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*

Allagium Therapeutics

Yale SCHOOL OF MEDICINE

Inhibition of protein tyrosine phosphatases: A novel approach to fatty liver disease

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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)

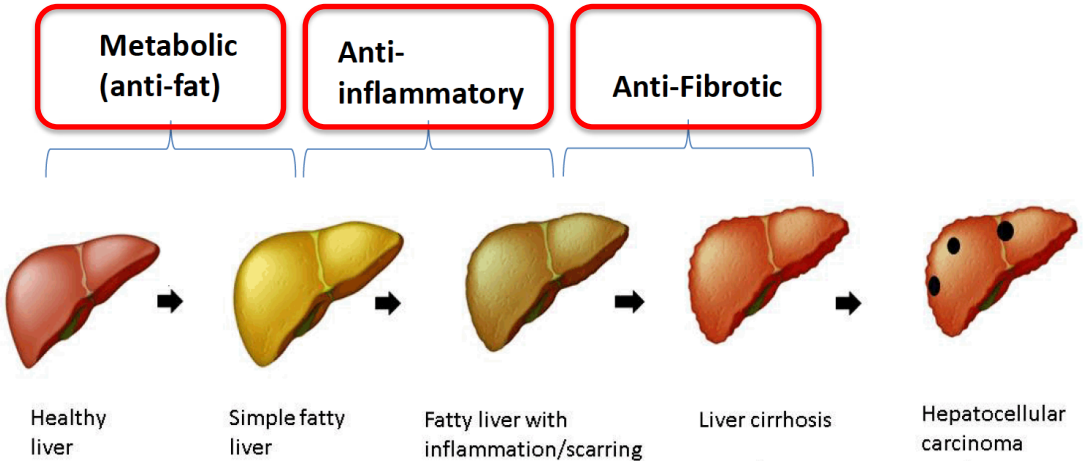
David Kolb, MBA
Raphael Capital Partners, Managing Director; **Yale University,** Entrepreneur In Residence
Over 25 years of experience. Founder & CEO of four life science companies including 2 clinical stage; Completed over 100 transactions valued at over $2.5 billion. Published papers in peer-reviewed 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



Proprietary solutions to address fatty liver disease and NASH

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

1) Nat Med 2018 Jul;24(7):908-922.

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

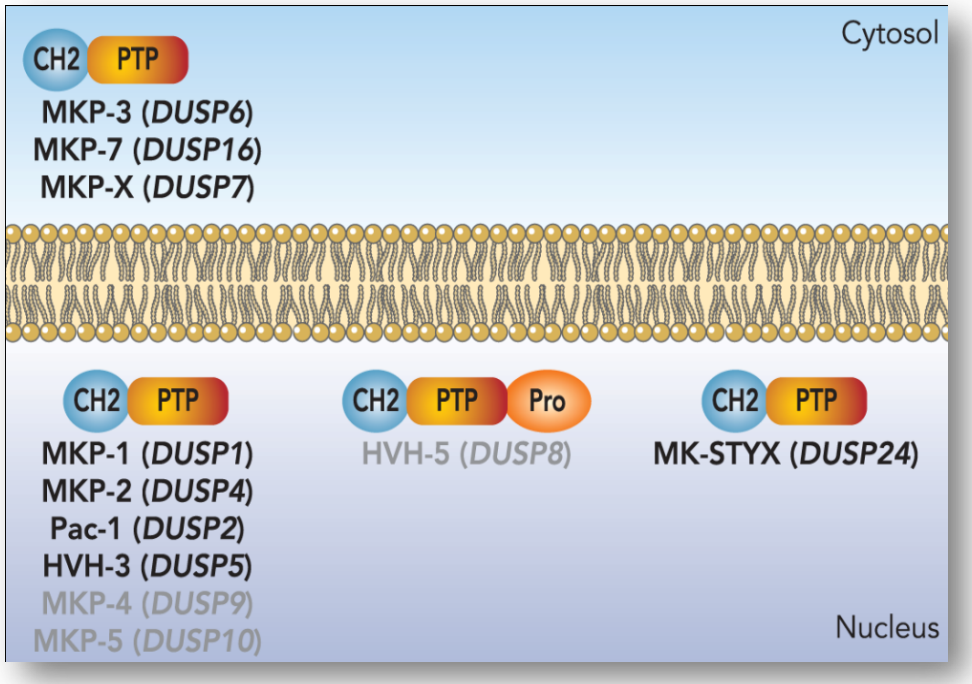
PPAR / PPAR-related mechanisms against NASH dominate market

