

# About OMICS Group

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UniSA

# Towards pharmacological validation of MNKs as anti-cancer drug targets

Dr Hugo Albrecht

School of Pharmacy and Medical Sciences  
University of South Australia

# Kinases as Cancer Drug Targets

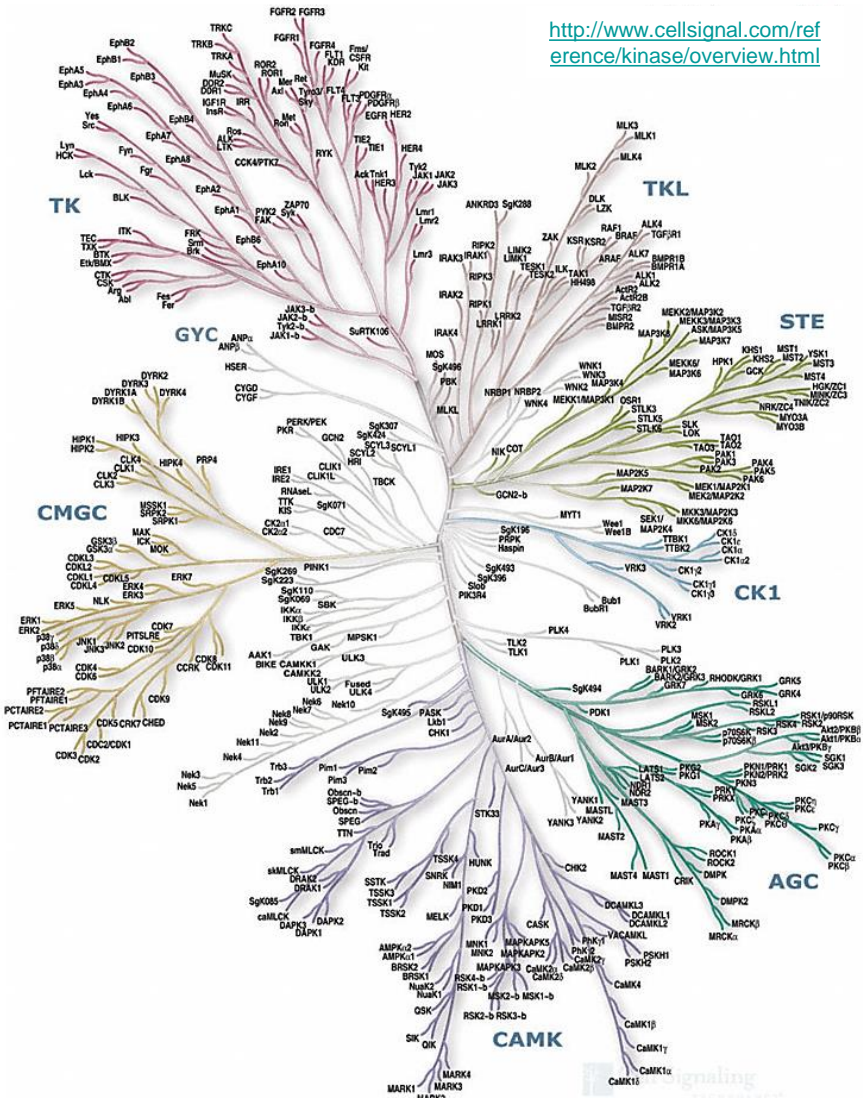
## “Hard Targets”

KO leads to strong or lethal phenotype (e.g. PLK1)

Adverse effects are expected. Use of advanced formulation to target cancer cells (e.g. nanoparticles, liposomes etc.)

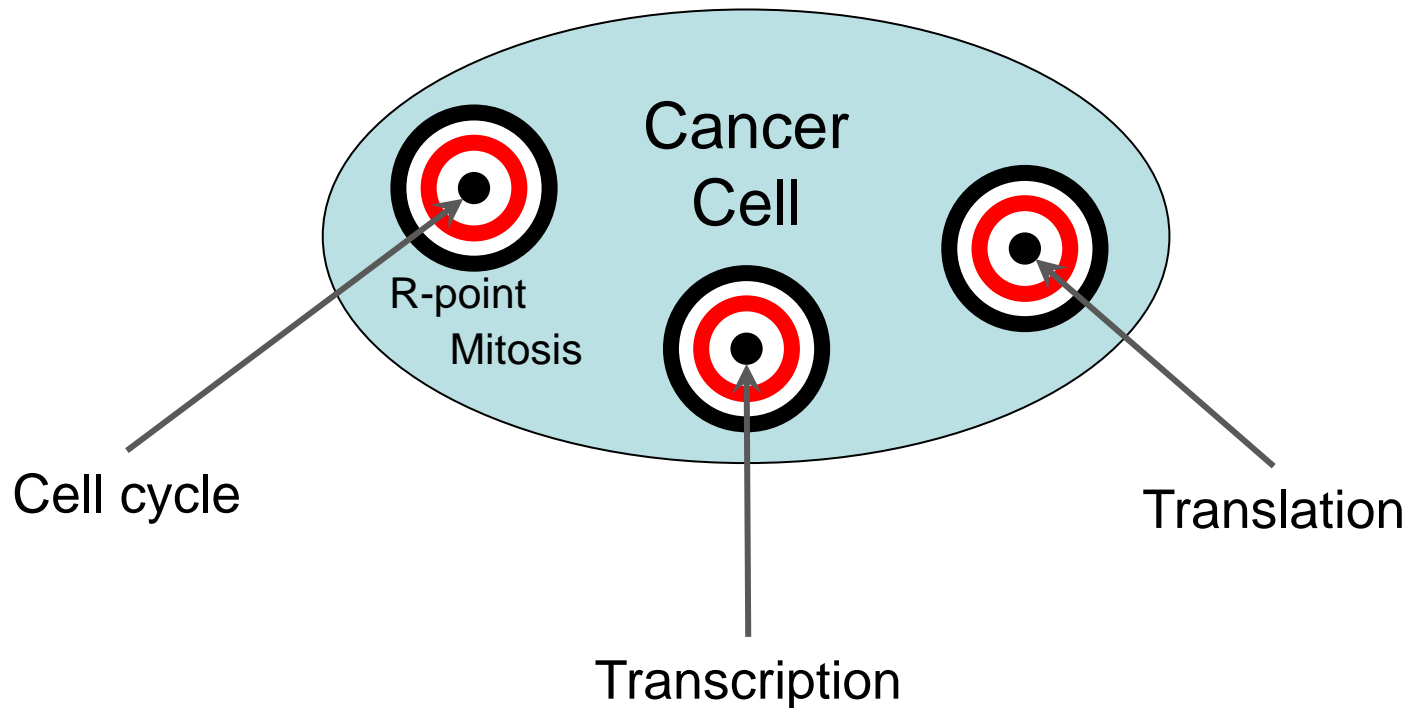
## “Soft Targets”

KO with no obvious or mild phenotype (e.g. Mnk1/2)

