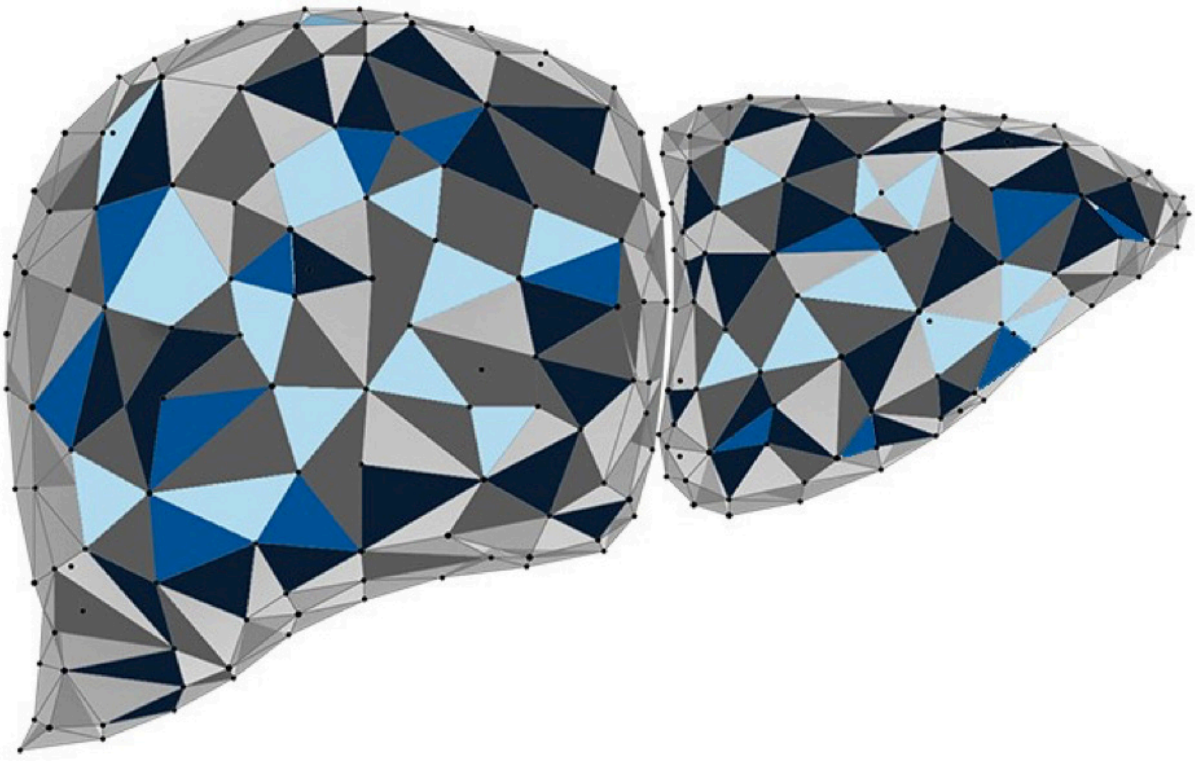


Biomarker Assays for MASH Clinical Trials

Cytokeratin 18 (CK18 and ccK18): Non-Invasive Biomarkers for Assessing Hepatocyte Apoptosis and Necrosis

Challenges in MASH Drug Development

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic, progressive condition caused by a build-up of fat in the liver in individuals with one or more metabolic risk factors. Metabolic dysfunction-associated steatohepatitis (MASH) is the more advanced form of the disease, in which the liver shows signs of inflammation and fibrosis (scarring) that may lead to cirrhosis and hepatocellular carcinoma. There are currently no approved therapies for the treatment of MASLD or MASH, and many clinical trials are underway to fulfill the need for pharmacological treatment options.

Currently required endpoints for regulatory approval are based on histopathological assessments of liver biopsies. However, the variability inherent to this methodology has proven to pose a major challenge to the success of MASH drug trials. Non-invasive tests (NITs) for biomarkers that correlate with liver histology - and that are ultimately predictive of outcomes - are used especially in early phase trials to measure the effects of drug candidates. These NITs enhance the go/no-go decision-making process for drug developers.

The Role of Cytokeratin 18 (CK18) in MASH

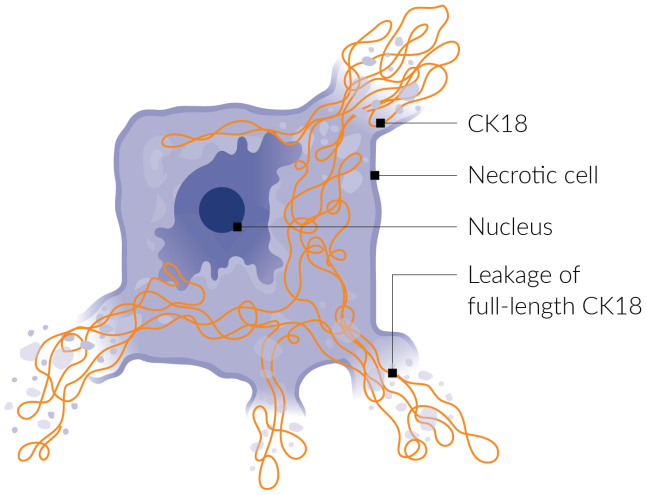
Cytokeratin 18 (CK18) is an intermediate filament protein that is abundantly expressed in hepatocytes. Hepatocyte death due to apoptosis is one of the hallmark features in the pathogenesis of MASH and it contributes to inflammation, fibrosis, and disease progression. In the early stages of apoptosis, caspases that cleave CK18 are activated. The resulting fragments, termed caspase-cleaved CK18 (ccK18), are released into the bloodstream. Measuring ccK18 in serum or plasma can therefore serve as a direct and sensitive indicator of ongoing hepatocellular injury, which positions ccK18 as an ideal biomarker for measuring disease activity and tracking therapeutic response in MASH drug trials.

