Allagium Therapeutics

Driving change to better health

Progress is impossible without change, and those who cannot change their minds, cannot change anything.
- George Bernard Shaw
Inhibition of protein tyrosine phosphatases: A novel approach to fatty liver disease

Anton Bennett, PhD
Yale University, Dorys McConnell Duberg Professor of Pharmacology & Professor of Comparative Medicine; Co-Director, Program in Integrative Cell Signaling and Neurobiology of Metabolism; Winner Burroughs-Wellcome Award for New Investigators in Pharmacology (2001); Winner Pharmaceuticals Manufacturers Association Young Investigators Award (2000)

David Kolb, MBA
Raphael Capital Partners, Managing Director; Yale University, Entrepreneur In Residence
Over 25 years of experience. Founder & CEO of four life science companies including 2 clinical stage; Completed over 100 transactions valued at over $2.5 billion. Published papers in peer-reviewed journals (oncology); inventor on issued and pending patents (oncology and neurology).

David Lewin, PhD
Yale University; Director of Business Development, Office of Cooperative Research
Over nine years of licensing and marketing experience in life sciences and has spent over 15 years successfully managing scientific-based business alliances with pharmaceutical leaders in the U.S., Europe and Japan. Has been instrumental in establishing new ventures at OCR, including Kolltan Pharmaceuticals, NovaTract, Eli Nutrition, BioHaven Pharmaceuticals and Kleo Pharmaceuticals.
There is space in NASH market – single and multi-modal therapeutics

Space for combinatorial therapies:
- Metabolic (anti-fat)
- Anti-inflammatory
- Anti-fibrotic

Healthy liver  →  Simple fatty liver  →  Fatty liver with inflammation/scarring  →  Liver cirrhosis  →  Hepatocellular carcinoma
Proprietary solutions to address fatty liver disease and NASH

Over 80 million people have fatty liver disease (NAFLD)\textsuperscript{1}
20% have liver damage, inflammation and/or fibrosis (NASH)\textsuperscript{1}
No approved therapeutic currently for NAFLD or NASH


Significant big pharma interest in the space

Significant investor interest with over $800M in NASH related IPOs over the past 18 months and nearly $17B in public equity market capitalizations
## PPAR / PPAR-related mechanisms against NASH dominate market

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Companies</th>
<th>Completed Clinical Stage</th>
<th>Published Data</th>
<th>PPAR-α agonist</th>
<th>PPAR-γ agonist</th>
<th>PPAR-δ agonist</th>
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<tbody>
<tr>
<td>Direct PPAR Mechanisms</td>
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<tr>
<td>PPAR agonists</td>
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<td>26%**</td>
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<td></td>
<td>Genfit</td>
<td>Phase 3</td>
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<td>✓</td>
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<td>CymaBay</td>
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<tr>
<td></td>
<td>Zydus</td>
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<td>Indirect PPAR Mechanisms</td>
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<td>THRβ agonists</td>
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<td>18%**</td>
<td></td>
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<tr>
<td>FXR agonists</td>
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<td>Phase 3</td>
<td>4%</td>
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<td>Gilead</td>
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<td>4%</td>
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<tr>
<td></td>
<td>Akero</td>
<td>Phase 2</td>
<td>N/A</td>
<td>✓</td>
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1) % over placebo for NASH resolution without worsening of fibrosis.
N/A indicates either alternative endpoint not commonly recognized or that data is unavailable.
** indicates statistical significance was met. This list is not meant to be all-inclusive.
Mitogen-activated Protein Kinase Phosphatase-1 (MKP-1) is a novel target against fatty liver disease and NASH.

MAPK Phosphatases (MKPs) **INACTIVATE** the MAPKs by direct dephosphorylation.

MAPK Phosphatases (MKPs) represent critical **nodal** regulators of MAPK signaling that liberate specific cellular outputs.
MKP-1-deficiency protects from hepatosteatosis in distinct models of liver disease

- Hepatic MKP-1 is overexpressed in obesity.
- Genetic deletion of MKP-1 protects against the development of hepatosteatosis.
Hepatic MKP-1 deficiency protects from the development of NASH

**NASH Model**: Mice subjected to choline-deficient and Iron Supplemented Amino Acid defined diet (CDAA) for 22 weeks.

*Mkp-1^fl/fl*: "floxed" *m kp-1* mice

MKP1-LKO; Liver-specific MKP-1-deficient mice.

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Yale School of Medicine
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*Mkp-1*/*floxed*; "floxed" *mkp-1* mice
MKP1-LKO; Liver-specific MKP-1-deficient mice.
MKP-1 multi-modal antagonism intersects with PPAR pathways targeting NASH.

Lawan and Bennett, Trends in Endocrinology & Metabolism, December 2017, Vol. 28, No. 12

PPAR engagement: MKP-1 inhibition attenuates lipogenesis and promotes fatty acid oxidation

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Yale SCHOOL OF MEDICINE
MKP-1 is “druggable” – Proof-of-principle established by novel allosteric inhibition of MKP-5 family member

- Recent work out of our lab using a high-throughput screen focusing on allosteric modulation has led to the discovery of inhibitors for a related family member, MKP-5\(^1\)

- Binding allosteric site inhibits via conformational change in the active site

Use of proceeds and milestones

$200,000

- Production of protein (MKP-1 & active site binding peptide); acquire other materials necessary for project

$100,000

- Initial screen (activity); retest actives & check against promiscuity; assay for selectivity vs. other family members

- Synthesis development and production of lead molecules; determine mechanism; MKP-1 crystals grown w/lead & solved; residue analysis

- Cell-based assays to confirm modulation of downstream targets

- In vivo study (rodents) to confirm cell-based evidence and to prepare for pre-IND meeting with FDA
Inhibition of MKP-1 – Is there a path to drugability?

- Protein tyrosine phosphatases/MKPs have been considered “undruggable”.
- Poor specificity, hard to progress chemically, intractable drug-like properties.
- Allosteric targeting of MKP-1 circumvents barrier of poor development path presented by active-site inhibitors.
- Allosteric targeting of MKP-1 provides opportunity to achieve specificity.
Project Assets and Goals

- **ASSET**: Established novel screening platform to identify allosteric MKP inhibitors.

- **ASSET**: Library of high value MKP allosteric inhibitors as a platform to develop focused MKP-1 small molecule scaffolds and high potency compounds.

- **ASSET**: Deep knowledge of MKP-1 biology (~25 years) and screening.

- **ASSET**: Proven development model demonstrated for MKP-5 (partnered).

- **GOAL**: Establish IP protection for MKP-1 composition of matter specific to NASH.
Differentiation by moving upstream of PPAR’s

• **MKP-1 INHIBITION DRIVES INCREASED MAP KINASE ACTIVITY WHICH PREVENTS FATTY LIVER AND DRIVES A LEAN BODY PHENOTYPE BY:**
  - Increasing fatty acid oxidation via increases in CPT (PPAR-\(\alpha\))
  - Lowering body fat mass by increasing energy consumption (PPAR-\(\alpha\))
  - Increasing lipid turnover (PPAR-\(\alpha\))
  - Lowering the production of lipid droplet forming genes (PPAR-\(\gamma\))

• **MKP-1 INHIBITION APPROACH UNIQUELY ADDRESSES LIPID STORAGE**
  - PPAR-\(\gamma\) agonists actually increase Cidec/Fsp27 and lipid storage
  - PPAR-\(\gamma\) levels are increased in fatty livers\(^1\)
  - MKP-1 levels are increased under conditions of high-fat feeding\(^2\)