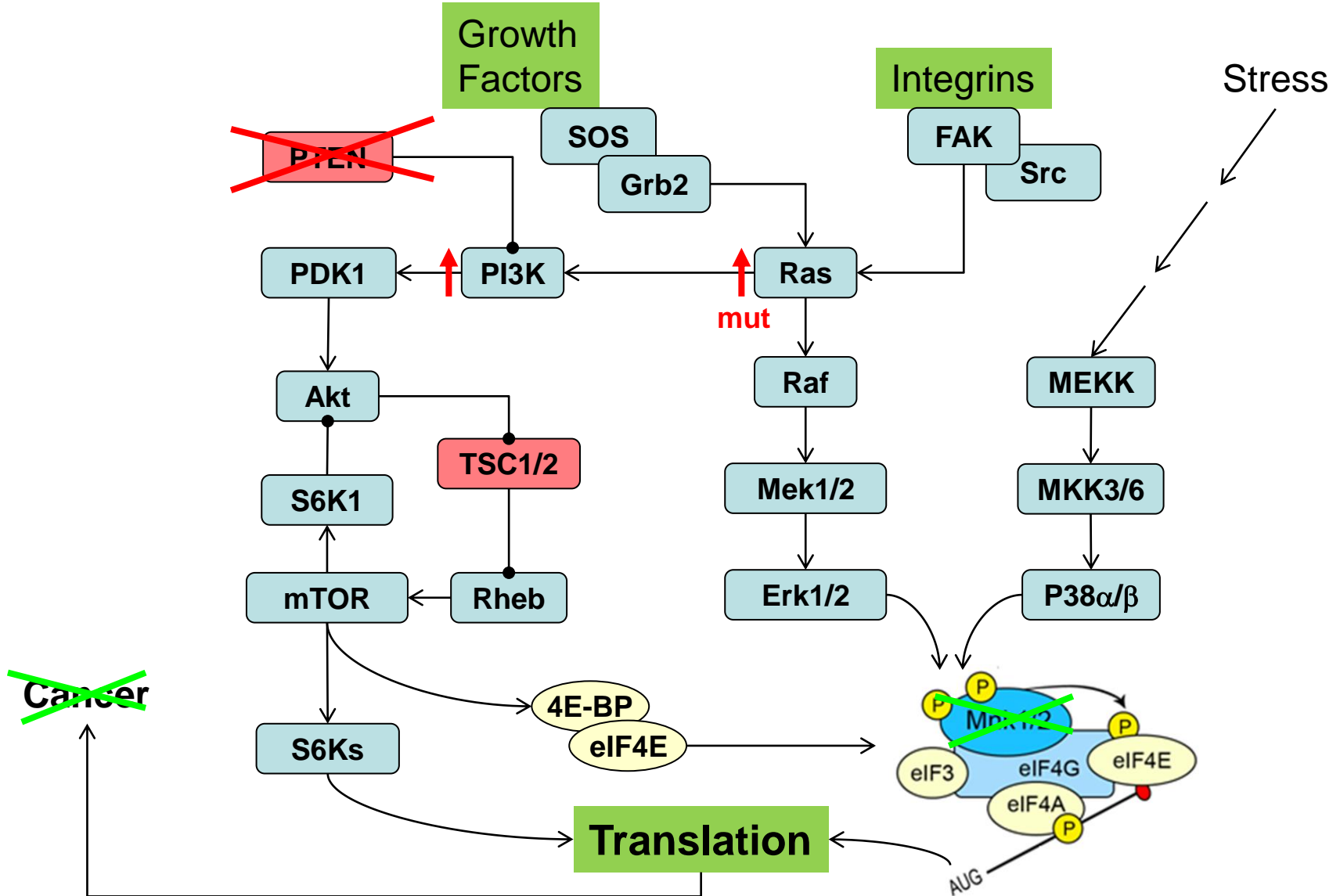


# Anti-cancer strategy

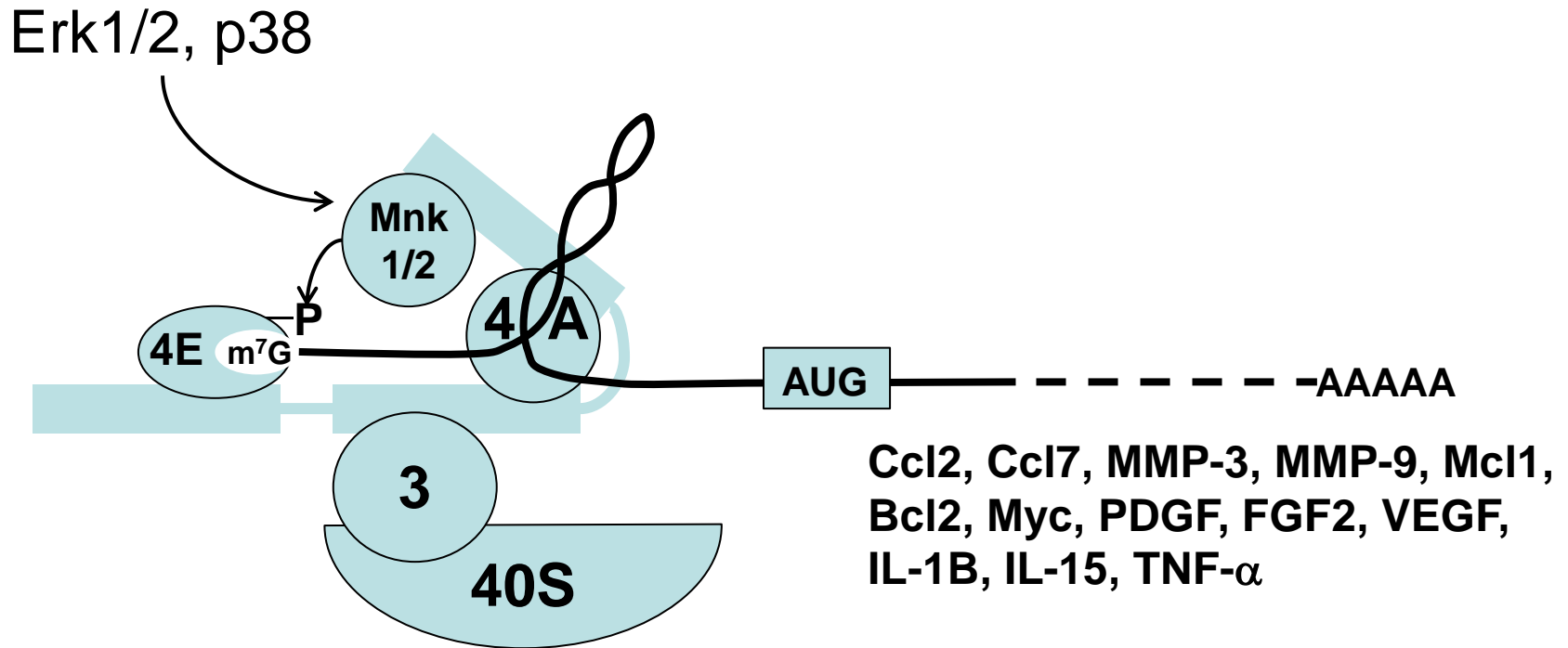
- Targeting cancer cells through block of several pathways



# Targeting Translation: Mnk1/2

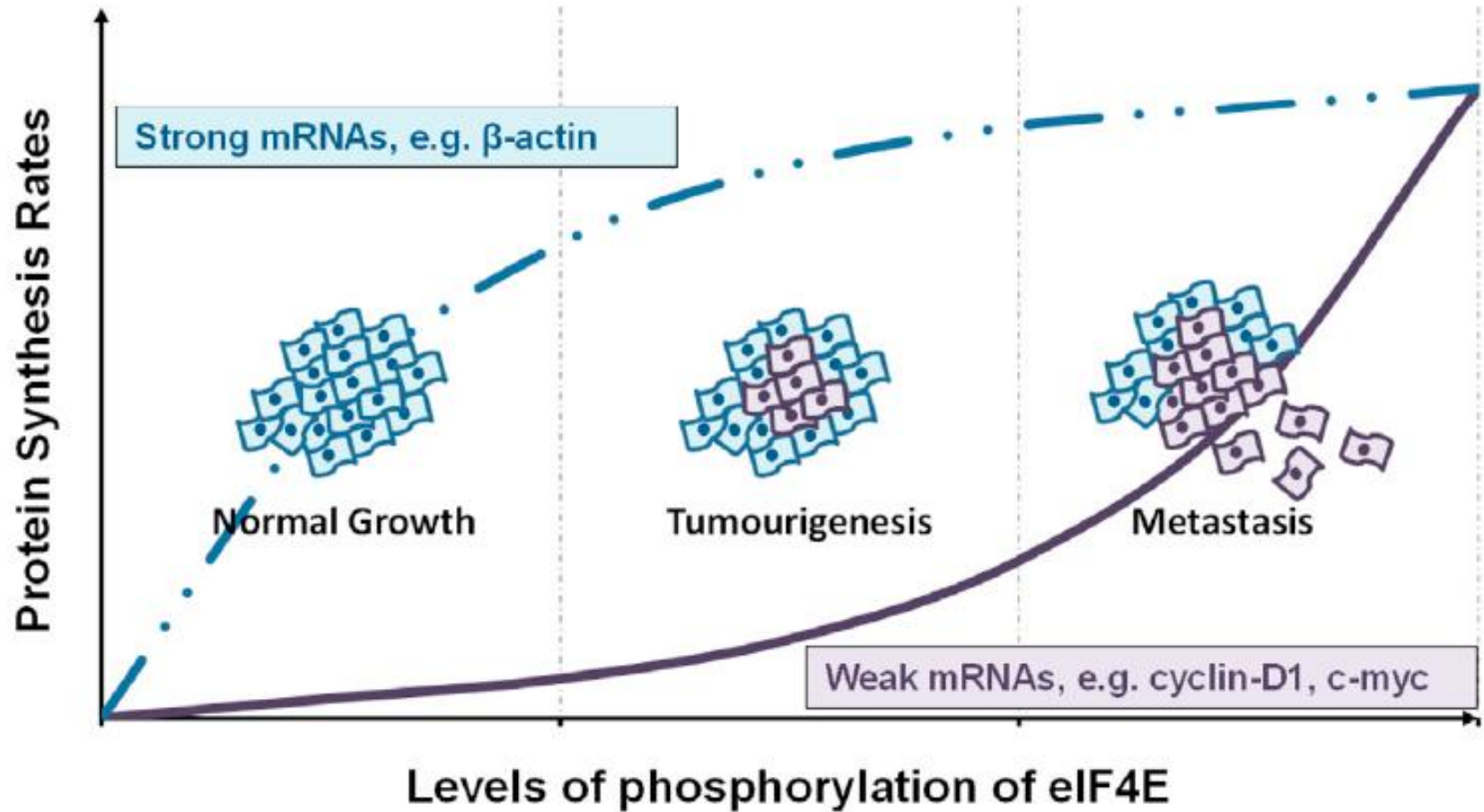


# Phosphorylation of eIF4E by Mnks



Adapted from Hay N., 2010, PNAS, Vol.107, No. 32, 13975-13976 and Pyronnet, S.; Imataka, H.; Gingras, A. C.; Fukunaga, R.; Hunter, T.; Sonenberg, N. *The EMBO journal* **1999**, 18, 270

