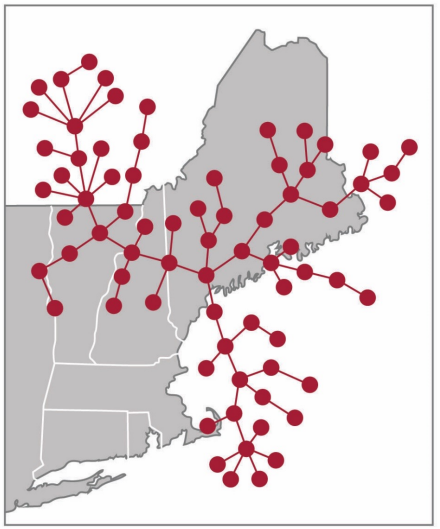
MIT SRP
Data Management and Analysis Core

Team: Doug Lauffenburger, Stuart Levine, Forest White



Specific Aim 3) Develop and apply novel functionality that includes computational tools to integrate data streams for mechanistic understanding and to inform risk.

a) Integrate multi-omics and phenotypic data to develop a mechanistic understanding of the biological impacts of *N*-nitrosamines and their relationships to the exposome.

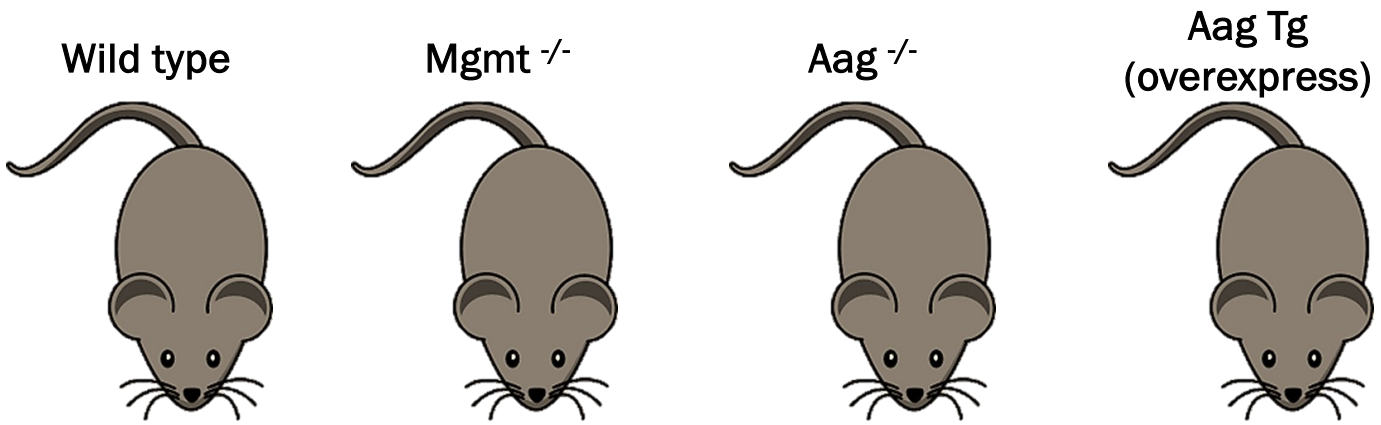
b) Leverage mathematical modeling to predict the DNA damaging effects of mixtures of *N*-nitrosamines

Multi-omic analysis data types within MIT SRP

- Transcriptomic / spatial transcriptomic data
- Proteomic data (protein expression levels)
- Phosphoproteomic data (quantitative data of protein phosphorylation sites)
- Phenotypic data: cell proliferation / cell death / tumor number / tumor volume / mouse survival
- Drug Concentration and Spatial Drug Distribution

The challenge: How best to integrate these data to define cellular response, at a molecular level, to exposure to environmental contaminants? What are the critical factors that define phenotypic response?

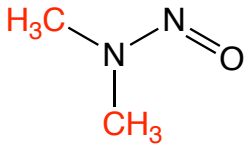
What are the molecular mechanisms underlying the carcinogenic effects of NMDA exposure?



24 Hrs
(Early response)

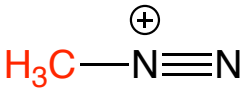
10 weeks
(Late response)

NDMA is a DNA Methylating Agent that is Carcinogenic Primarily in the Liver in Animal Models

