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

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- Allagium Therapeutics is a **platform-based** company focused on mining the allosteric space of MAP kinase phosphatases (MKPs) as a therapeutic strategy for the treatment of human diseases.

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Therapeutic areas of potential focus.

- Cancer
- Metabolic disease
- Rare diseases

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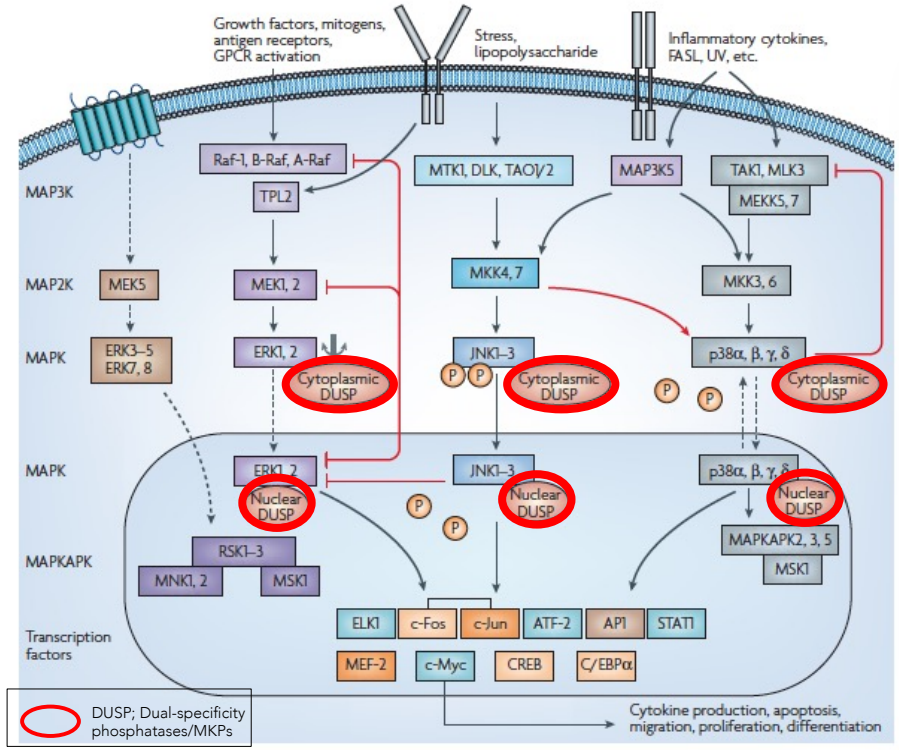
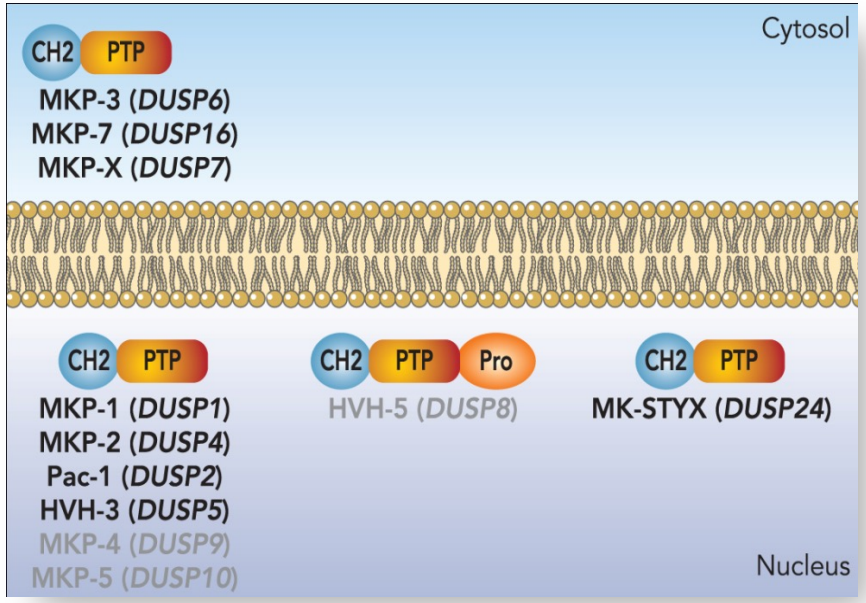
Targeting the MAP kinase pathway through MKP antagonism reveals unique and non-obvious biology and thus novel therapeutic strategies.





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- MKPs are thought to be an **untapped** druggable landscape. Representing pathways linked to cancer, metabolic and rare diseases.

- MKPs function as **nodal** regulators of the MAPK pathway and function through novel mechanisms via MAPK dephosphorylation on **validated** disease pathways.