# Elevated eIF-4E phosphorylation promotes tumorigenesis



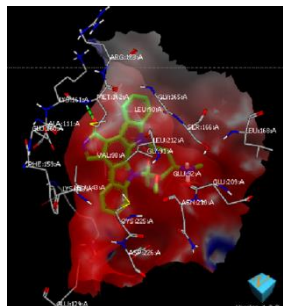
Diab, S.; Kumarasiri, M.; Yu, M.; Teo, T. H. S.; Milne, R.; Proud, C.; Wang, S. *Chem. Biol.* **2014**, *21*, 441  
 Graff, J. R.; Konicek, B. W.; Carter, J. H.; Marcusson, E. G. *Cancer research* **2008**, *68*, 631.



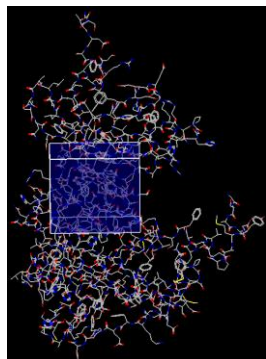
- eIF4E is frequently overexpressed in cancers and is associated with cellular transformation, tumorigenesis and metastatic progression.
- In **Mnk1/2 DKO** mice:
  - eIF4E phosphorylation is completely abolished**
  - Cells are **resistant to transformation** by Ras and tumour formation is significantly delayed in PTEN<sup>-/-</sup> x Mnk DKO mice **lymphoma model**<sup>2)</sup>
- Knock-in mice with a **eIF4E S209A mutation** are resistant to:
  - Oncogene induced transformation<sup>1)</sup>
  - PTEN loss-induced **prostate cancer**<sup>1)</sup>
- **Normal growth** of Mnk DKO and eIF4E S209A KI mice.

**Mnk1 and Mnk2 inhibitors may be effective and non-toxic anticancer drugs**

# Aim: Design and characterization of Mnk1/2 inhibitors

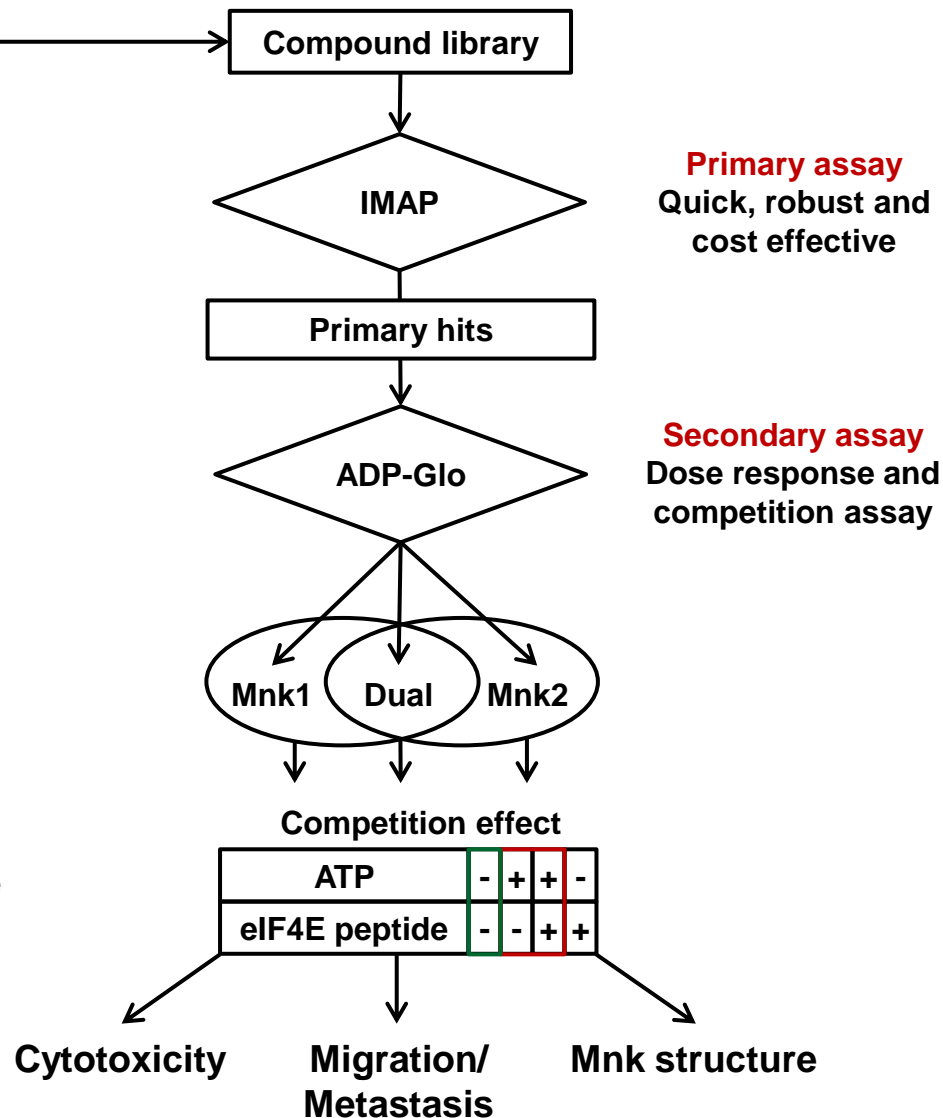


Default active site detected by FRED receptor program as shown in the blue box



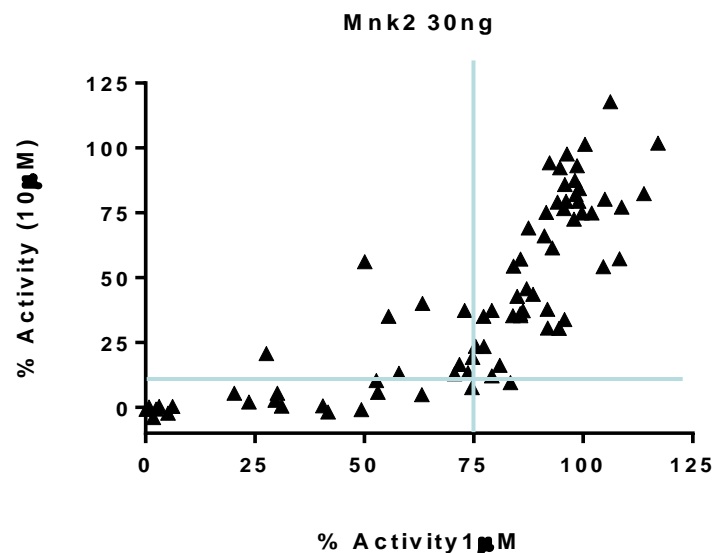
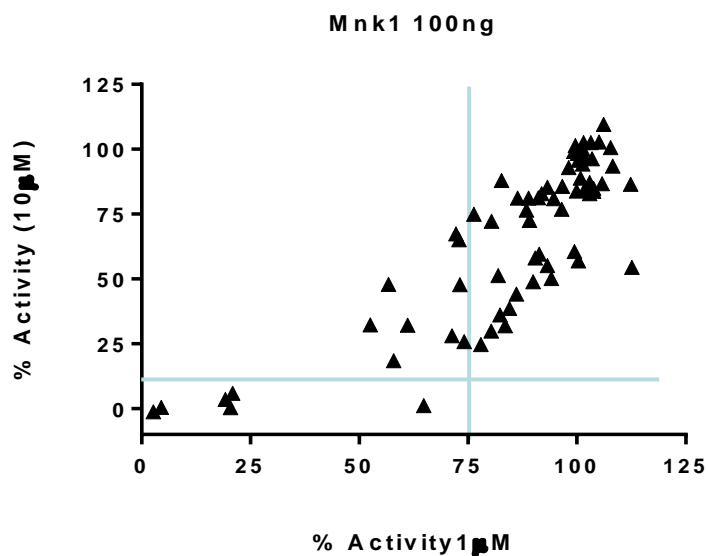
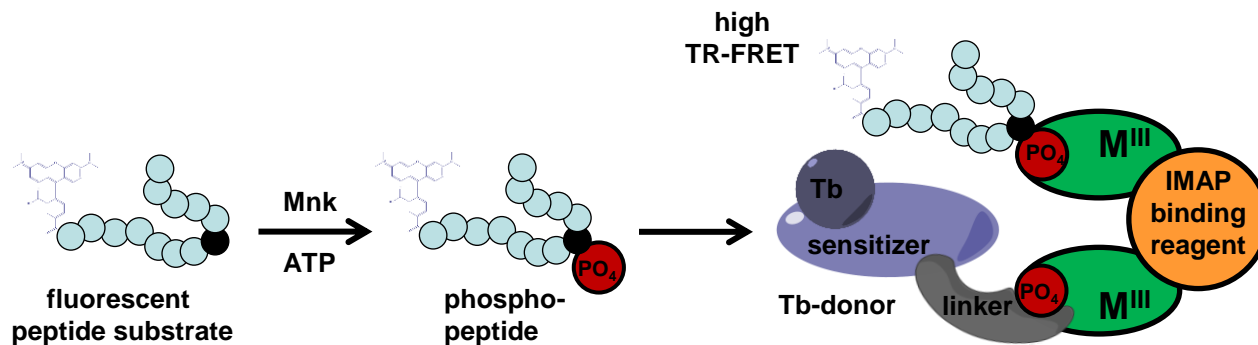
Default active site created by FRED receptor program