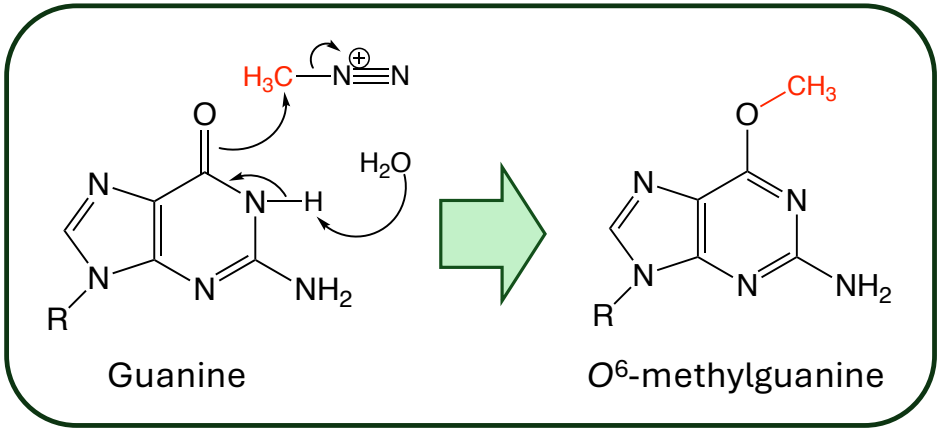


NDMA

CYP2E1

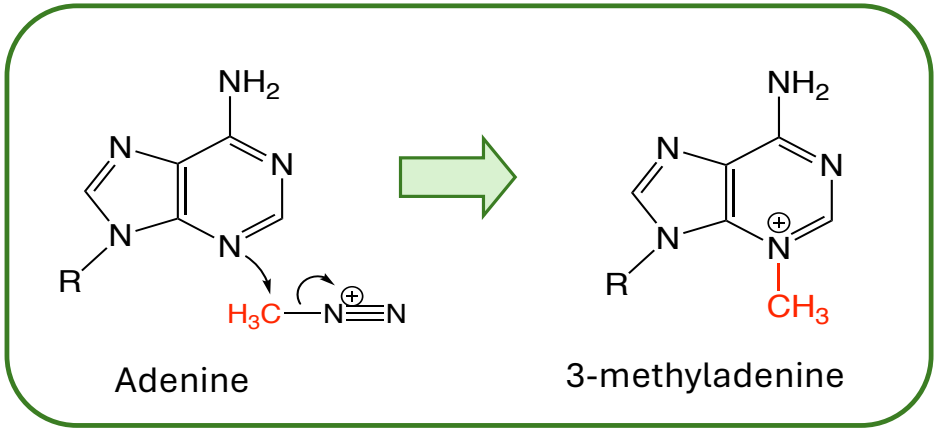


Methyldiazonium ion



Guanine

O^6-methylguanine

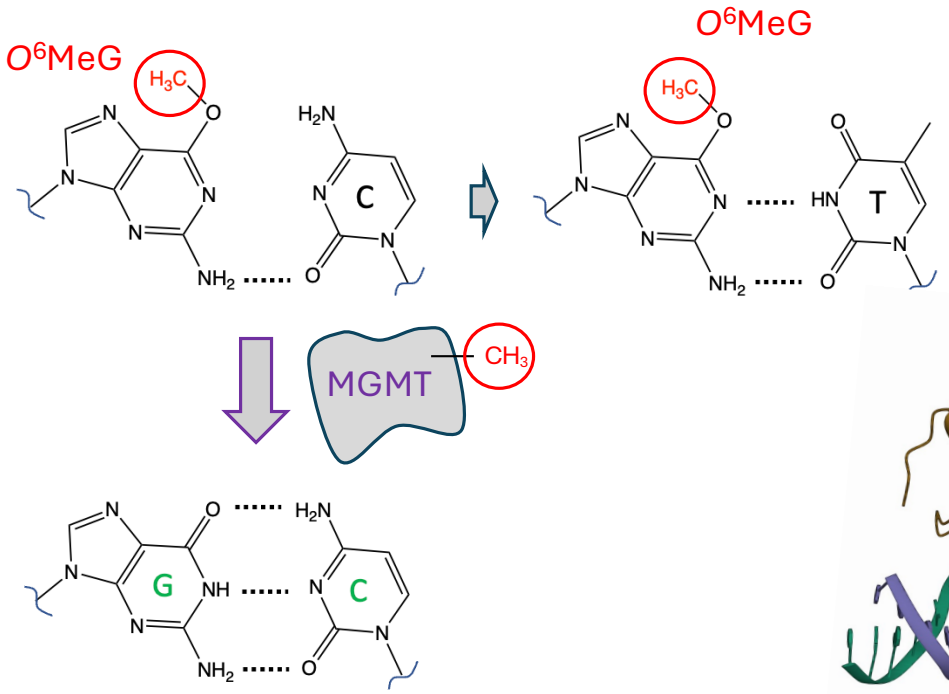


Adenine

3-methyladenine

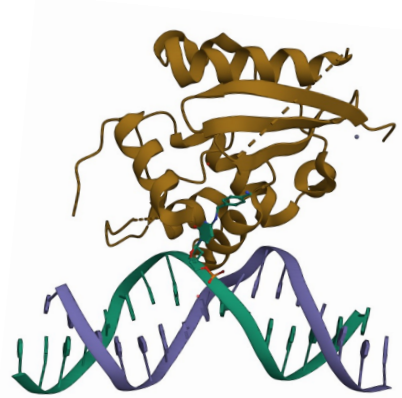
NDMA-Induced O^6MeG Lesions Promote Mutations

However, Methylguanine Methyltransferase (Mgmt) Removes the Methyl Group from Guanine



Direct Reversal by MGMT

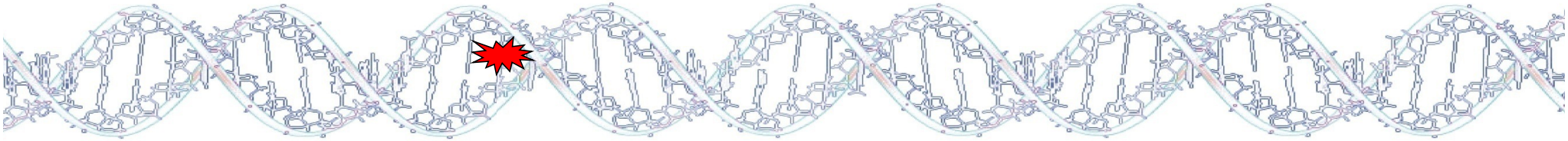
(*O*^{6}-MethylGuanine-DNA MethylTransferase)