- Targeting platform for the identification of lead **allosteric inhibitors** of the MKPs.

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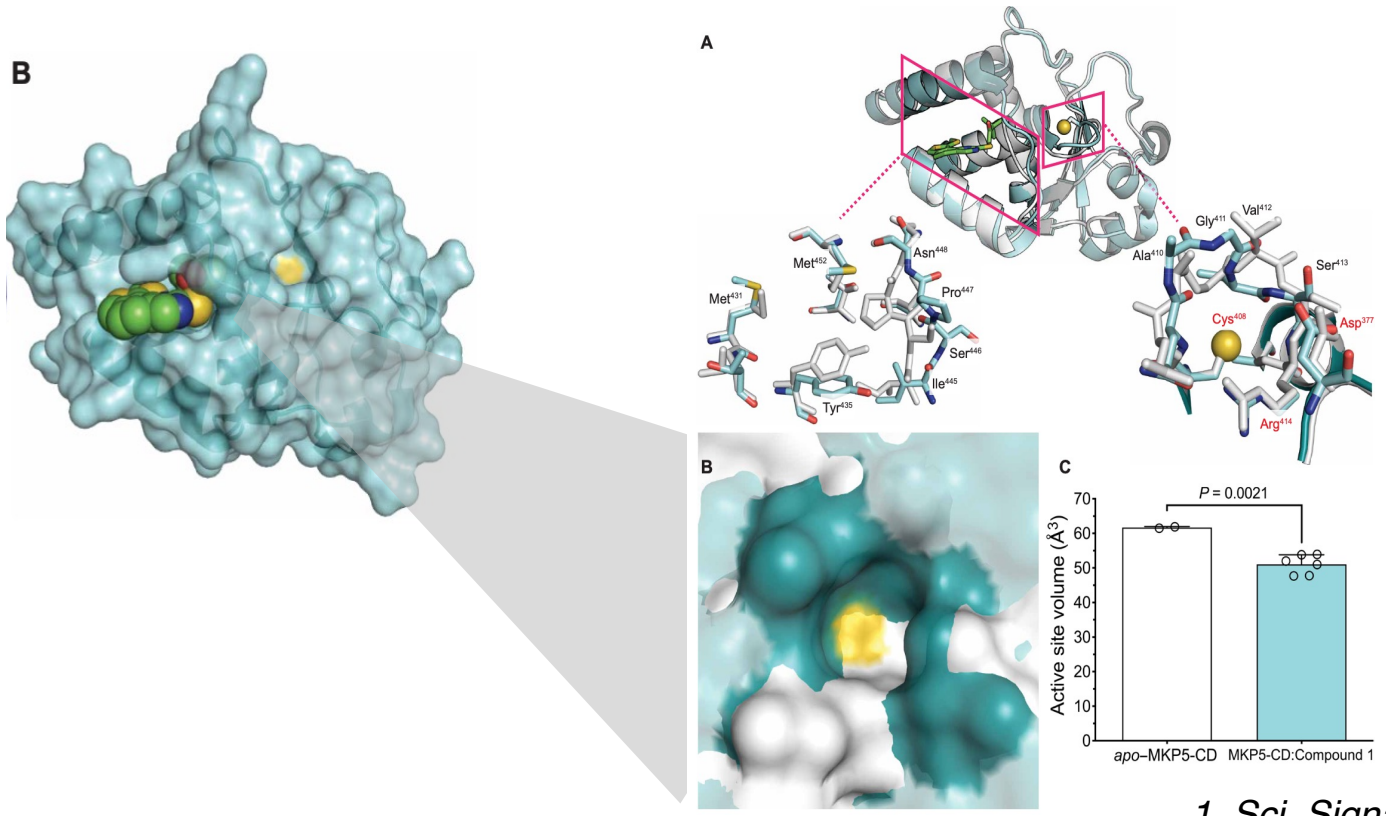
- Work from the Bennett lab and colleagues led to the discovery of allosteric inhibitors for MKP-5[1]
- Binding allosteric site inhibits via conformational change in the active site[1] and MAPK substrate interference.