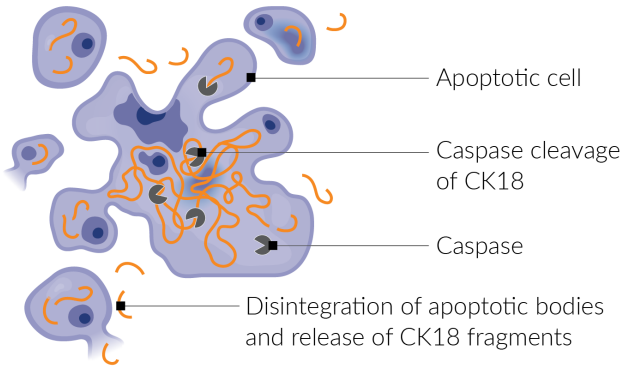
ccK18 as a Biomarker in MASH Clinical Trials

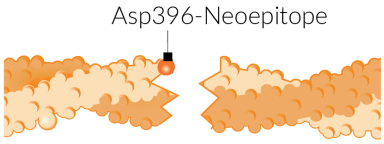
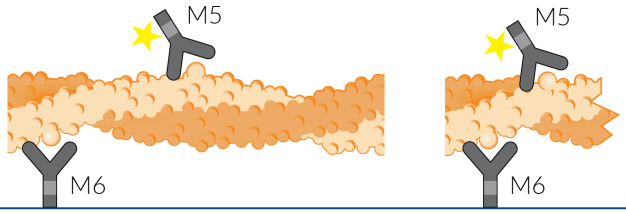
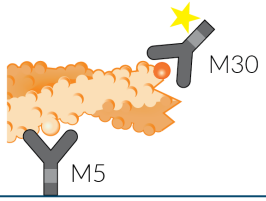
Hepatocyte apoptosis plays a central role in MASH pathogenesis since it is a downstream effector of many of the pathways that are thought to contribute to disease progression. Changes in ccK18 levels may thus serve as an indicator of the effective manipulation of these signaling pathways by potential MASH drug candidates with a diverse range of mechanisms-of-action. Serum levels of ccK18 have been shown to correlate with liver histology, specifically with the composite NAFLD Activity Score (NAS) and fibrosis stage. Furthermore, decreases in ccK18 have been associated with histological improvements in MASH trials, with greater reductions seen in histological responders vs. non-responders.

CK18 Assays: M30 Apoptosense® ELISA and M65® ELISA

The M30 Apoptosense® ELISA and M65® ELISA are robust, reliable, and easily accessible tools to measure the concentration of CK18 and ccK18 in serum and plasma samples for MASH research studies. The M30 Apoptosense® ELISA specifically detects ccK18, indicative of apoptosis, while the M65® ELISA detects both intact CK18 and ccK18, indicative of total cell death (apoptosis and necrosis).





Intact CK18	Only Caspase-Cleaved CK18 (ccK18)
	
M65® ELISA	**M30 Apoptosense® ELISA**
	
Measurement of intact and cleaved CK18	Measurement of cleaved CK18 (ccK18) only
The M65® ELISAs measure total cell death (necrosis and apoptosis)	**The M30® ELISAs measure only apoptosis**

Why Include M30 Apoptosense® ELISA and M65® ELISA in MASH Clinical Trials

- Non-invasive biomarker: ccK18 can be measured in serum and plasma samples using standard ELISA methodology.
- Mechanistic biomarker: Hepatocyte apoptosis is a key mechanism involved in the progression of MASLD.
- Disease activity biomarker: Apoptosis is an indicator of active disease.
- Drug mechanism-of-action (MAO) agonistic biomarker: Many pathways involved in MASLD/MASH pathogenesis that are targeted by emerging therapeutics culminate in hepatocyte apoptosis.
- Reflective and predictive of liver histology:
  - ccK18 levels correlate with ballooning NAS grade and fibrosis stage.
  - Changes in ccK18 correlate with changes in liver histology.
- Early indicator of treatment efficacy: Changes in ccK18 can be observed within weeks - before there are significant changes in histology.
- Early decreases in ccK18 are associated with subsequent histological improvements.
- More specific for liver injury than ALT & AST: ccK18 data can confirm results of conventional biomarkers.
- Elevated baseline ccK18 may help identify individuals with more active disease who may have a more robust response to therapeutic intervention.
- Collecting data on both CK18-M65® and CK18-M30® could ascertain whether hepatocyte death pathways are still being activated despite (or because) of treatment.

PEVIVA® Product Line		
ELISA Products	Use	Prod. No.
M30 Apoptosense® ELISA	RUO	P10011
M30 CytoDeath™ ELISA	RUO	P10900
M65® ELISA	RUO	P10020
M65 EpiDeath® ELISA	RUO	P10040
M65 EpiRat™ ELISA	RUO	P10060

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