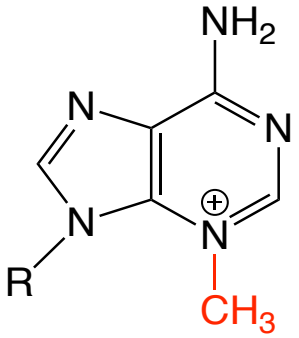


MGMT

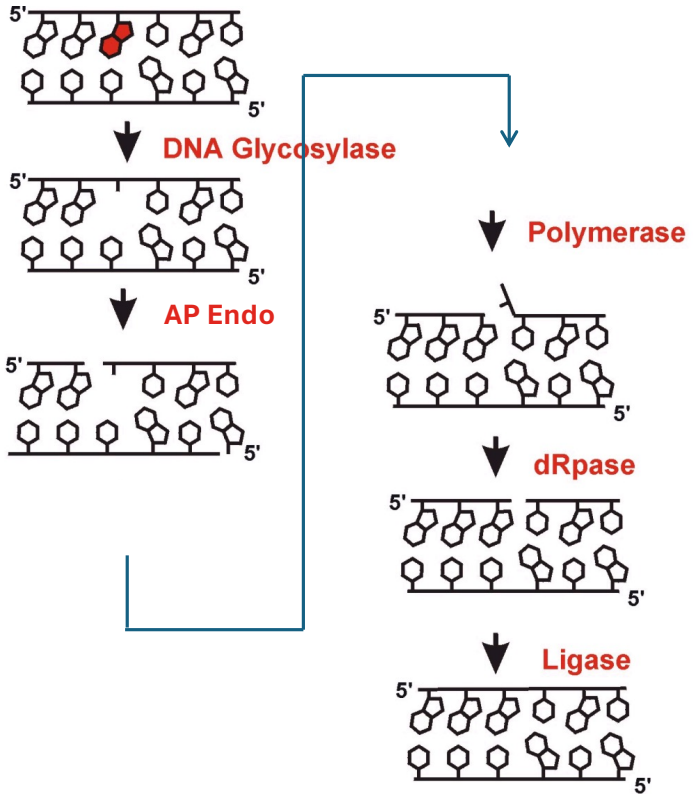
Duguid, E.M., Rice, P.A., He, C

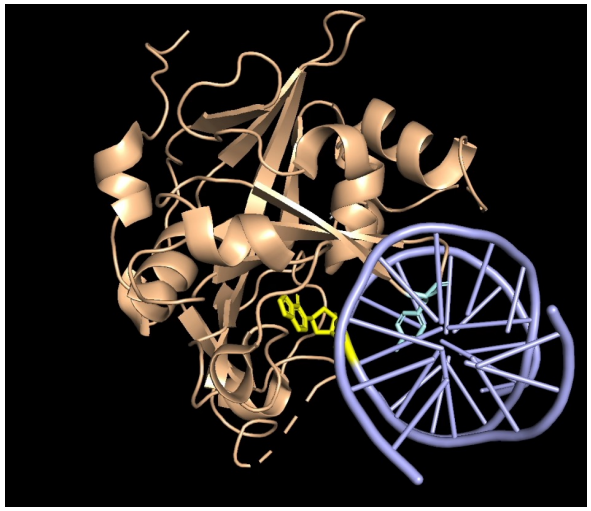
Aag-Initiated Base Excision Repair





3MeA

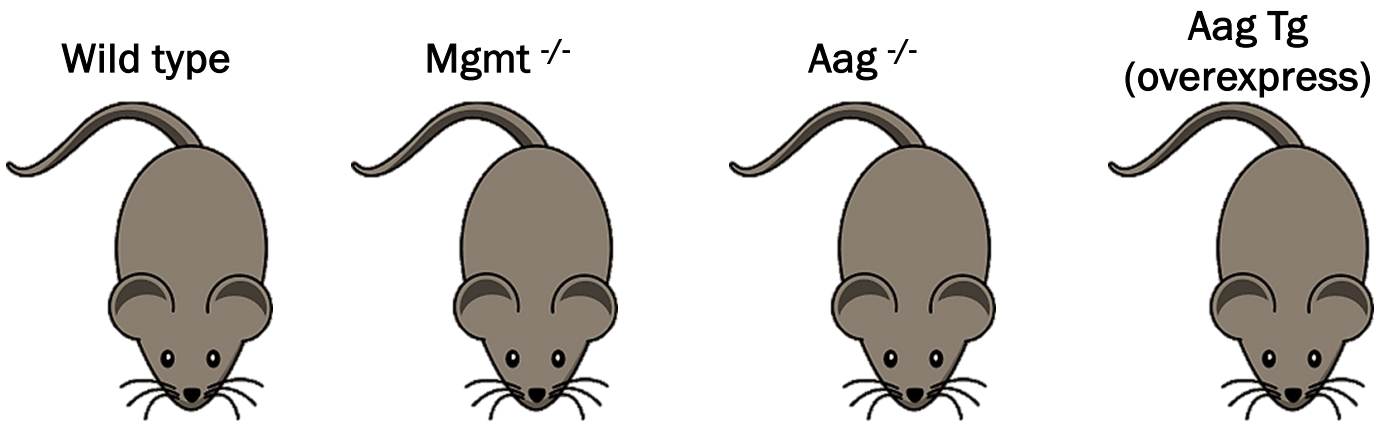




A. Lau...L. Samson, T. Ellenberger

AAG = Alkyladenine DNA Glycosylase

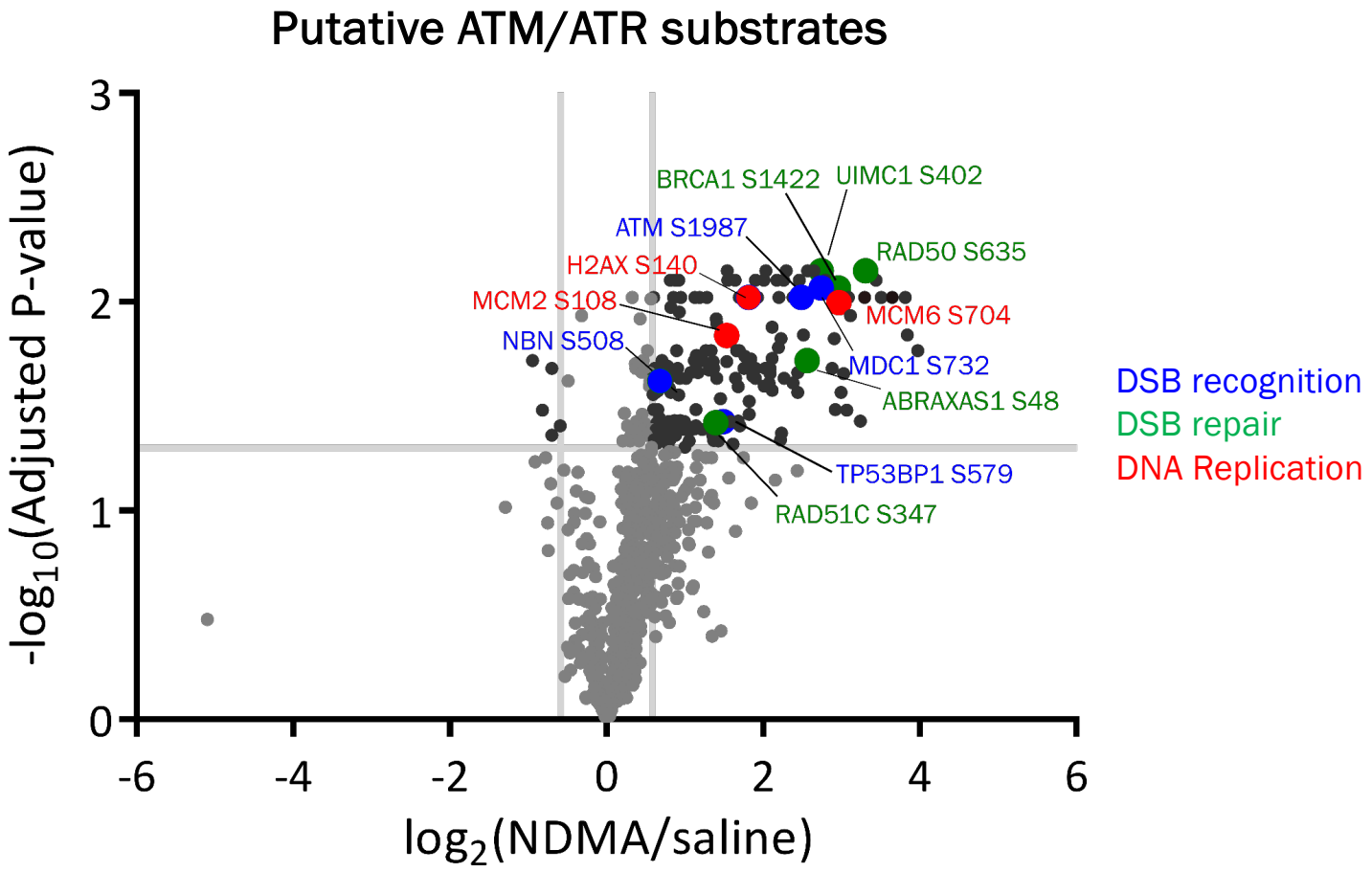
What are the molecular mechanisms underlying the carcinogenic effects of NMDA exposure?



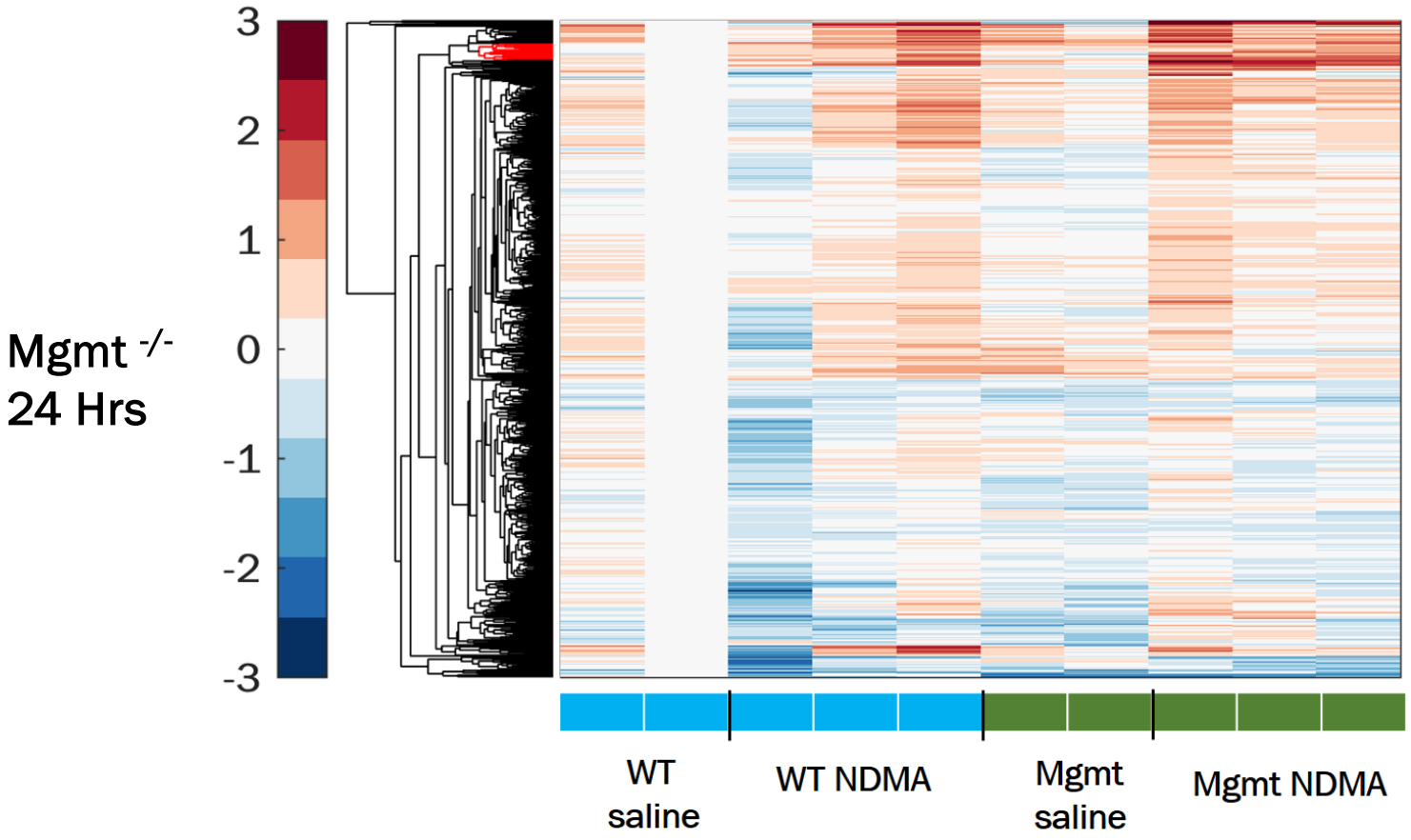
24 Hrs
(Early response)

10 weeks
(Late response)