3D structure of staurosporine-bound Mnk2-KR obtained from the Protein Databank (PDB: 2HW7)

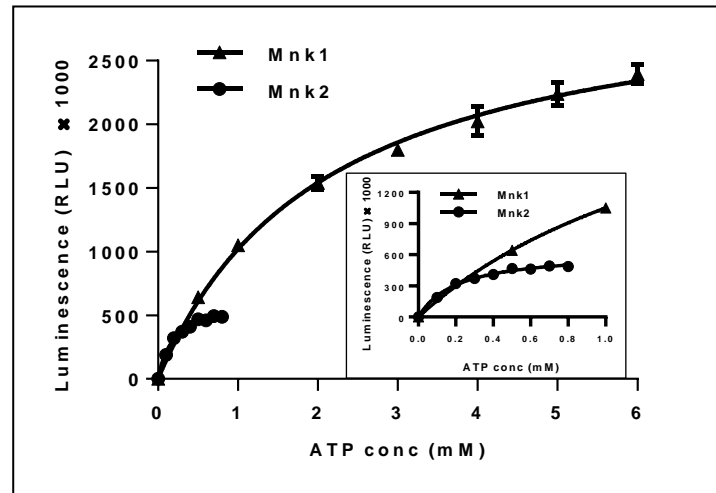
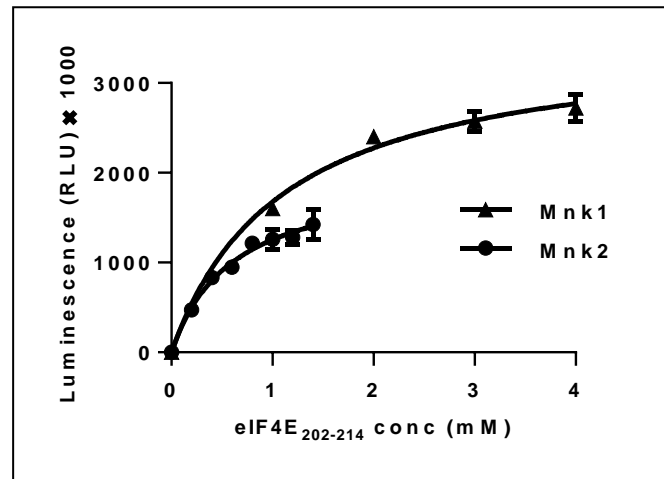
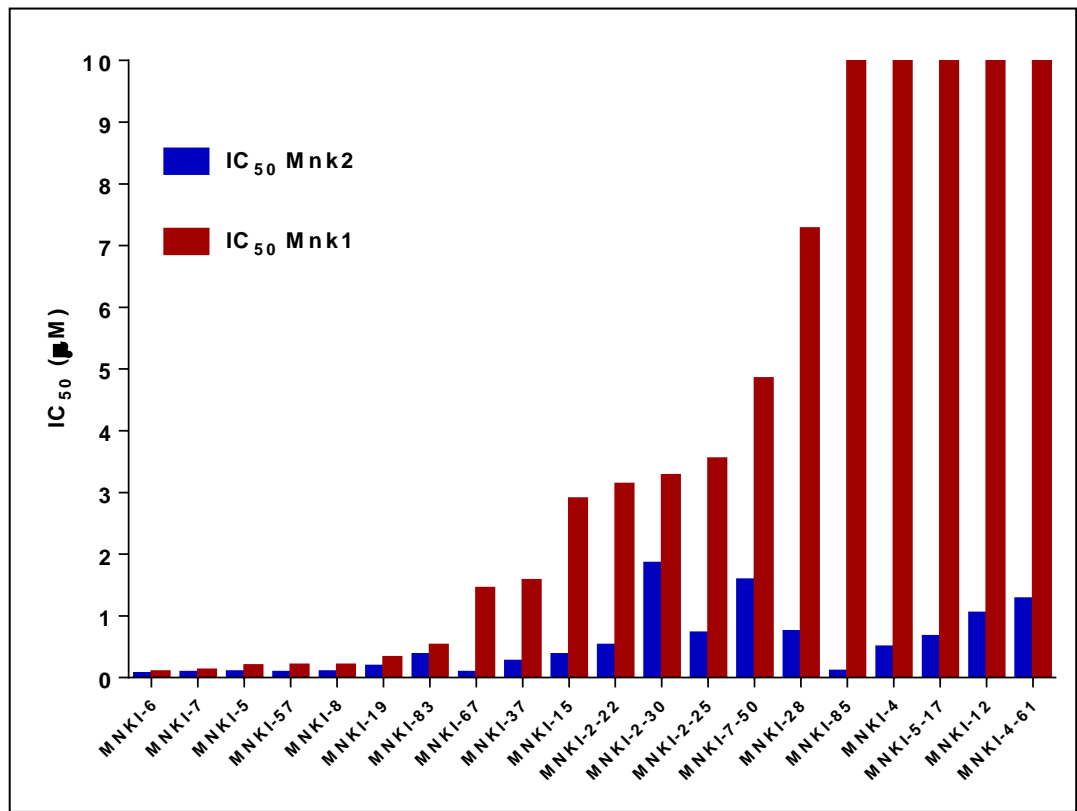
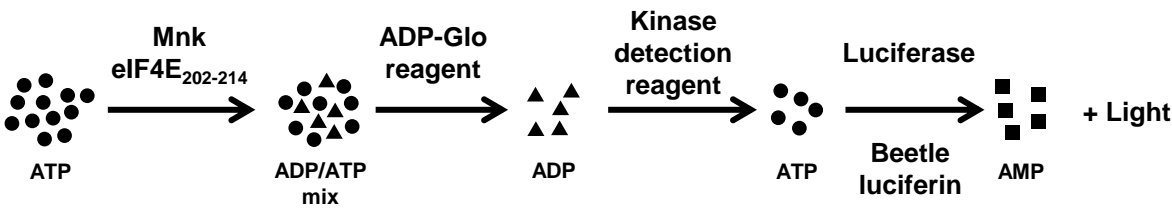