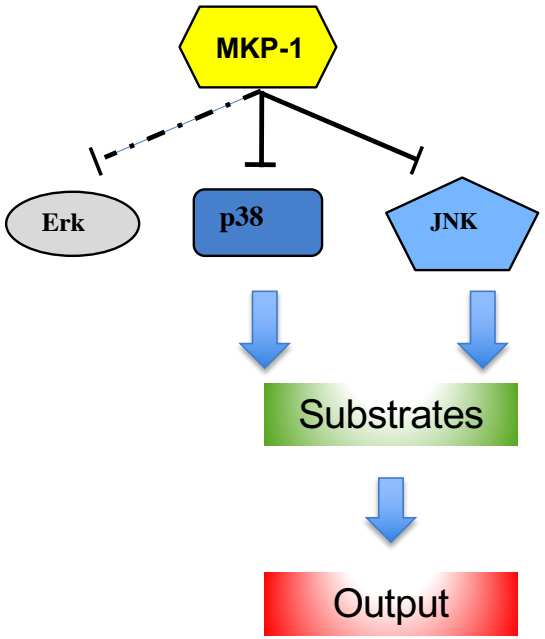
Mechanism of Action	Companies	Completed Clinical Stage	Published Data[1]		PPAR-α agonist	PPAR-ɣ agonist	PPAR-δ agonist
Direct PPAR Mechanisms							
PPAR agonists	Inventiva	Phase 2	26%**		✓	✓	✓
	Genfit	Phase 3	4%		✓		✓
	CymaBay	Phase 2	N/A				✓
	Zydus	Phase 2	N/A		✓	✓	
Indirect PPAR Mechanisms							
THRβ agonists	Madrigal	Phase 2	18%**			x	
FXR agonists	Intercept	Phase 3	4%			✓	
	Gilead	Phase 2	4%			✓	
	Enanta	Phase 2	N/A			✓	
FGF21 analogs	Bristol-Myers	Phase 2	N/A		✓		
	NGM	Phase 2	15%		✓		
	Akero	Phase 2	N/A		✓		

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.

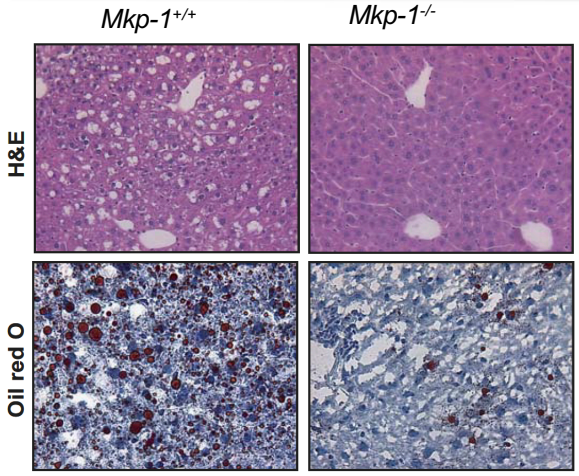




MAPK Phosphatases (MKPs) represent critical **nodal** regulators of MAPK signaling that liberate specific cellular outputs.