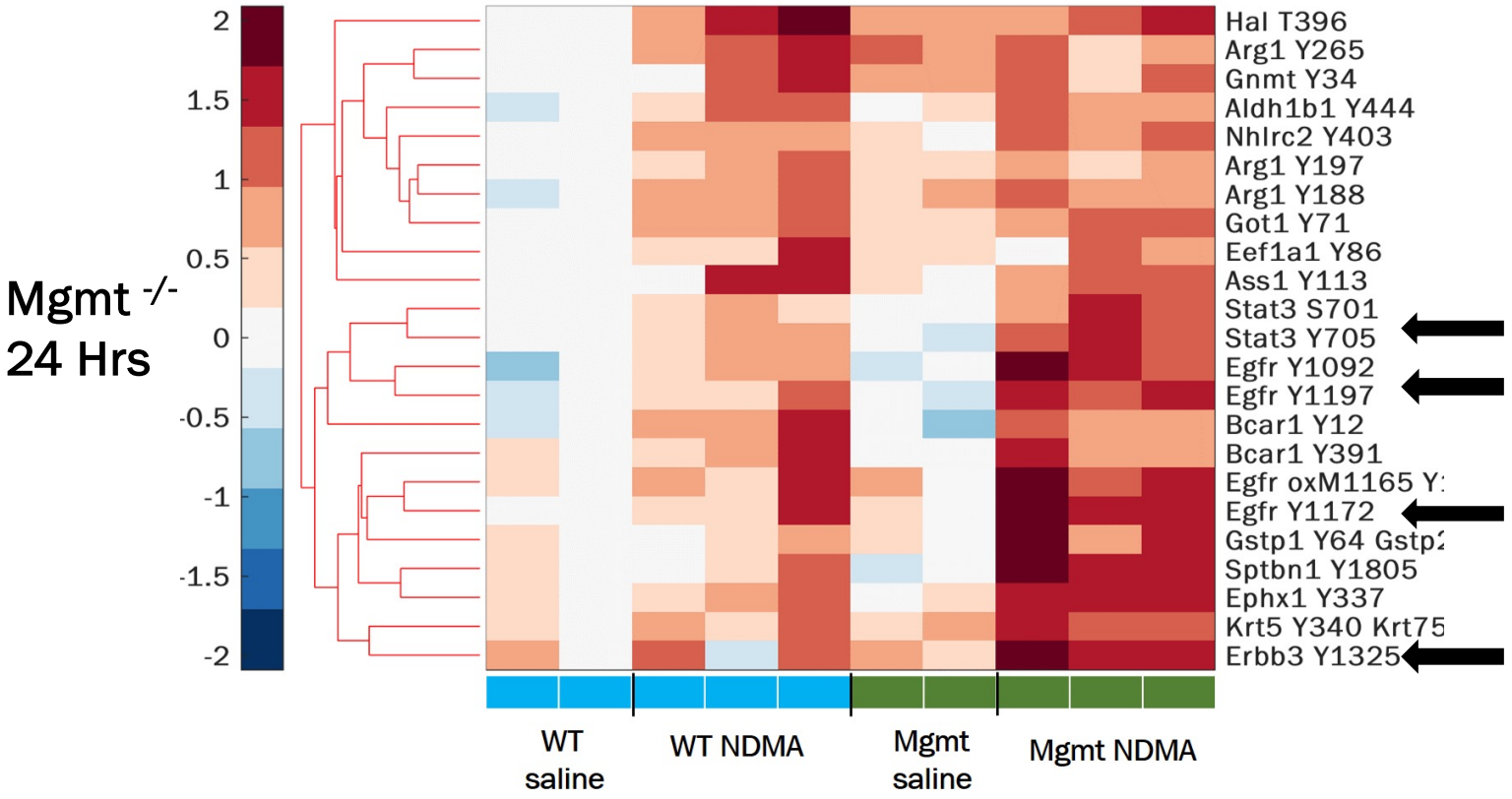
NDMA treatment induces phosphorylation of proteins involved in DNA damage response (24 hour timepoint)