# Primary compound profiling with IMAP assays

IMAP: Immobilised Metal Ion Affinity Particle Progressive Binding System



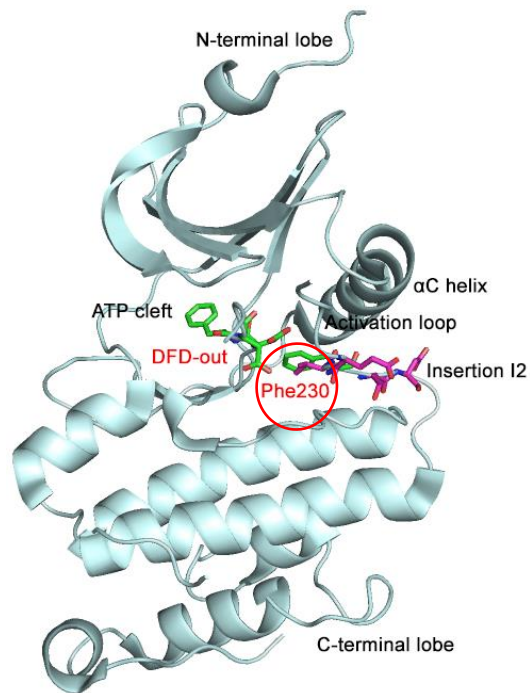
# ADP-Glo Assay



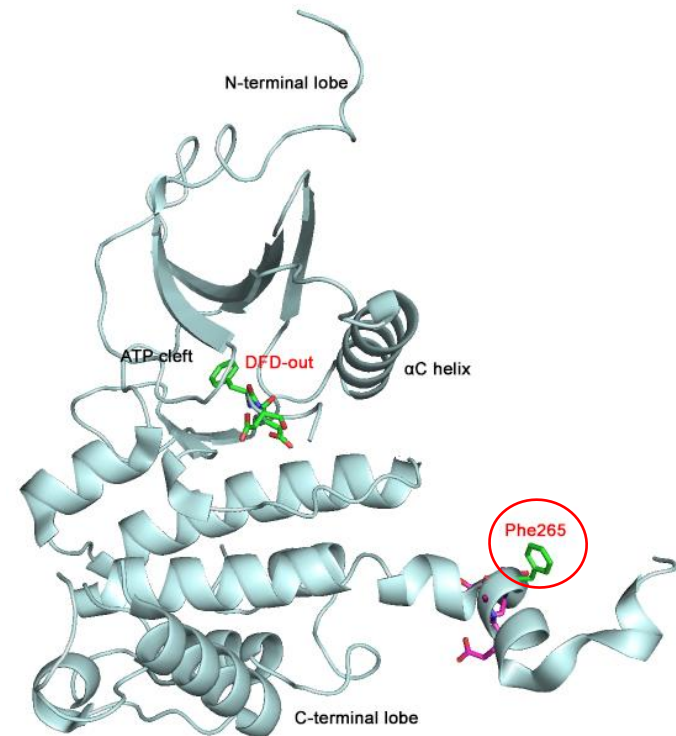
7 dual inhibitors  
 13 Mnk2 specific (Mnk1 > 10x Mnk2)

# Mnk1/2 Crystal Structure Discrepancy

Crystal structure of Mnk1 (PDB entry 2HW6)

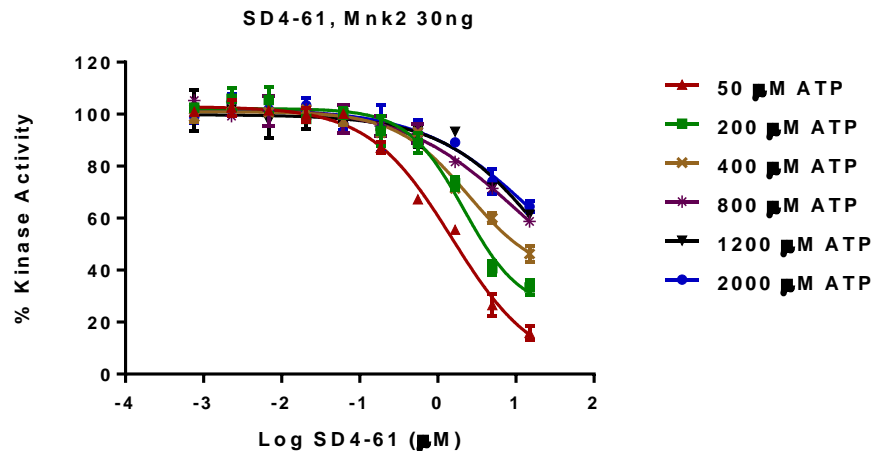


Crystal structure of Mnk2 (PDB entry 2AC3)

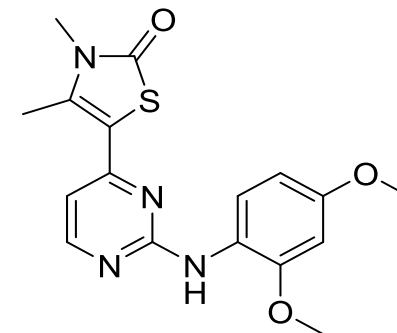
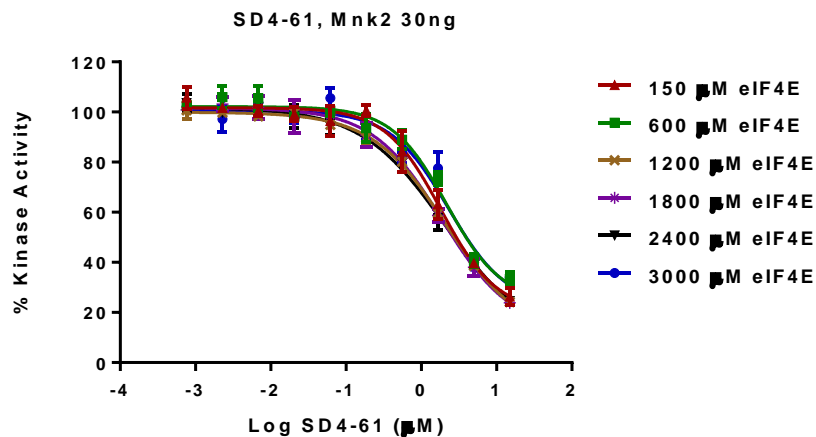


# Identification of Type I/II Mnk inhibitors

eIF4E fixed  
at 600  $\mu\text{M}$  ( $K_M$ )



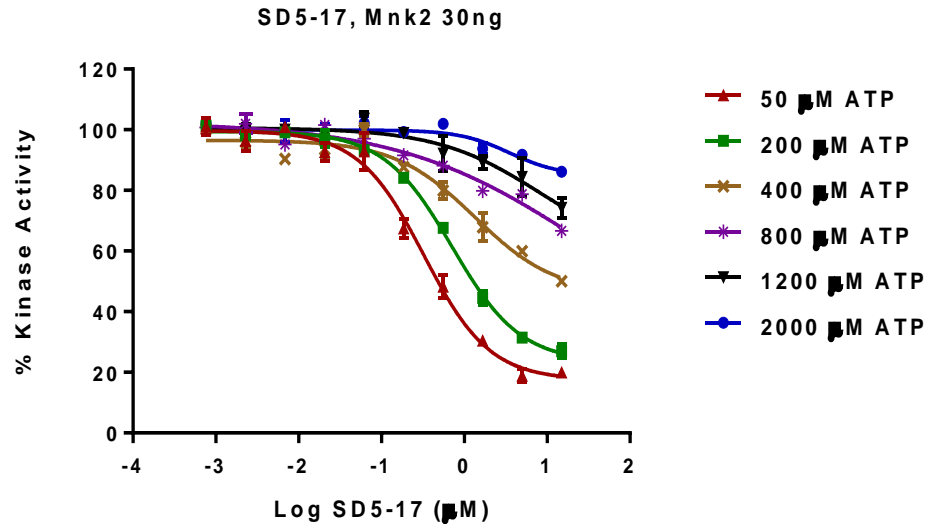
ATP fixed  
at 200  $\mu\text{M}$  ( $K_M$ )



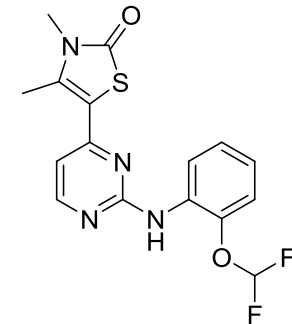
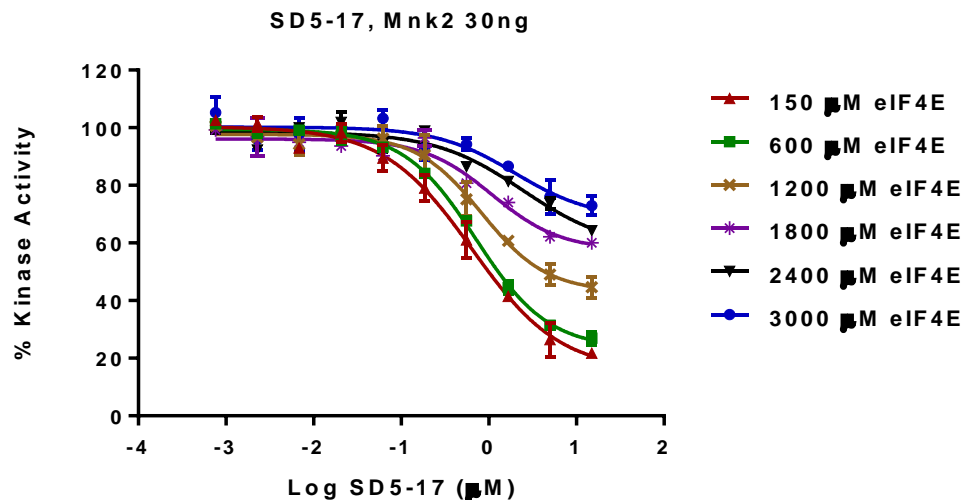
MNKI-4-61