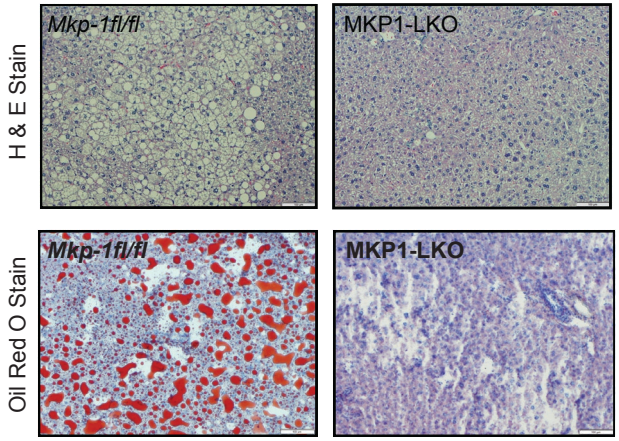
MKP-1-deficiency protects from hepatosteatosis in distinct models of liver disease

Whole body MKP-1-deficient mice on a high fat-diet.



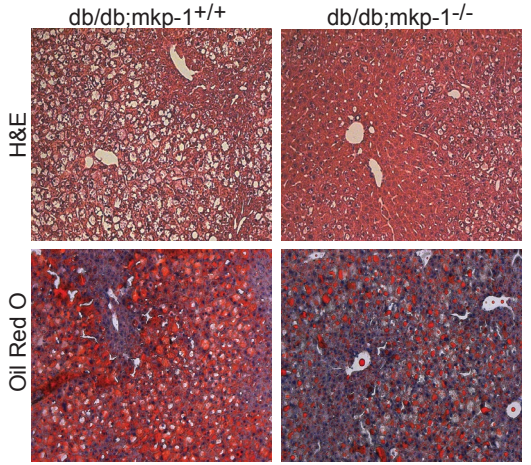
Wu *et al*, *Cell Metab.*, (2006), 35: 26-40.

Liver-specific MKP-1-deficient mice on a high fat-diet.

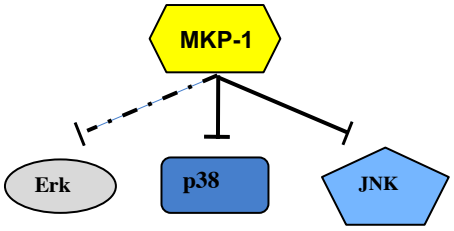


Lawan *et al*, *Mol Cell. Biol.*, (2015), 35: 26-40.

Genetically obese (*ob/ob*) mice lacking MKP-1.



Roth-Flach *et al*, *J. Biol. Chem.*, (2011), 35: 26-40.