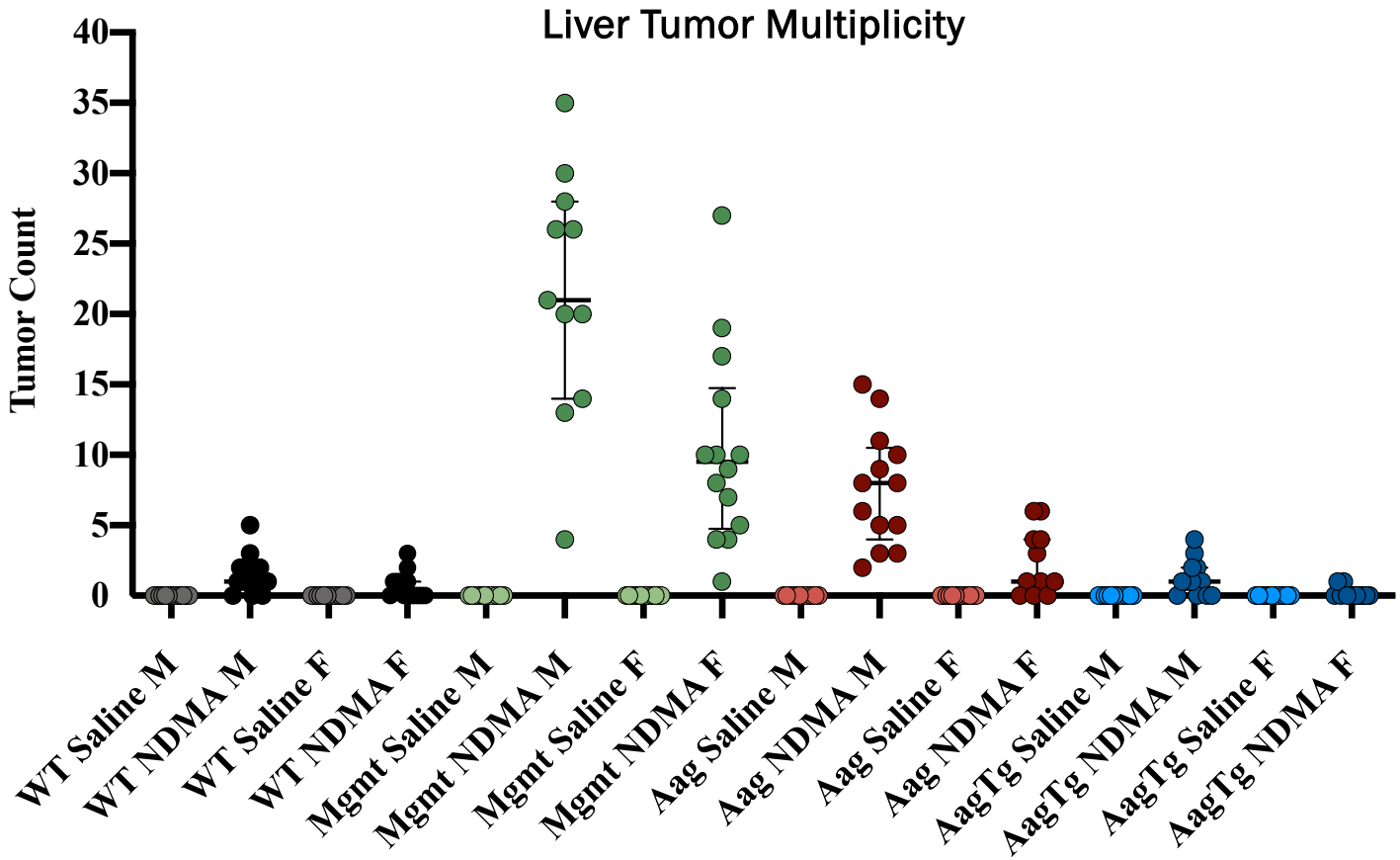
NDMA leads to phosphotyrosine changes



Inflammation and growth associated proteins are upregulated in response to NDMA



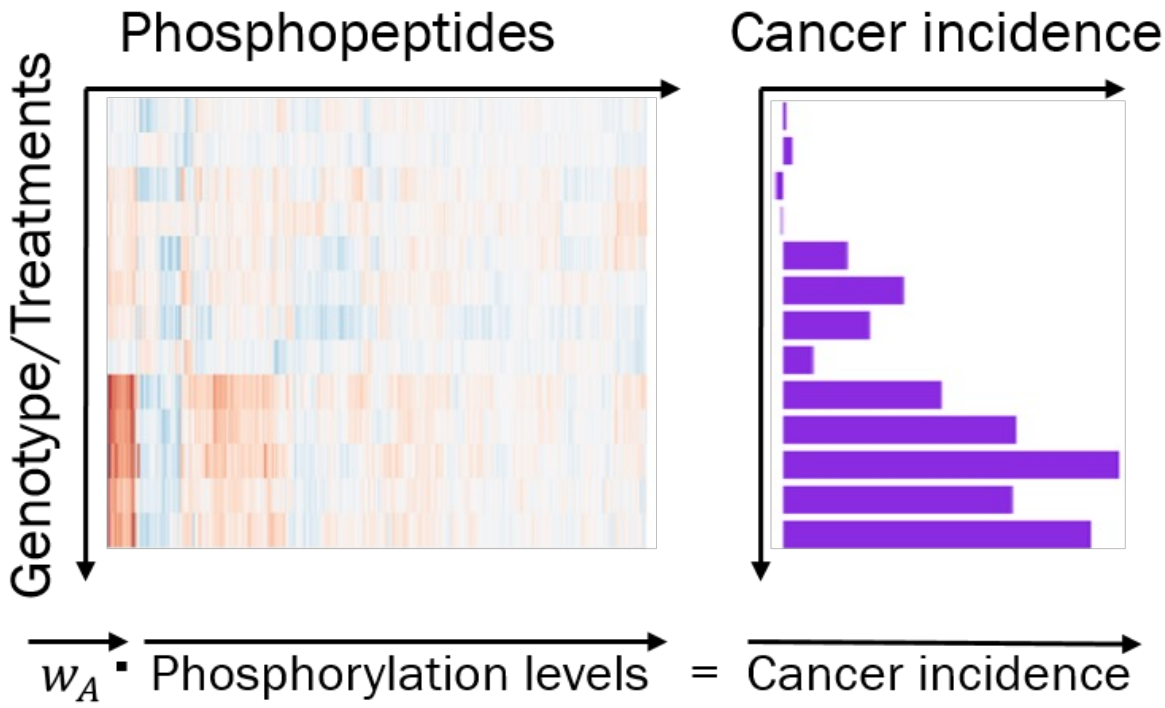
NDMA induces liver cancer at 10 months



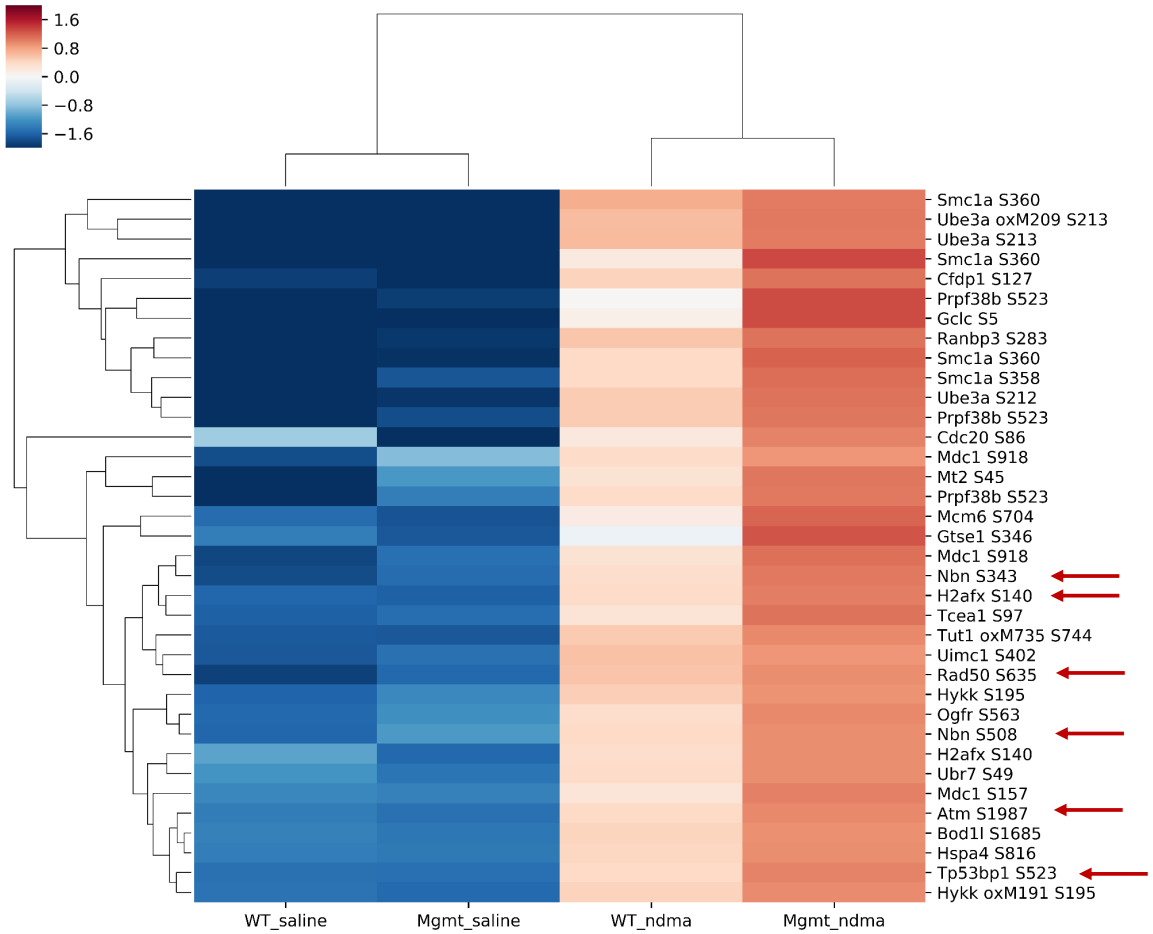
Jenny Kay, Joshua Corrigan

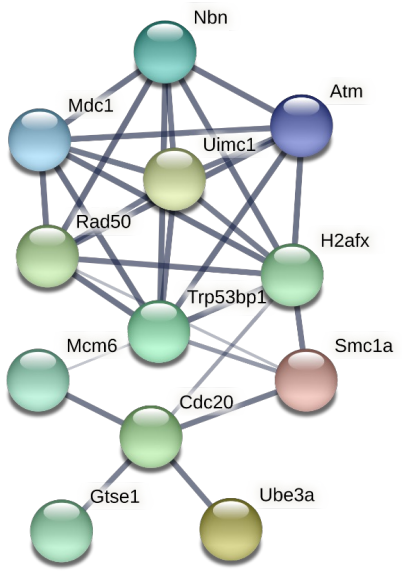
Is phosphorylation at early time points predictive of liver cancer at 10 months?

Are phosphorylation levels at early time points correlated with cancer incidence phenotype?