# Identification of Type I/II Mnk inhibitors

eIF4E fixed  
at 600  $\mu\text{M}$  ( $K_M$ )



ATP fixed  
at 200  $\mu\text{M}$  ( $K_M$ )

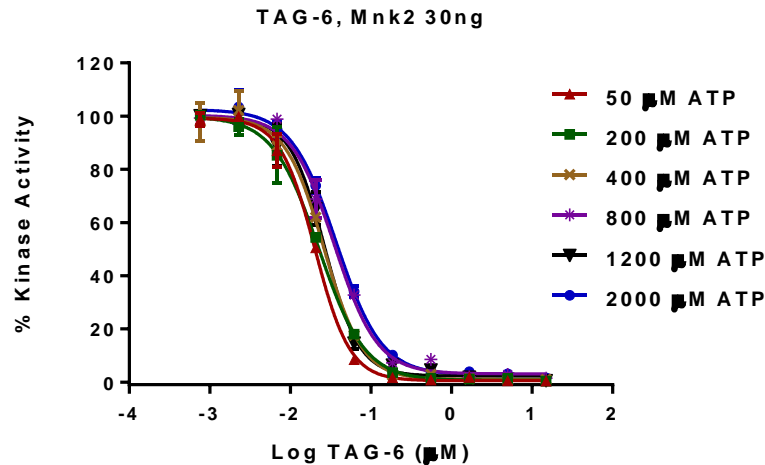


MNKI-5-17

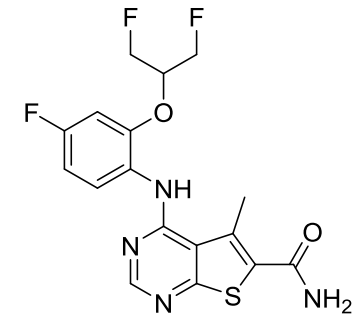
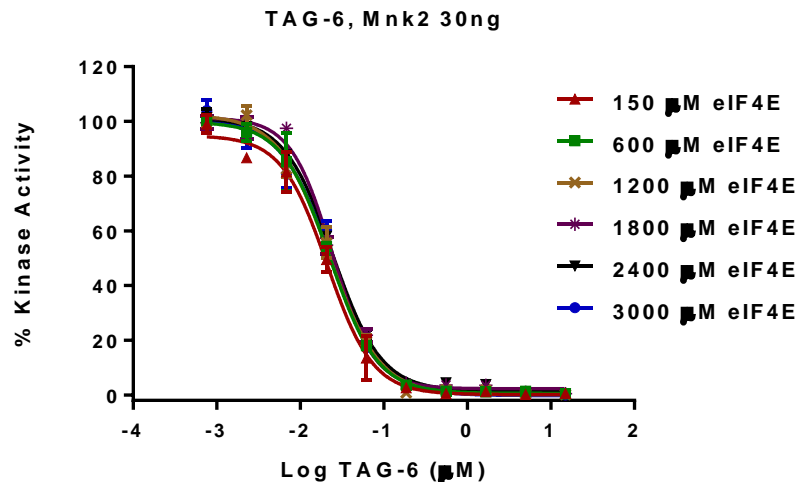
Data Mean  $\pm$  SEM, n=2

# Identification of Type III Mnk inhibitors

eIF4E fixed  
at 600  $\mu\text{M}$  (Km)



ATP fixed  
at 200  $\mu\text{M}$  (Km)



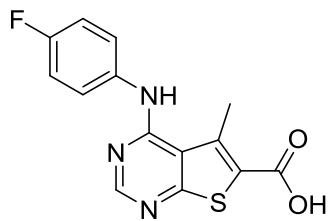
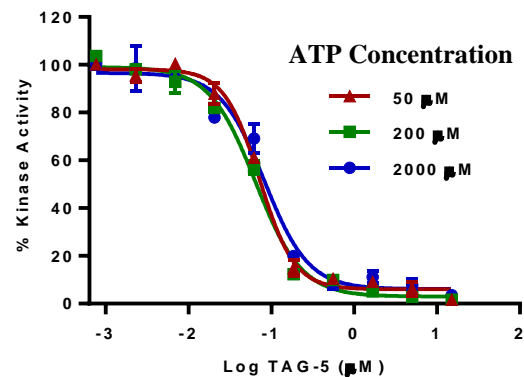
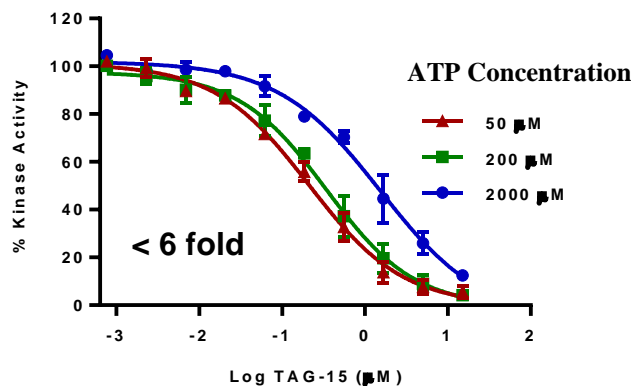
MNKI-6