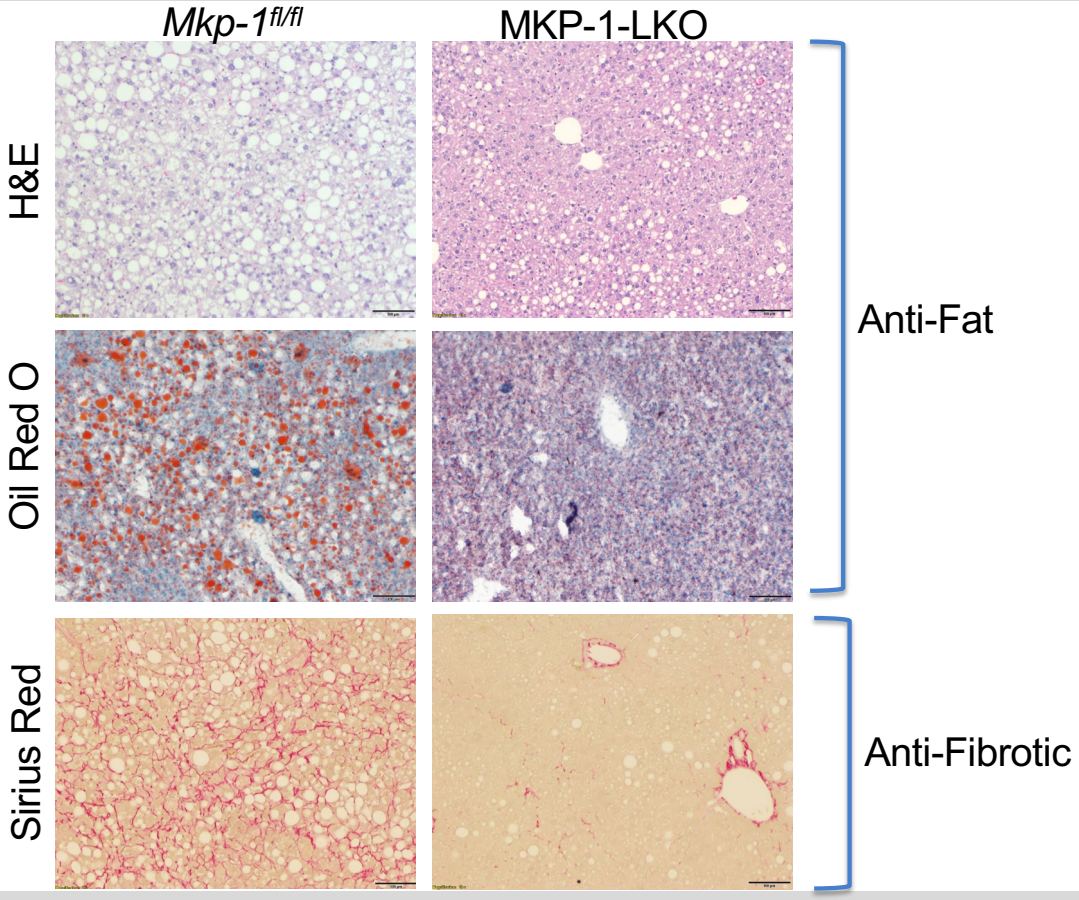


- Hepatic MKP-1 is overexpressed in obesity.
- Genetic deletion of MKP-1 protects against the development of hepatosteatosis.

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" *mkp-1 mice*
MKP1-LKO; Liver-specific MKP-1-deficient mice.