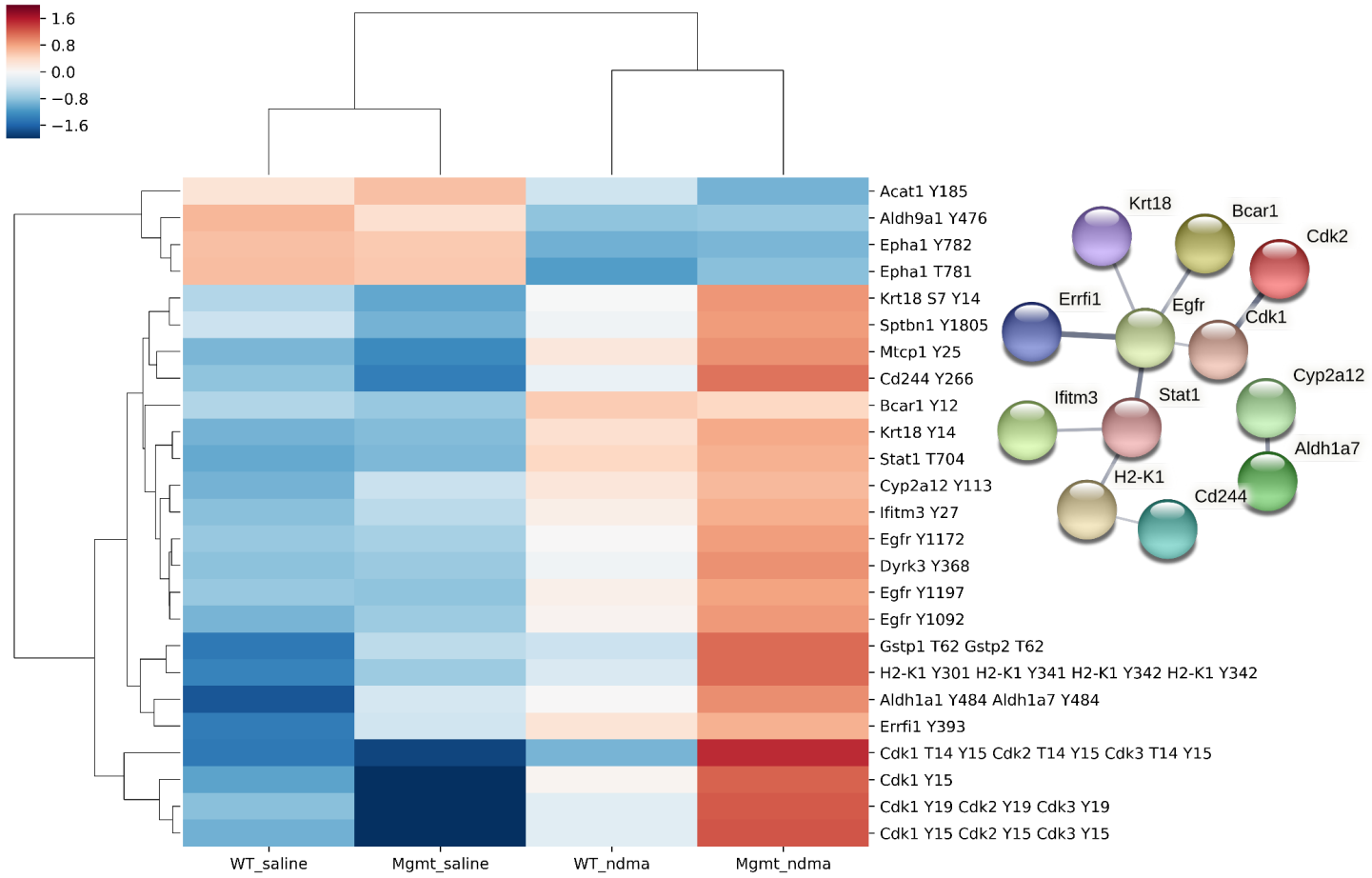


DNA Damage Response phosphorylation sites associated with cancer incidence





Phosphotyrosine sites associated with cancer incidence



What do we learn from these models?

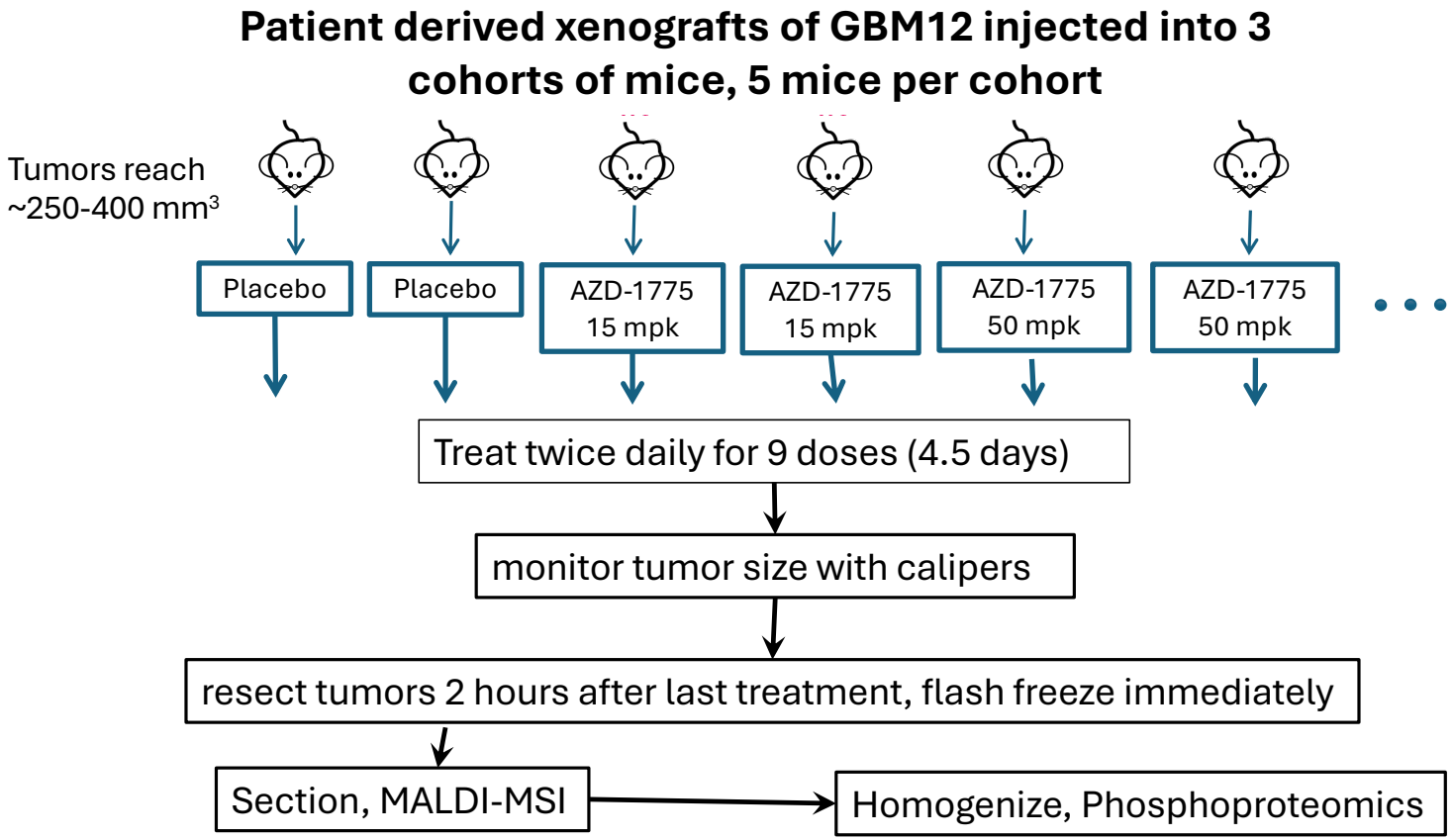
Exposure level (e.g., amount of DNA damage incurred) in early days is highly predictive of tumor development almost a year later

Exposure to environmental contaminants leads to a systems-level response, including upregulation of inflammation / growth / repair pathways --- these pathways include multiple oncogenic kinases and their levels are also highly predictive of future tumor development.

Data not shown – DNA damage response is largely repaired within 6 weeks, but growth / inflammation signaling remains high. This suggests that inhibiting or otherwise interfering with these pathways/networks may delay or block tumor progression.

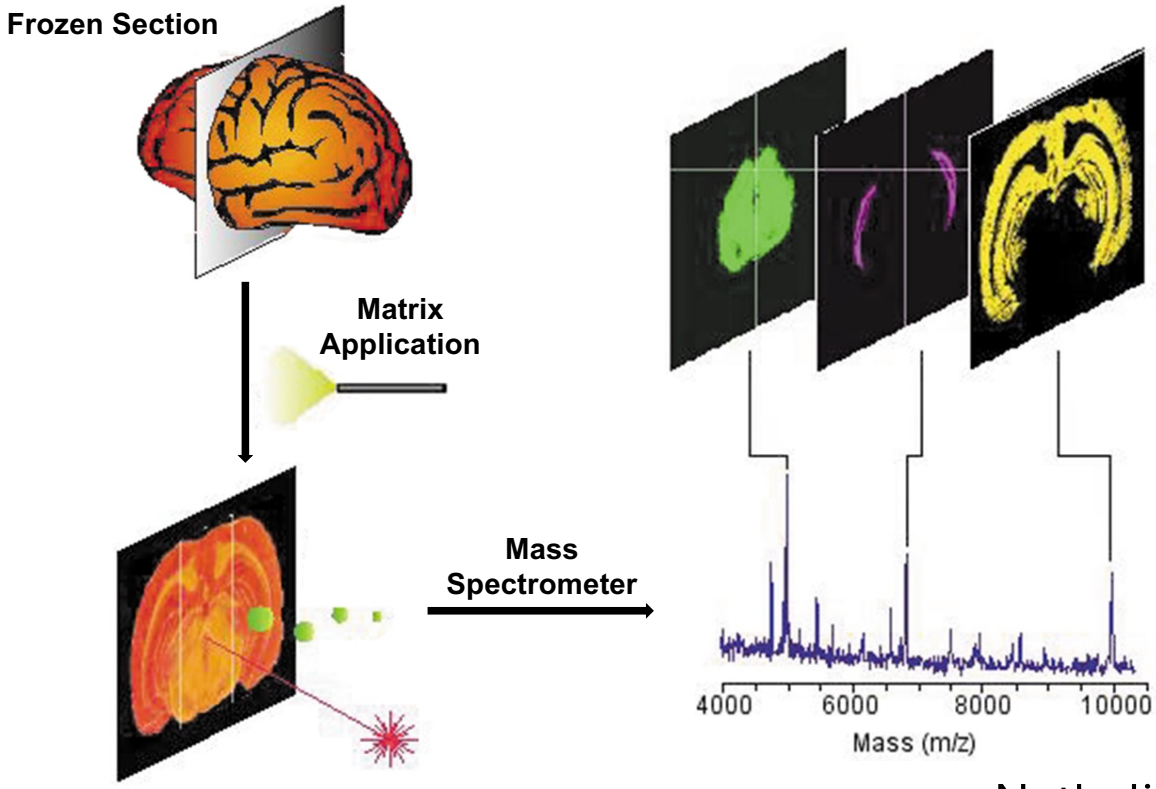
Adavosertib (MK-1775 / AZD-1775) is a wee1 kinase inhibitor that blocks the G1/S checkpoint, causing the cell to undergo mitotic catastrophe due to proliferation in the presence of DNA damage. Adavosertib is in multiple clinical trials – can we use this same framework to define biomarkers of drug efficacy in pre-clinical and clinical trials?