Allosteric inhibitors

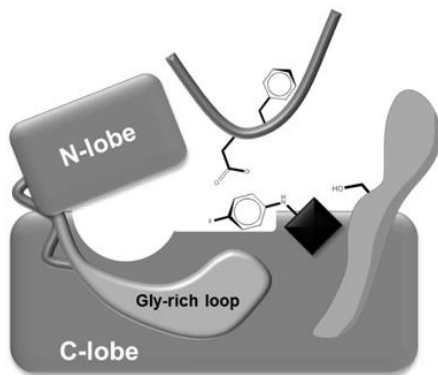
Data Mean  $\pm$  SEM, n=2



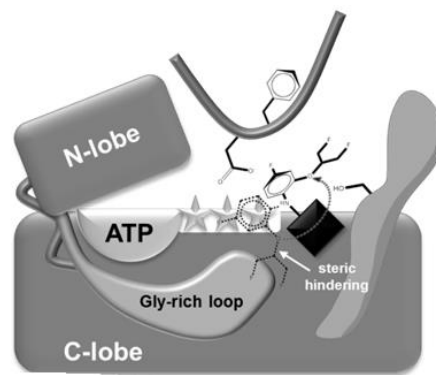
# Type I/II vs. Type III inhibitors



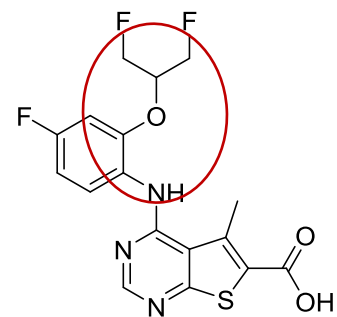
MNKI-15



DFD in with MNKI-15

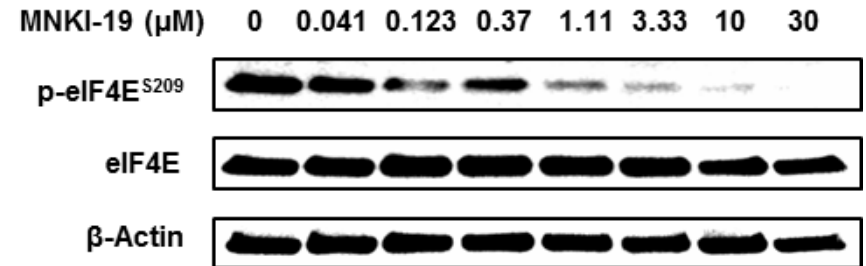
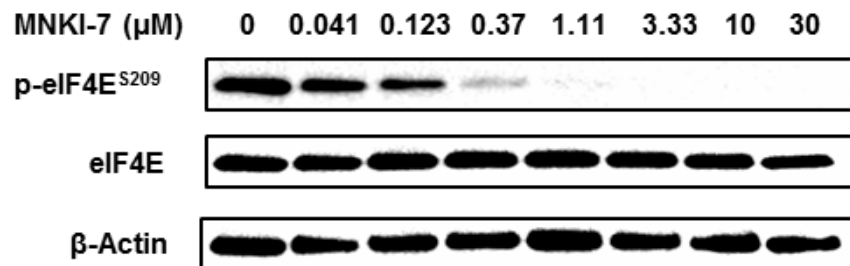
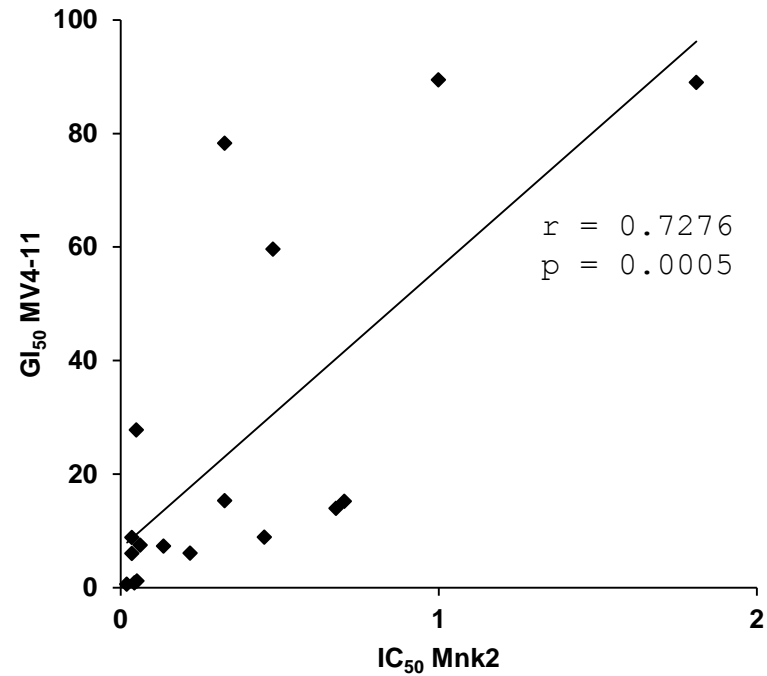
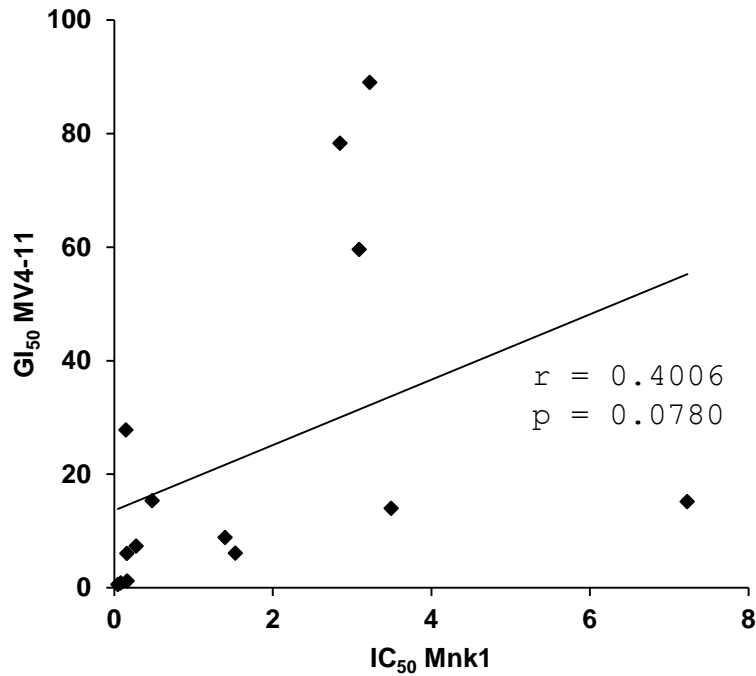


DFD in with MNKI-5

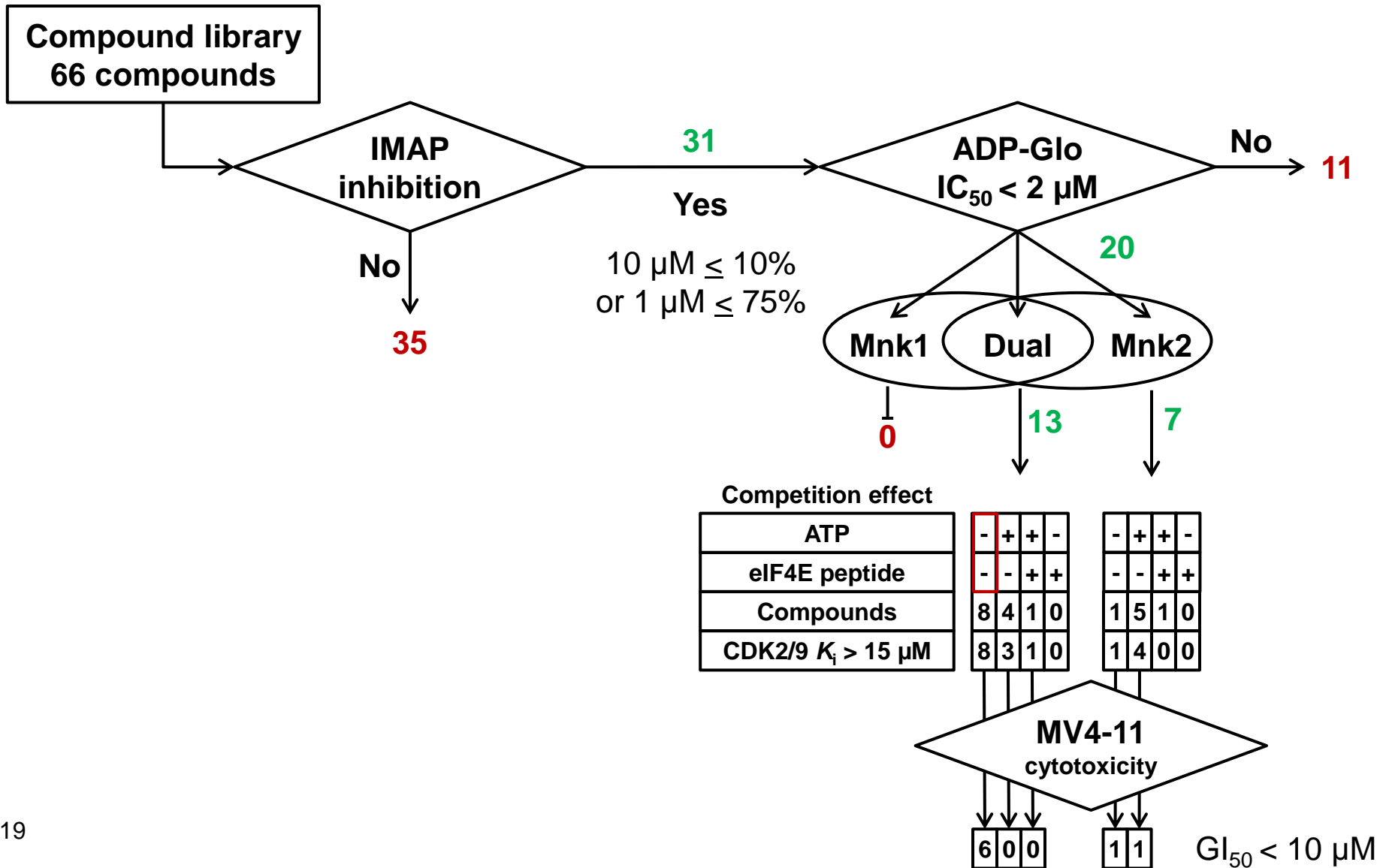


MNKI-5

# MV4-11 Leukemia cells



# Summary

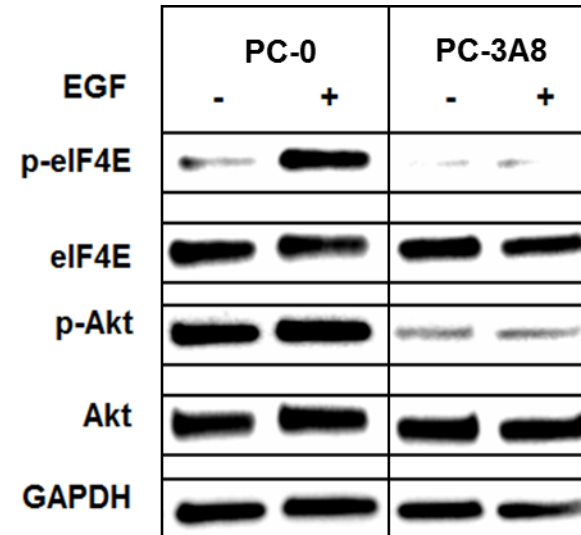
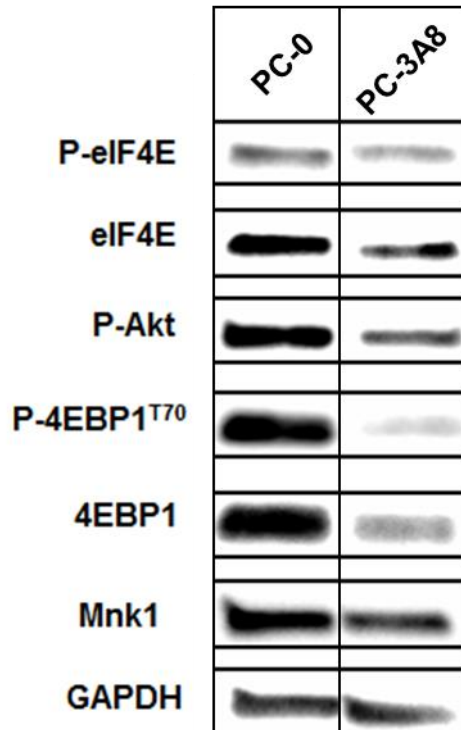