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

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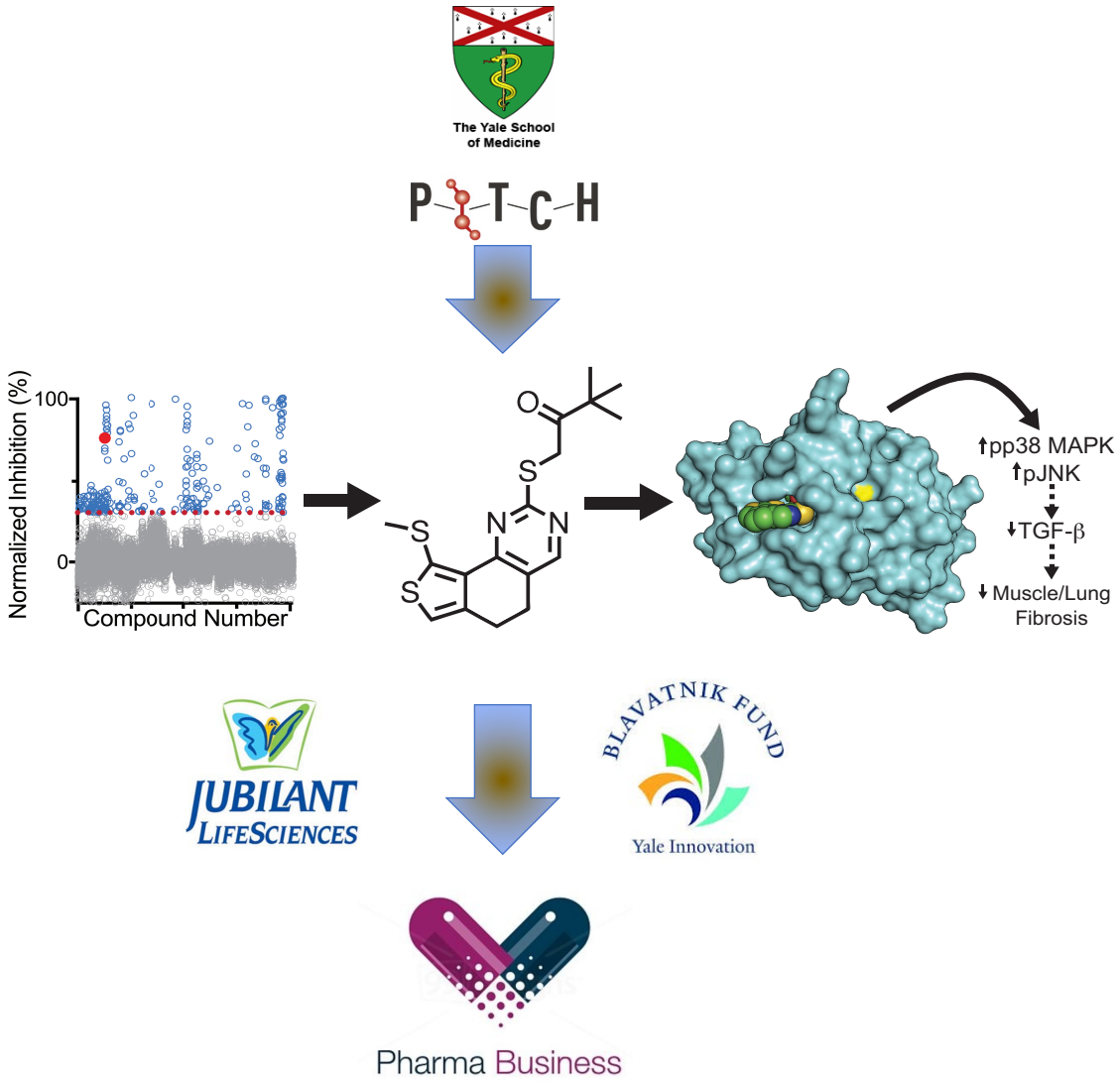
MKP-5-specific Allosteric Modulators Partnered.



Bennett Lab, PITCH, and Jubilant

- Proof of concept of allosteric MOA
- Sub-micromolar; MKP5-specific hits
- Tractable chemistry

MKP5 Program Licensed to Pharma

- Sub-micromolar MKP5-specific
- MKP5 in fibrosis only
- Significant royalties
- Multi-million $ milestones
- Active collaboration