Quantifying AZD-1775 distribution and drug efficacy in vivo: GBM PDX



Study repeated with GBM22 and GBM84, with flank and intracranial tumors

Matrix-assisted laser desorbtion-ionization mass spectrometry imaging (MALDI-MSI) analysis of drug concentration, lipids, metabolites, and other biomolecules



Nathalie Agar, BWH/DFCI

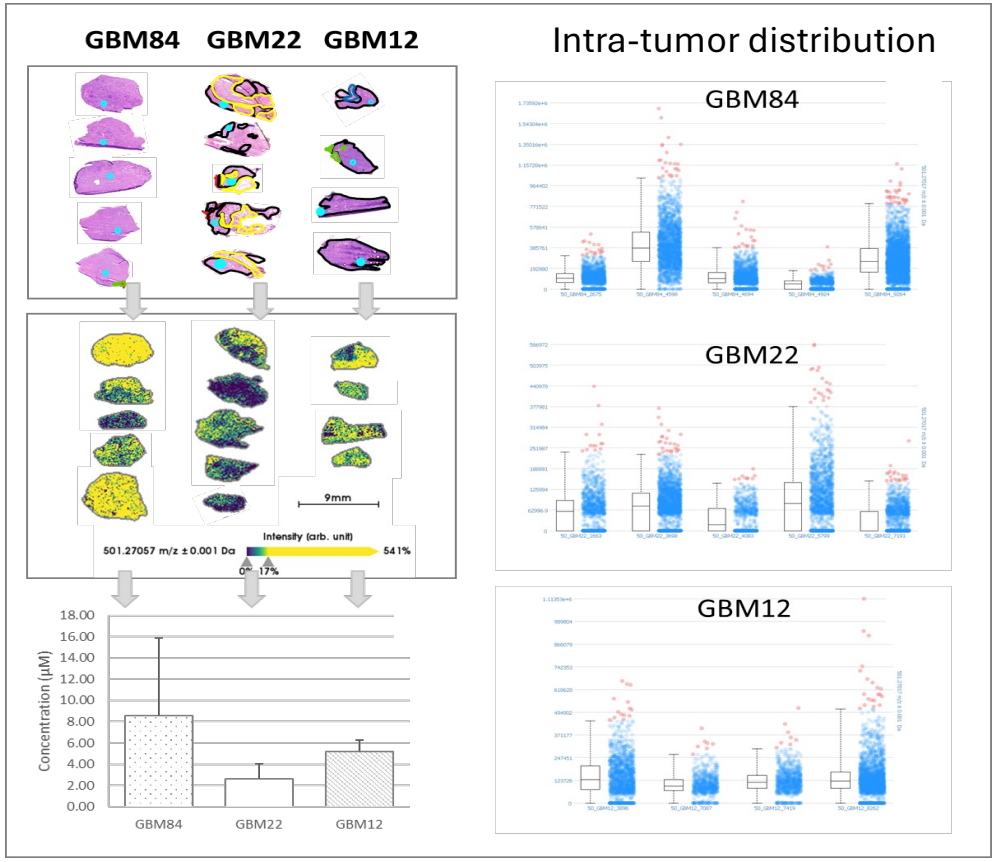
Stoeckli M, Chaurand P, Hallahan DE, Caprioli RM. (2001) Imaging mass spectrometry: a new technology for the analysis of protein expression in mammalian tissues. *Nat Med.* **7**(4):493-6.