# Prostate cancer cells

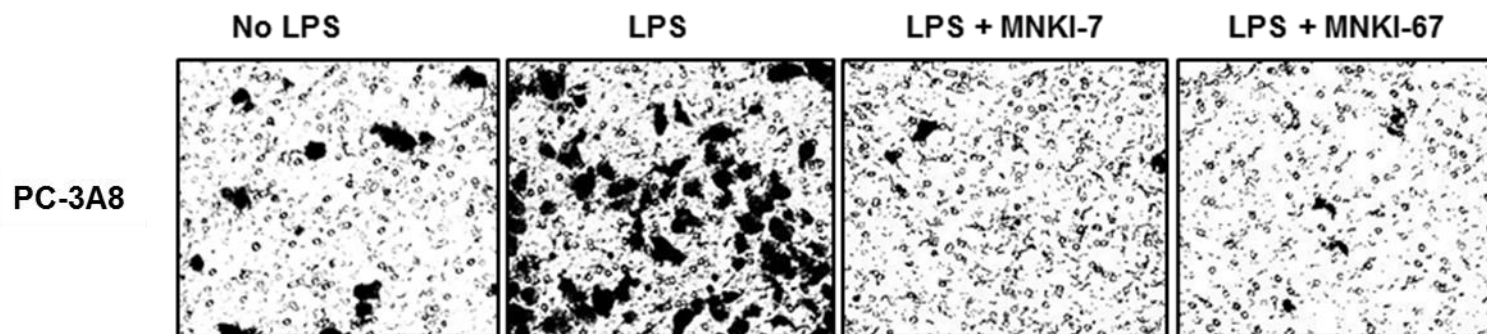
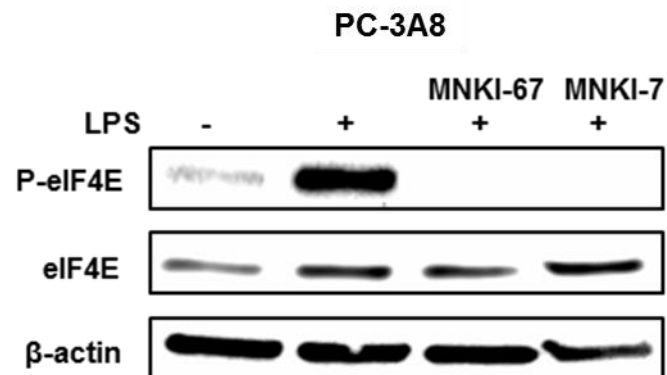
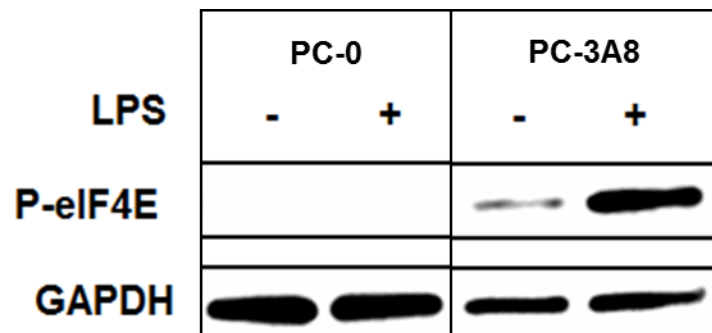
	PC-0	PC-3A8
PTEN	-	-
P-Akt	+	+
Androgen dependent	+	-
Metastatic	-	+

	Mnk1	Mnk2	eIF4E WB	MV4-11	PC-0	PC-3A8
MNKI-7	83	44	35	0.83	>10	8.65
MNKI-19	279	136	135	7.30	>10	>10
MNKI-67	1400	36	X	8.84	>10	>10

IC<sub>50</sub> (nM)
GI<sub>50</sub> (μM)



# Prostate cancer cells



# Conclusions

**Potent Mnk1/2 and selective Mnk2 inhibitors have been identified.**

**Detailed kinetic studies revealed three types of binding modes.**

**Our studies confirm different structural properties of Mnk1 and Mnk2 at the ATP-binding pocket.**

**But they share a common allosteric binding site.**

**Mnk inhibitors are cytotoxic against some leukemia cells.**

**No cytotoxicity has been observed against prostate cancer cells.**

**Mnk inhibitors blocked LPS induced migration of prostate cancer cells.**

# Acknowledgement

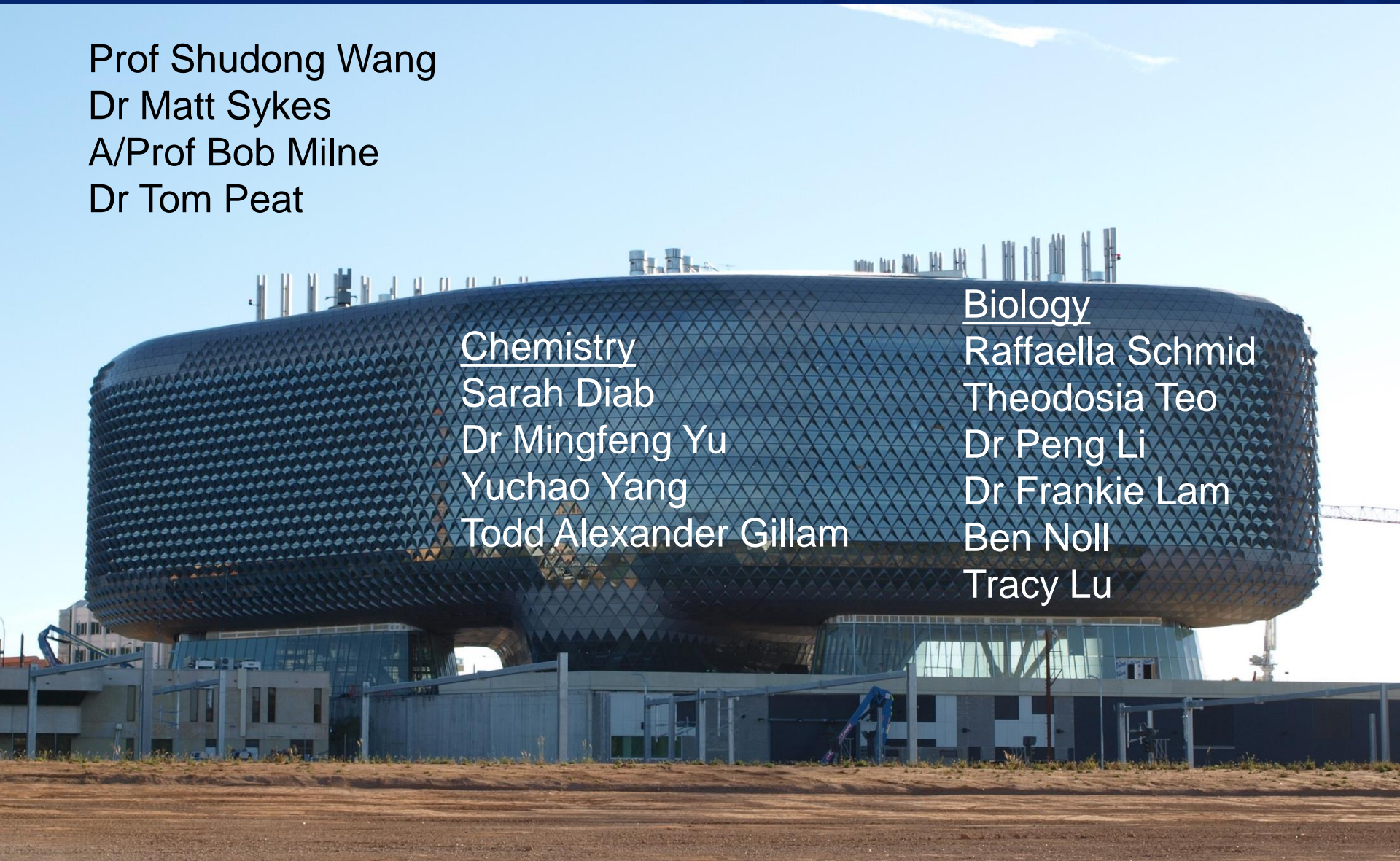
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Subheading when required

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International

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Congress

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<http://europe.pharmaceuticalconferences.com/>