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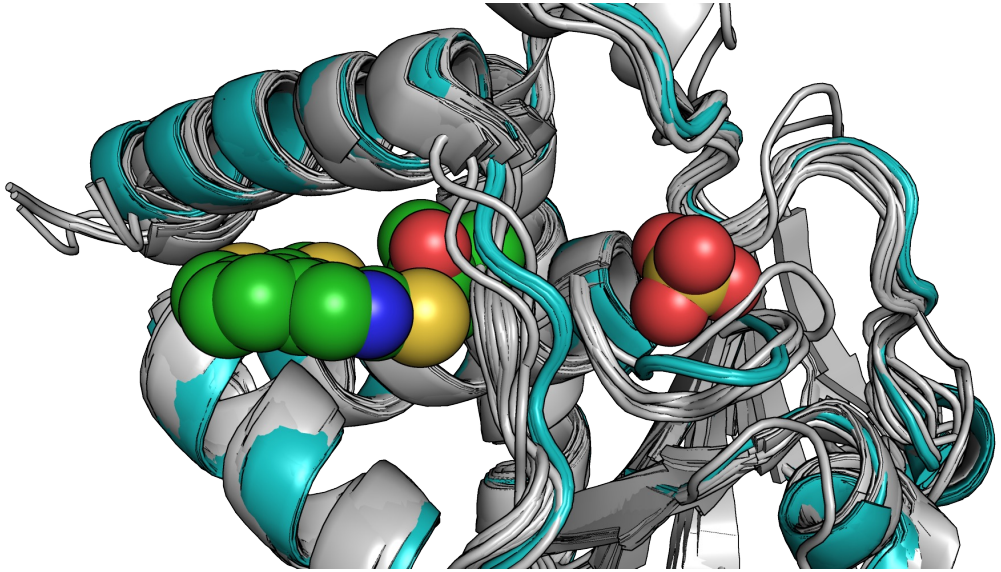
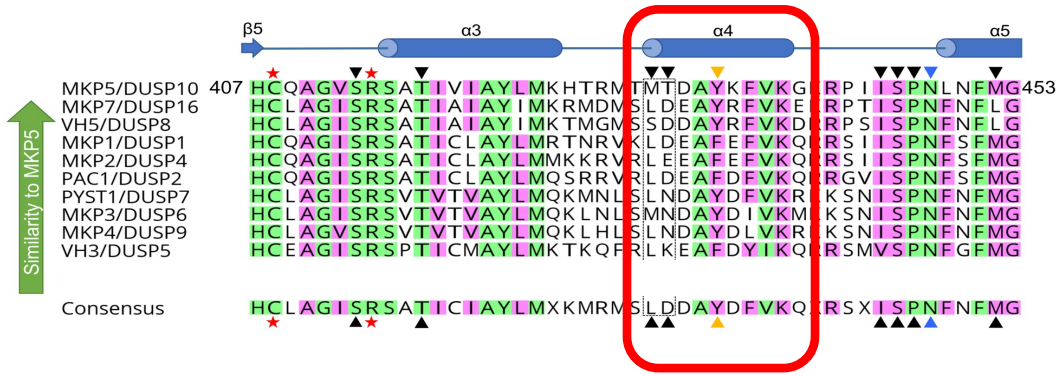
The MKP **platform** will leverage the **conserved pocket** in the MKPs to identify and develop novel MKP-specific allosteric inhibitors.





Allosteric pocket in the MKPs

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MKPs in **validated** disease areas represent attractive therapeutic targets.

- *Cancer* – MKP1/Dusp1 (Hepatocellular carcinoma) and MKP3/Dusp6 (breast cancer and melanoma drug-resistant cancers)

- *Metabolic* – MKP1/Dusp1 (Non-alcoholic steatohepatitis)

- *Rare diseases* – MKP5/Dusp10 (Duchenne muscular dystrophy)

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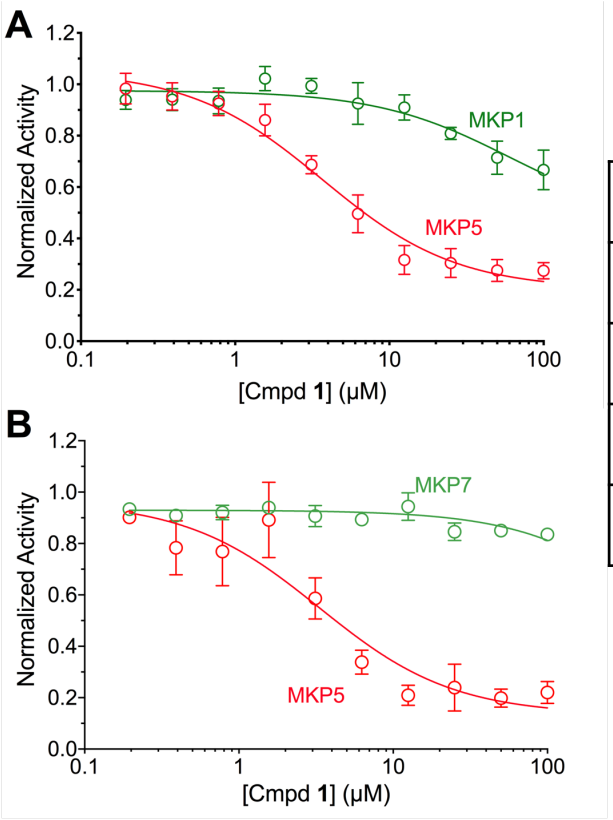
Drugging MKPs; the selectivity problem is solved.



