Diseases to Watch

Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic steatohepatitis (NASH)

- Prevalence and Symptoms
- Risk Factors and Potential treatments
- Target identification for NASH

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Featured Speakers

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What is Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)?

- Fat (triglyceride) accumulation in the liver in >5% of hepatocytes, in the absence of excessive alcohol consumption
- Inflammation, oxidative damage, scar tissue and eventually fibrosis
- Progressive disease
  - Can lead to cirrhosis, fibrosis and liver cancer
- Reversible until Cirrhosis

Sources: [www.arthritis-rheumatism.com](http://www.arthritis-rheumatism.com) and Integrity Disease Briefings
What is the prevalence of NAFLD and NASH?

- Until recently considered to be relatively rare and harmless
- Growing global obesity epidemic
- NAFLD is the most prevalent chronic liver disease
- Projected to be the leading indication for liver transplant within the decade
- 2017 Prevalence
  - NAFLD – 24% North America, 25% Europe, 27% Asia, 30% South America
  - NASH – 7.5% USA, 5% UK, 5% Japan, 4% Worldwide

Sources: Clarivate IPD (Disease Forecasts) and Integrity Disease Briefings
What are the symptoms and risk factors for NAFLD and NASH?

**Symptoms:**
- Usually asymptomatic
- Abdominal discomfort
- Tiredness
- NASH:
  - jaundice
  - abdominal swelling
  - bleeding
  - fluid retention

**Diagnosis:**
- Liver function tests
- Liver enzyme tests
- Ultrasound or MRI
- Biopsy

**Risk Factors:**
- Obesity and old age
- Predisposing conditions - diabetes, hypertension and hyperlipidemia
- Ethnicity – e.g. Asian and Hispanic populations
- Lifestyle – high fat diets, smoking and inactivity
- Genetic factors – genetic polymorphisms
- Alterations in gut microbiome composition
What are the potential treatments for NAFLD and NASH?

- First line: Intense lifestyle modifications

- Second line: Medical and surgical treatments BUT No approved drug for NASH
- Drugs being investigated for NAFLD and NASH

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Representative</th>
<th>Mode of action</th>
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<tbody>
<tr>
<td>Anti-diabetics</td>
<td>Metformin, Pioglitazone</td>
<td>Improve insulin sensitivity</td>
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<tr>
<td>GLP1 analogues</td>
<td>Exenatide, Liraglutide</td>
<td>Suppress appetite, increase weight loss and increase insulin production</td>
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<tr>
<td>DPP4 inhibitors</td>
<td>Sitagliptin, Linagliptin</td>
<td>Enhances insulin production</td>
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<tr>
<td>Anti-oxidants</td>
<td>Vitamin E</td>
<td>Reduce oxidative stress</td>
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<td>Statins</td>
<td>Atorvastatin</td>
<td>Lowers plasma lipids</td>
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<td>Lipase inhibitors</td>
<td>Orlistat</td>
<td>Decrease fat absorption from intestine</td>
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<tr>
<td>Farnesoid XR agonist</td>
<td>Obeticholic acid</td>
<td>Reduce steatosis and inflammation</td>
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<tr>
<td>PPAR-α/γ agonist</td>
<td>Elafibranor</td>
<td>Reduce steatosis, inflammation and fibrosis</td>
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How to discover novel druggable targets for NASH and NAFLD?

**Problem:**
- Complex genetic factors and Multi-factorial disease
- Lack of validated clinical trial endpoints
- Scattered information
- Difficulty in prioritizing druggable targets

**Solution:**
- Database of curated scientific data which rank targets based on evidence to support target/disease association
  - Identify novel targets in causative areas (metabolic, inflammation, fibrosis)
  - Consider a combination approach

**Target Druggability**
- Allows users to effectively visualize and analyze target/disease information
- Enhanced target information – Integrity and Metacore
- Simple, easy to use interface
- Customized Exploration views – group by target family, highest phase or genetic evidence
- Protein Atlas tissue expression information
- Animal models, References, Patents and Biomarker information

**LIVE Demo** - Drug Research Advisor (DRA)
Novel targets for NASH

A search of *Drug Research Advisor* for NASH retrieves 209 Targets (109 enzymes + receptors).
If these 109 enzymes + receptors are prioritized by “Complete novelty,” **Patatin-like phospholipase domain-containing protein 3 (PNPLA3)** is ranked 3rd.

**Narrowing the search for a novel target for NASH**
Patatin-like phospholipase domain-containing protein 3, also known as adiponutrin, is a membrane protein with triacylglycerol lipase activity that mediates triacylglycerol hydrolysis in adipocytes. It may be involved in the balance of energy usage/storage in adipocytes.
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

Tissue expression of Patatin-like phospholipase domain-containing protein 3 can be viewed from the Link to The Human Protein Atlas.
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH
Genetic evidence for Patatin-like phospholipase domain-containing protein 3 as a target in NASH can be viewed from the 55 literature, conference and patent citations which have identified specific genetic polymorphisms in the protein that are associated with a greater risk of NASH.
Genetic evidence for Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

Examination of references suggests that Genetic evidence for Patatin-like phospholipase domain-containing protein 3 could be a valid target for the treatment of NASH.
Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

Experimental Pharmacology

Examination of Experimental Pharmacology data associated with Patatin-like phospholipase domain-containing protein 3 and NASH suggests that Patatin-like phospholipase domain-containing protein 3 could be a valid target for the treatment of NASH.
Examination of Biomarkers suggests that *Patatin-like phospholipase domain-containing protein 3* is used as a biomarker for diagnosis of NASH and hence could be a valid target for the treatment of NASH and its complications.