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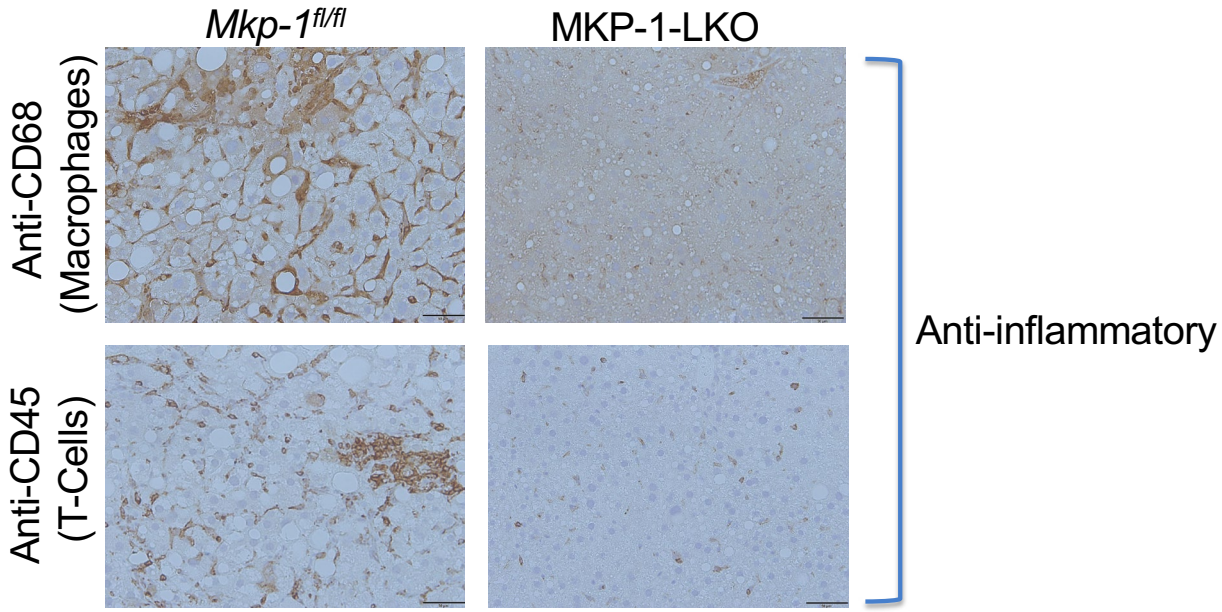
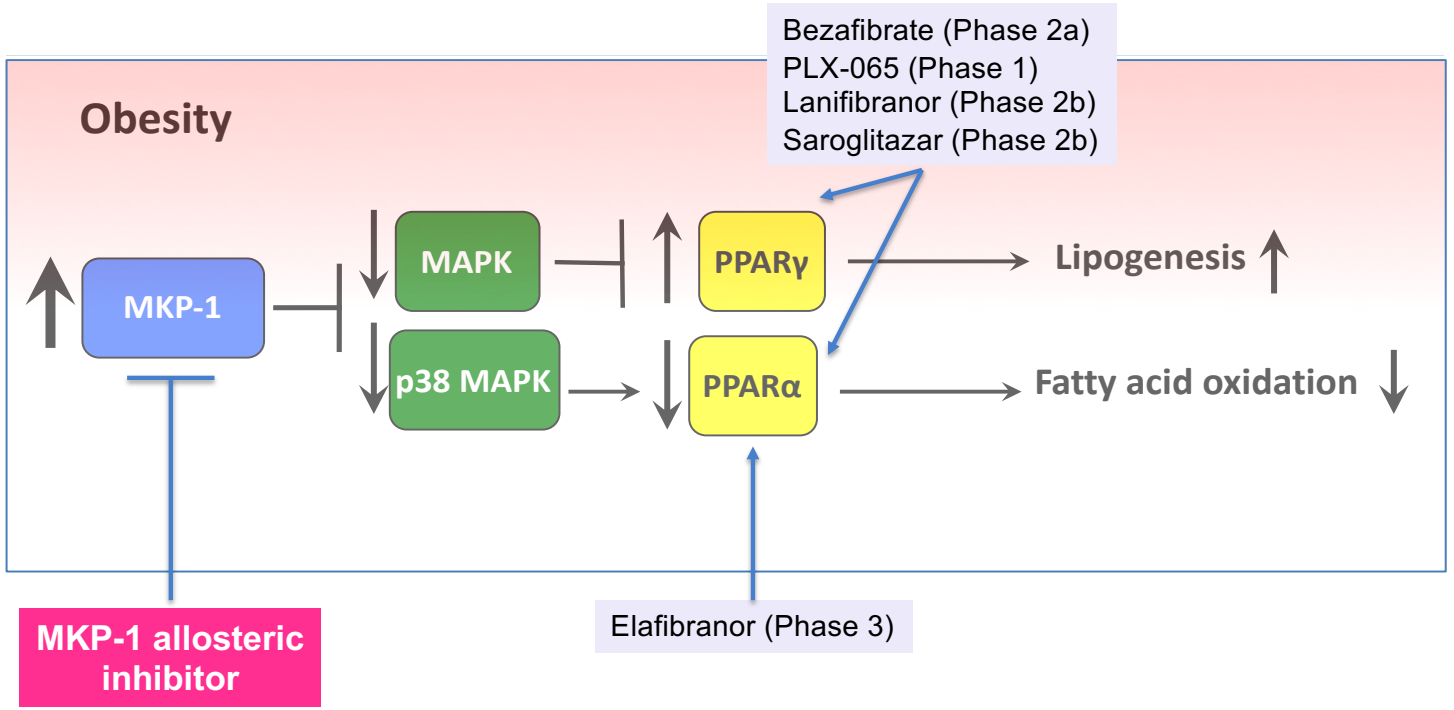


MKP-1 multi-modal antagonism intersects with PPAR pathways targeting NASH.