Sci. Signal. 13, eaba3043 (2020)

MKP allosteric pocket is amenable to high selectivity

MKP	IC_{50} (μM)	Fold Difference
MKP5-CD	3.8 ± 0.6	——
MKP5, full-length	2.2 ± 0.3	——
MKP1-CD	60 ± 22	16
MKP7-CD	580 ± 180	~180

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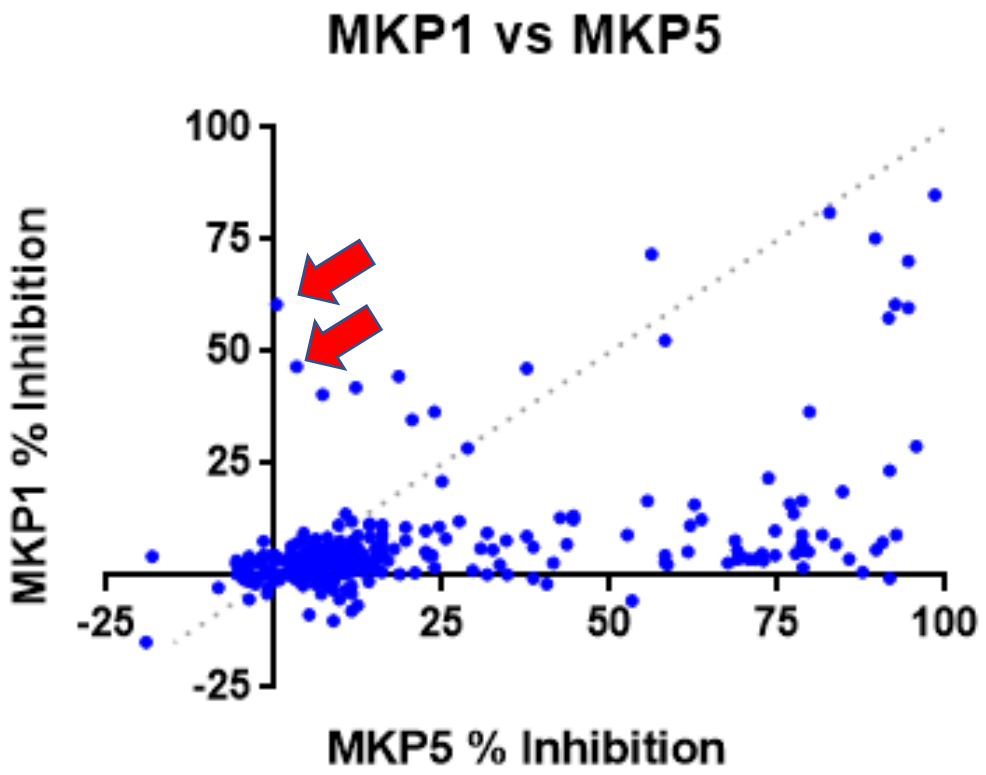
- Screening data for MKP-1 and MKP-5 reveals MKP-1-selective inhibitors.
- Proof-of-principle that library can be mined to identify selective MKP inhibitors.



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Bennett/Yale Center for Molecular Discovery – Unpublished.

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- ASSET: Established novel screening platform to identify allosteric MKP inhibitors.
- ASSET: Deep knowledge of MKP biology in cancer, metabolism and rare diseases.
- ASSET: Proven development model demonstrated for MKP-5 with granted IP protection (Application US16/954,514).
- *GOAL*: Establish IP protection for MKP-1 and MKP-3 and expanded portfolio development.
- *GOAL*: Early entry assets of an otherwise untapped therapeutic space previously considered "undruggable".

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Hit Identification and target validation

- Test existing MKP targeted allosteric library for MKP-1 and MKP-3 inhibitors.
- Co-crystal structure of hits to test allosteric pocket binding.
- SAR for improved activity and physical properties.
- 0-12 months.

Lead Identification

- SAR for sub-micromolar activity and solubility.
- Establish cell-based SAR activity.
- Confirm selectivity (in vitro against other PTPs and MKPs and cell-based specificity).
- Evaluate PK/ADME properties of the lead compounds.
- Proof-of-concept in vivo studies
- 12-36 months.

Lead Testing and IND FDA filing

- Demonstrate *in vivo* efficacy of the lead series in disease mouse models.
- Select optimal lead indication for IND filing to FDA.
- 36 - 60 months.

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Blavatnik support

Projected cost : $300K

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END