TARGETING THE COMPLEXITIES OF NASH

Complete Solutions for NASH Research
The Silent Disease

It’s called nonalcoholic fatty liver disease (NAFLD): It affects nearly one quarter of the population. It displays few signals or symptoms. And by the time it progresses to the more advanced stage of nonalcoholic steatohepatitis (NASH), it can be too late to reverse. It’s the silent disease.

NAFLD is characterized by fat accumulation in the liver that’s not caused by alcohol. When it progresses to the NASH stage, with inflammation and damage to liver cells, it can cause fibrosis, cirrhosis, and liver failure or cancer. A liver transplant may be necessary.

NAFLD and NASH rarely cause symptoms, and though the exact cause remains unknown, risk factors include obesity, insulin resistance, high levels of LDL cholesterol, and type 2 diabetes.

There are currently no approved treatments for NAFLD or NASH, and diagnosis remains challenging. But studies show that fat and scar tissue can leave the liver, suggesting that NAFLD and NASH are reversible.
NASH Development and Progression

NAFL
(Non-Alcoholic Fatty Liver)
or SS (Simple Steatosis)
Fat accumulation

NASH
(Non-Alcoholic SteatoHepatitis)
Fat accumulation + inflammation and ballooning

Fibrosis
Excessive deposition of extracellular matrix (ECM)

Free fatty acid from high fat diet

Steatosis
Lipid Droplets

Inflammation and cellular death

Hepatocyte Damage

Breached Gut Epithelium

Pro-inflammatory and Fibrogenetic Mediators

Damage-associated Molecular Patterns (DAMPs)

Gut-Derived Bacterial Products (PAMPs)

Activated Kupffer Cells

Activation and Trans-differentiation

Quiescent HSCs → Activated HSCs → Myofibroblasts → Unbalanced ECM elaboration

Excessive Deposition of ECM
NASH AROUND THE WORLD: 6 KEY FACTS

RISK FACTORS FOR NAFLD include obesity, insulin resistance, high levels of LDL cholesterol, and type 2 diabetes.

Over 90% of obese, 60% of diabetic, and up to 20% of average-weight people are affected by NAFLD.

Instances of NASH range from 3% to 5% worldwide.

NAFLD is the most prevalent liver disorder, affecting 25% of the global population.

In the US, NAFLD- and NASH-related health expenditure is over $103 billion.

NAFLD is the leading cause of chronic liver disease and the second most common reason for liver transplantation in the US and Europe.

References:
Studying NAFDL/NASH, *In Vitro* and *In Vivo*

One of the main obstacles to developing effective NASH treatments is the lack of preclinical disease models that address the causes of NAFLD and NASH, including validated *in vivo* and *in vitro* models that enable further understanding of NASH pathophysiology, help identify new therapeutic targets, and characterize novel drug therapies.

*In vitro* models are used to study molecular pathways, for target identification, and for compound screening, and should be compatible with high-throughput techniques.

*In vivo* models are employed to study efficacy, pharmacokinetics, and pharmaco-metabolism. There are several *in vivo* models available, generated either by genetic manipulation or by nutritional induction. They often mimic only one aspect of the disease, so comprehensive, translatable models are needed.

All disease models must be validated, and we have the right solutions to help:

- **High-Content Screening**
  - Monitor morphological changes and identify steatotic phenotypes
- **Genomics**
  - Ensure quality and characterization of RNA-sequencing libraries
- **Radiation/Detection/In Vivo Imaging**
  - Study pharmacokinetics and biodistribution
- **In Vivo Imaging**
  - Study adipose tissue accumulation
- **Detection/High-Content Screening**
  - Check viability of cellular models
  - Study functional characteristics of disease models

Read about developing a phenotypic *in vitro* model for progression of liver steatosis.

Read about how the Murine NASH Model could provide insights into NASH development and progression.
There are currently no FDA-approved drugs to treat NAFLD/NASH, and the complex pathophysiology of the disease isn’t completely understood. The increasing global prevalence of the diseases highlights the urgent need for effective detection – and targeted treatments.

Improved understanding of inflammation and fibrogenesis in the liver has prompted advances in antifibrotic and anti-inflammatory therapies. And therapies that combine compounds that target various fibrosis pathways will have a major impact on future therapeutic interventions.
Diagnosis Begins with the Right Biomarker

Most NASH cases stay undetected and untreated until irreversible damage is already present. It’s usually uncovered through blood tests and confirmed by imaging, including ultrasound, CT, and MRI, or through histopathological evaluation, which is considered the gold standard for NASH diagnosis.

So there’s an urgent need for sensitive, cost-effective, noninvasive diagnostic biomarkers for staging NAFLD, identifying those at risk for developing it, and for following disease progression in vivo.

Though there are biomarkers to predict late-stage fibrosis, such as alanine transaminase (ALT) and aspartate transaminase (AST), early biomarkers are still lacking. Propeptides (small fragments of collagen) have become a focus in biomarker research because they’re produced during liver scarring and reflect the dynamics of hepatic fibrogenesis.

We help streamline and accelerate research by providing the right tools for:

- Analysis of adipose tissue accumulation and distribution as well as visualization and quantification of liver fibrosis over time using microCT
- Use of biomarker-specific fluorescent agents
- Biomarker detection using Alpha, HTRF, and LANCE® Ultra assay technologies, including AST, Alpha-SMA, procollagen, P3NP, and hyaluronic acid kits

Read the application note: “Three Step Diagnosis Holds Out Hope”

Read the application note: “Biomarker and Cell Signaling Assays”

Get the guide: “A Comprehensive Overview of Fibrosis Development”
NASH is characterized by three attributes present in the liver: steatosis, inflammation, and hepatocellular damage (ballooning). In a recent in vivo imaging study, researchers demonstrated a novel, noninvasive three-step approach for diagnosing NASH in mice using preclinical optical and microCT imaging. Optical imaging using Lucigenin (a chemiluminescent probe) and IVISense™ Annexin-V (a fluorescent probe) identified liver inflammation and apoptosis, respectively. MicroCT was used to quantify liver steatosis.