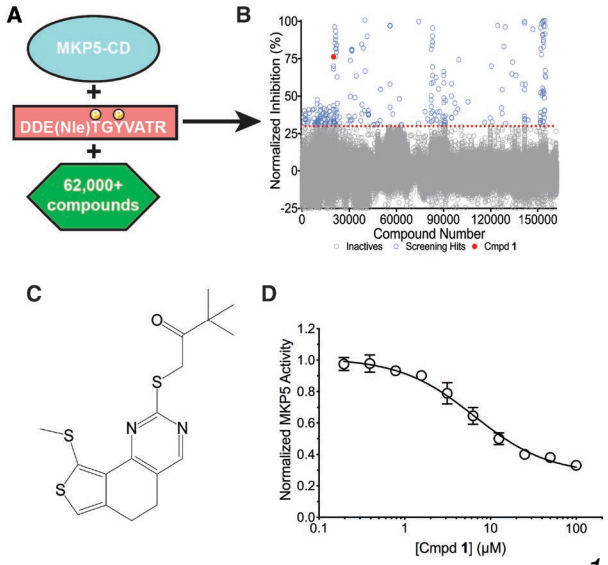


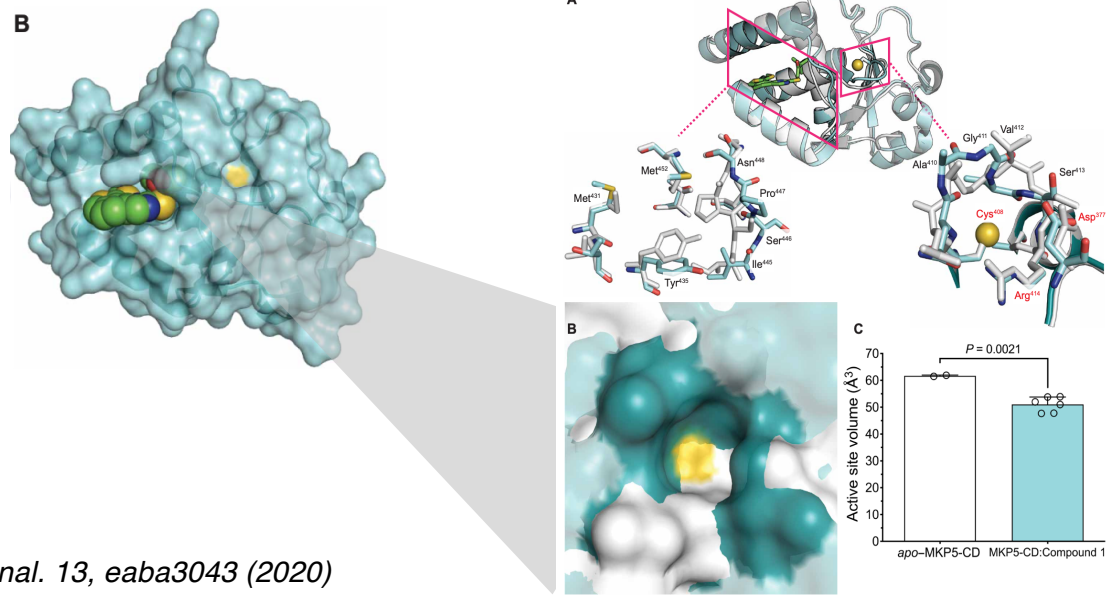
PPAR engagement: MKP-1 inhibition attenuates lipogenesis and promotes fatty acid oxidation

Lawan and Bennett, Trends in Endocrinology & Metabolism, December 2017, Vol. 28, No. 12
Lawan et al, *Mol. Cell Biol.*, 2015

MKP-1 is "druggable" – Proof-of-principle established by novel allosteric inhibition of MKP-5 family member

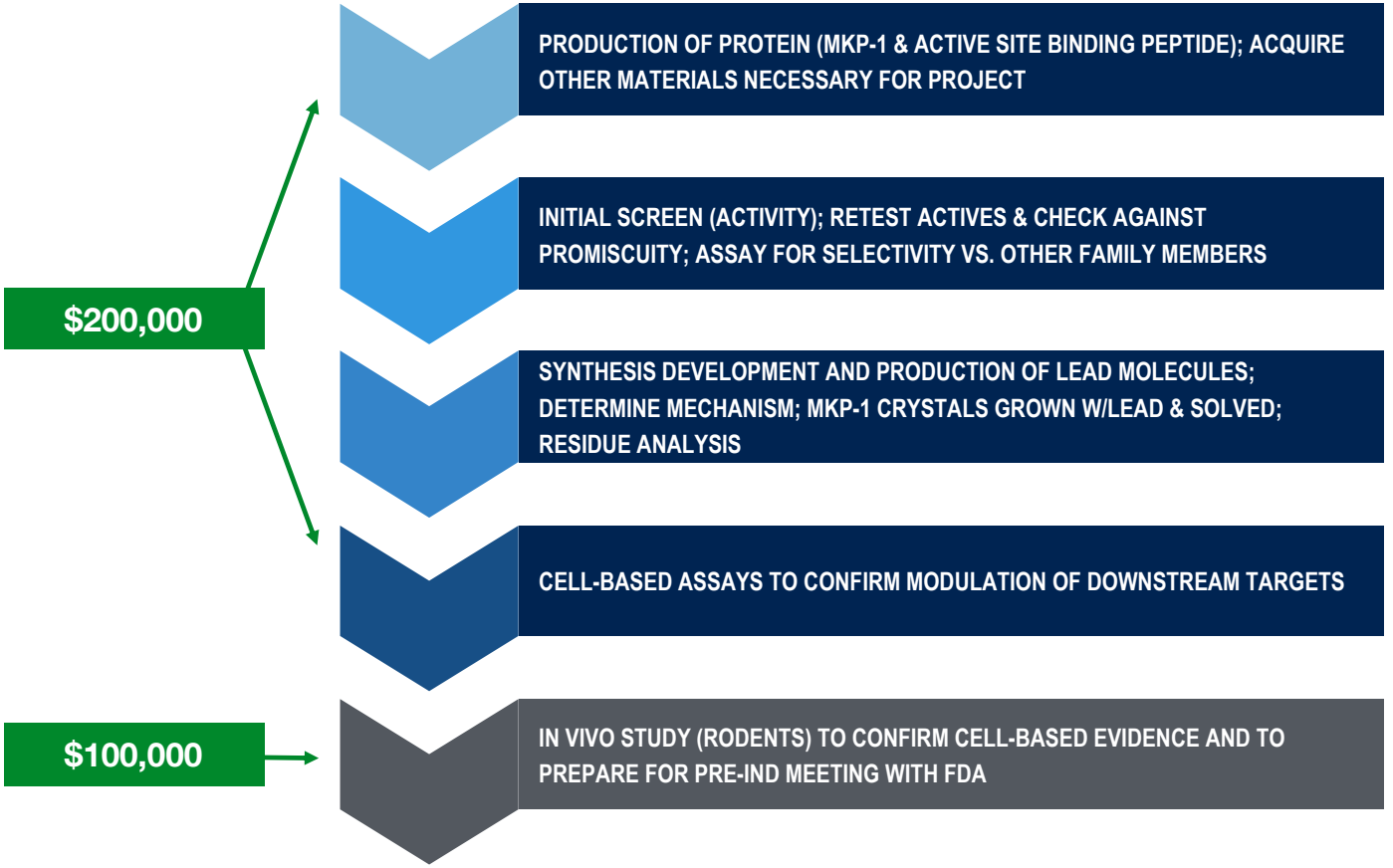
- Recent work out of our lab using a high-throughput screen focusing on allosteric modulation has led to the discovery of inhibitors for a related family member, MKP-5[1]
- Binding allosteric site inhibits via conformational change in the active site





1. Sci. Signal. 13, eaba3043 (2020)

Use of proceeds and milestones



SUPPLEMENTARY SLIDES

Inhibition of MKP-1 – Is there a path to drugabillity?

- 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-α)**
  - **Lowering body fat mass by increasing energy consumption (PPAR-α)**
  - **Increasing lipid turnover (PPAR-α)**
  - **Lowering the production of lipid droplet forming genes (PPAR-γ)**

- **MKP-1 INHIBITION APPROACH UNIQUELY ADDRESSES LIPID STORAGE**
  - **PPAR-γ agonists actually increase Cidec/Fsp27 and lipid storage**
  - **PPAR-γ levels are increased in fatty livers[1]**
  - **MKP-1 levels are increased under conditions of high-fat feeding[2]**

1) *J. Clin. Invest. 111, 737–747*
2) *Arterioscler. Thromb. Vasc. Biol. 24, 1676 –1681*