Read the full application note ➤
WHAT RESEARCHERS THINK

Prof. Jian Wu
Fudan University Shanghai Medical College

To address the lack of NASH preclinical models, Prof. Jian Wu of Fudan University Shanghai Medical College in China and colleagues have established a murine NASH model that presents with significant steatohepatitis, inflammation, insulin resistance, and fibrotic progression in a scalable fashion. “It is challenging to estimate the efficacy of pharmacotherapeutic candidates in a preclinical setting when no standardized murine NASH model is available,” says Prof. Wu. He anticipates that a novel treatment for NASH will be available relatively soon. “A combination of therapeutics may be needed to address multiple hits better than a single drug candidate,” he says.

Read the full interview

Prof. Yi Zang
Shanghai Institute of Materia Medica, Chinese Academy of Sciences

To identify novel small molecules, natural compounds, or TCM products, Prof. Zang Yi of the Chinese Academy of Sciences is using robust, high-quality enzyme activity-based assays and phenotype-based cellular functional assays modified for HTS and HCS. “The major gap for NASH/NAFLD research is the lack of detailed mechanisms available for understanding the multiple cells and tissues involved in this complex disease,” says Prof. Zang. Her institute is also collaborating with basic researchers who focus on liver physiology and pathology to establish 3D organoids that better mimic NASH in vivo to optimize for drug screening.
Smarter Questions, Better Answers

With all the advances in therapeutics discovery and development, we’re generating vast amounts of data. Making sense of it all is perhaps the challenge of our time. So our informatics solutions are designed to speed identification of vaccine or therapeutic candidates; help you import, align, and analyze biological sequences; and manage experimental, instrument, and outsourced pharmacology data.

**ELECTRONIC LAB NOTEBOOKS**
We offer ELNs to meet the needs of scientists and researchers, helping you organize and share experimental data efficiently and communicate seamlessly with the common instruments and devices you use. [READ MORE]

**LEAD DISCOVERY**
Our lead-discovery solutions provide a faster way to help you gain insights through a guided search and analysis workflow that queries and represents data in intuitive, intelligent ways. [READ MORE]

**DATA VISUALIZATION**
Our data visualization platform can empower your team or your entire organization to easily mine scientific and business data and gain insights, in real time. You can create simple dashboard metrics, predictive applications, or dynamic real-time analytics applications with capabilities such as visual, predictive, location, and streaming analytics; data wrangling; and much more. [READ MORE]

**CLINICAL ANALYTICS**
Our solutions streamline clinical trials with real-time access to data during all phases of clinical development, allowing you to interact with information as soon as it’s collected. You’re better able to explore key aspects of the protocol for specified follow-up, ensure adherence by identifying drop-outs and violations, facilitate data cleaning and data quality, and much more. [READ MORE]
GENOMICS: Automation Improves Workflow Efficiency

When studying variations in gene expression levels or mutations to better understand risk factors, our genomics solutions support you – from DNA/RNA extraction to automated library QC.

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DETECTION: Innovative Solutions That Accelerate Your Workflow

Whether you’re doing basic research, drug discovery screening, PK/PD, or safety and efficacy studies, our detection solutions help you accelerate your research.
CELLULAR IMAGING: Deeper Insights into Cell Phenotypes

To better understand cellular processes or investigate how drugs affect those processes, our cell-based assays are proven and powerful tools, delivering better insights into disease mechanisms.

IN VIVO IMAGING: The Power of Small-Animal Models

Whether you’re visualizing and quantifying the effects of metabolic diseases such as NASH or performing drug efficacy and toxicology studies, our small-animal imaging solutions can help with your next discovery.
Complete Solutions for NASH Research

Expert Services Wherever You Need Them

Most labs don’t maintain the in-house expertise needed to plan and implement the types of projects that can transform chaotic lab operations into the sleek, efficient, effective lab of the future. After all, you should be concentrating on your core competency – your science – and leaving the infrastructure, operations, and even lab management to the professionals. That’s why so many smart labs are looking to outsourcing to help them plan, design, deploy, and manage their lab environments.

COMPUTER SYSTEM VALIDATION (CSV)

CSV services range from full validation or commissioning for new systems to change-control validation for existing standalone and enterprise systems. Our team follows GAMP 5 templates and aligns with your site’s policies and procedures as they relate to the software development lifecycle. At the same time, we provide a range of software IQ/OQ offerings, including enhanced-security instrument software products. READ MORE

DATA INTEGRITY

Many regulatory agencies have determined that electronic data is more secure than paper documentation and less likely to be manipulated over the phases of a product’s development lifecycle. But that doesn’t mean electronic lab data is perfect: It must comply with other stringent regulations, including 21 CFR Part 11 and the EDQM Annex 11. READ MORE

INSTRUMENT QUALIFICATION

Our OneSource Instrument Qualification methods maximize your lab productivity while providing ongoing compliance capabilities. We guide your lab through automated, secure electronic or traditional paper qualification procedures with standard recommended OQ protocols customized to your specifications. READ MORE

GMP RADIOSYNTHESIS

Our experienced chemists work with you to design and prepare your radiochemical to your exacting specifications. You have access to our extensive technical support resources to help with protocol creation, custom synthesis of radioactive products, stability testing, special packaging, and analytical services. READ MORE

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