MALDI-MSI shows high heterogeneity of AZD-1775 distribution in flank tumors

H&E staining
Yellow = necrosis

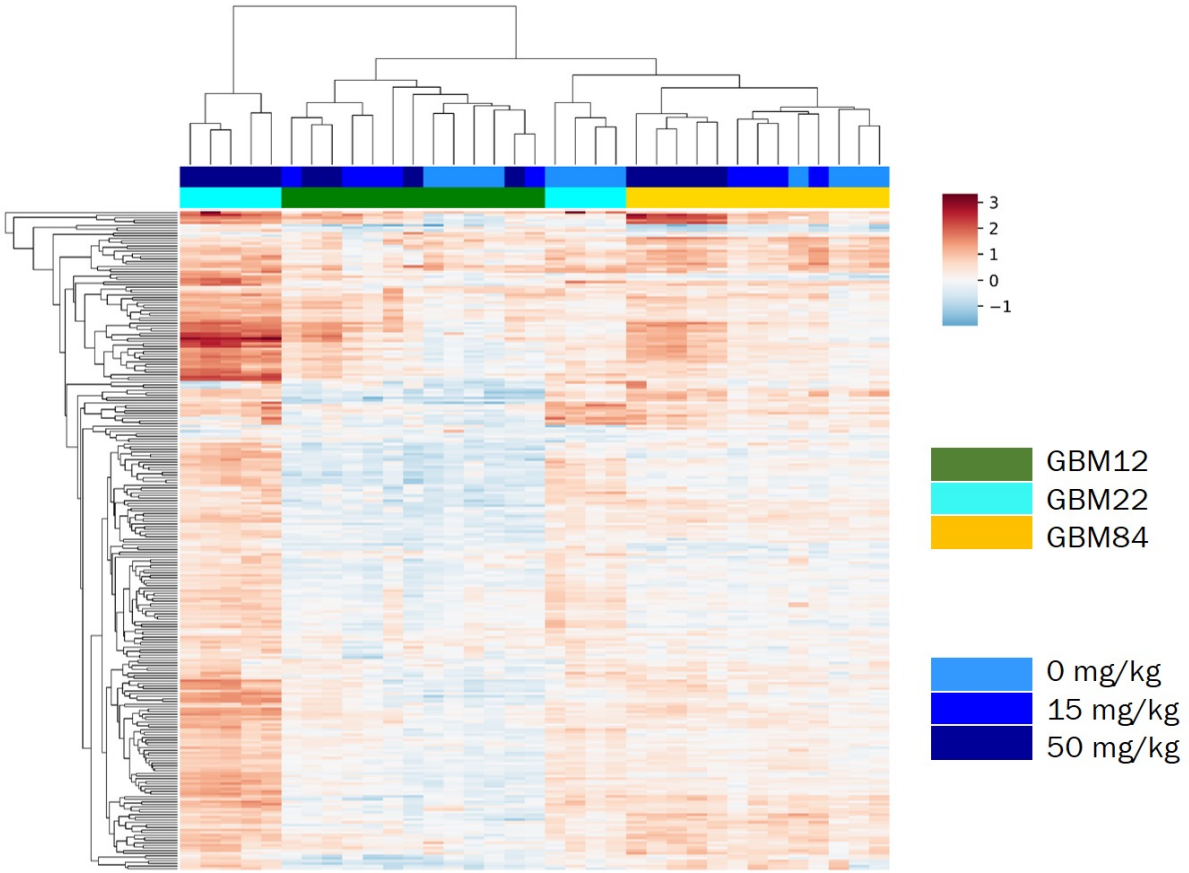
AZD1775 drug

Average AZD1775 drug

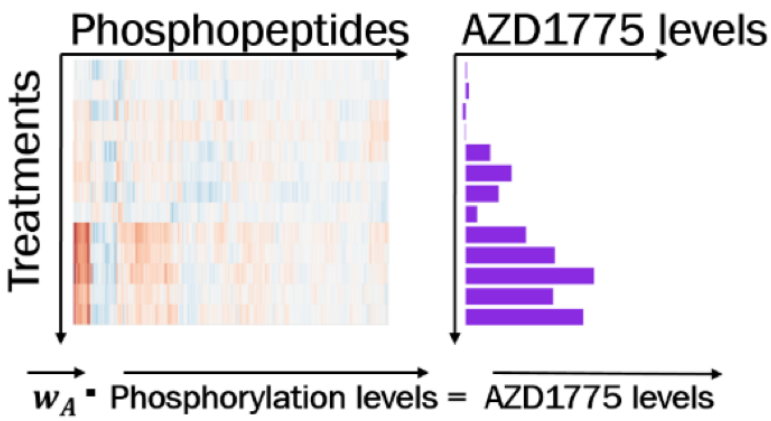


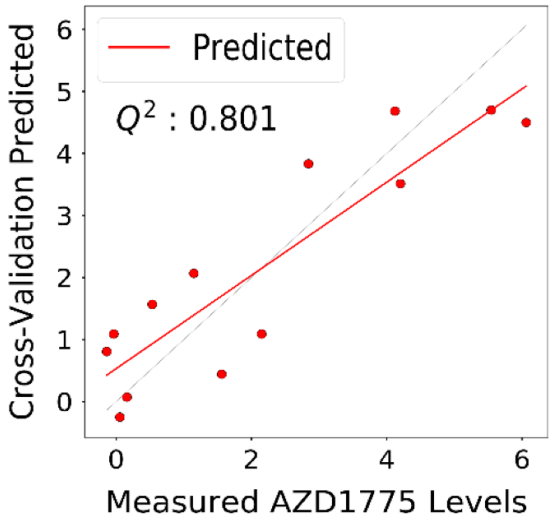
Take-home: Drug distribution can have high intra- and inter-tumor heterogeneity, even in flank tumors.

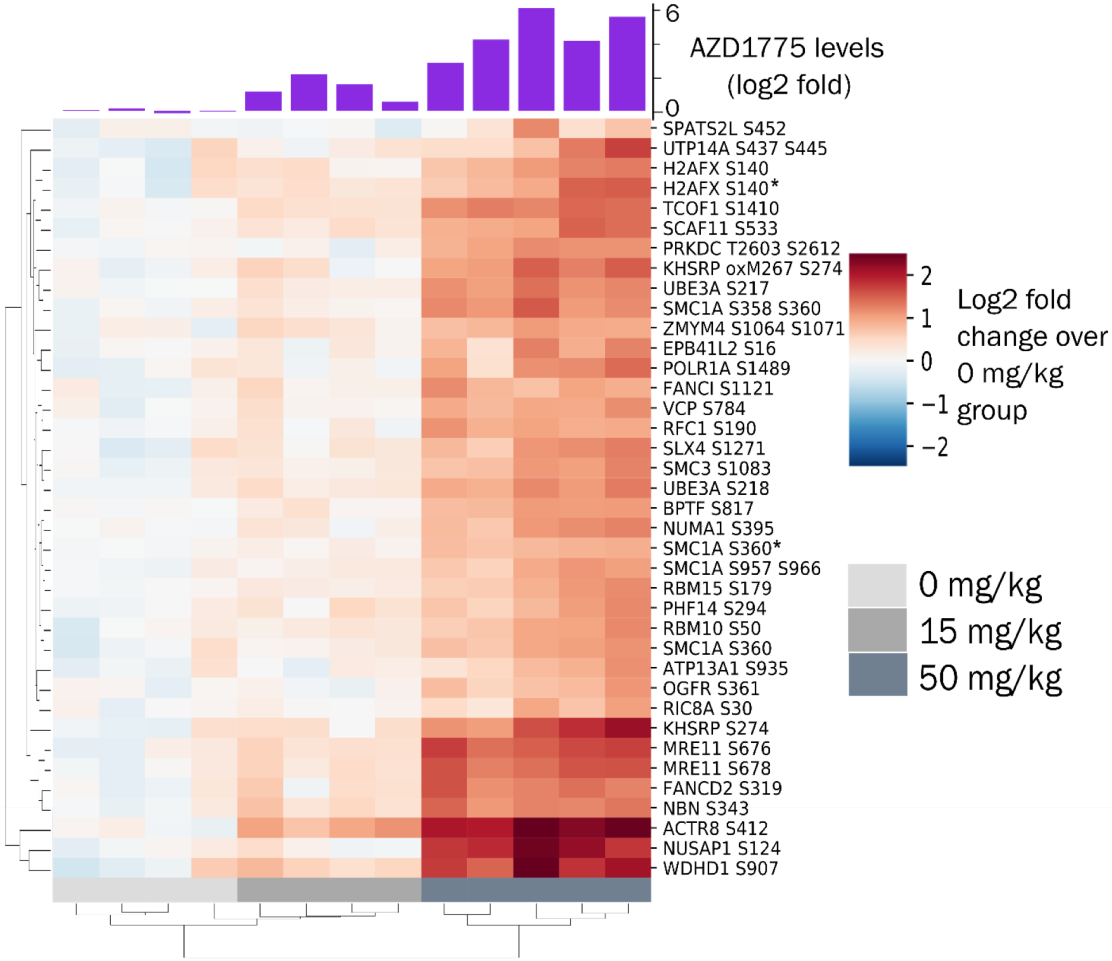
Quantifying AZD-1775 drug efficacy: DNA damage signaling in flank tumors



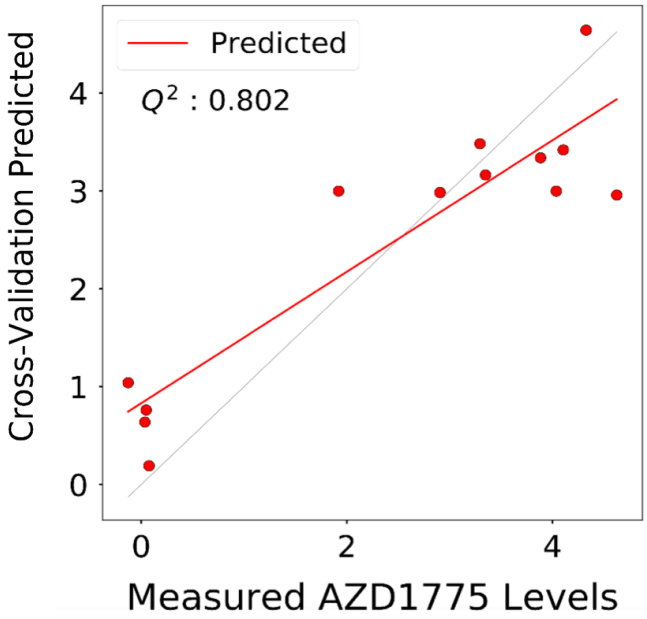
Data integration: Partial least-squares regression (PLSR) model to connect GBM84 phosphoproteomic and drug levels

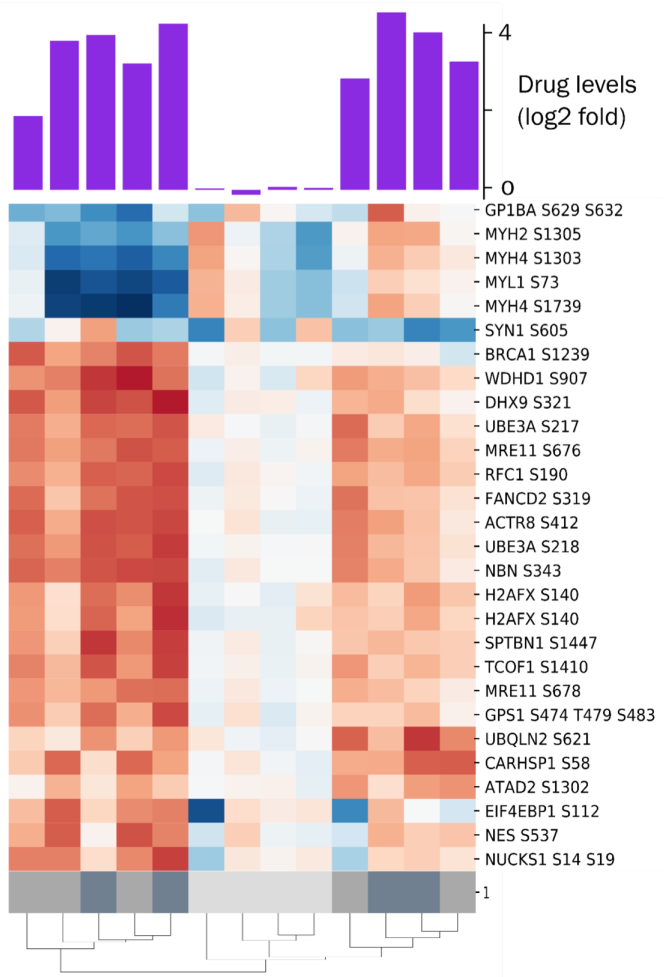




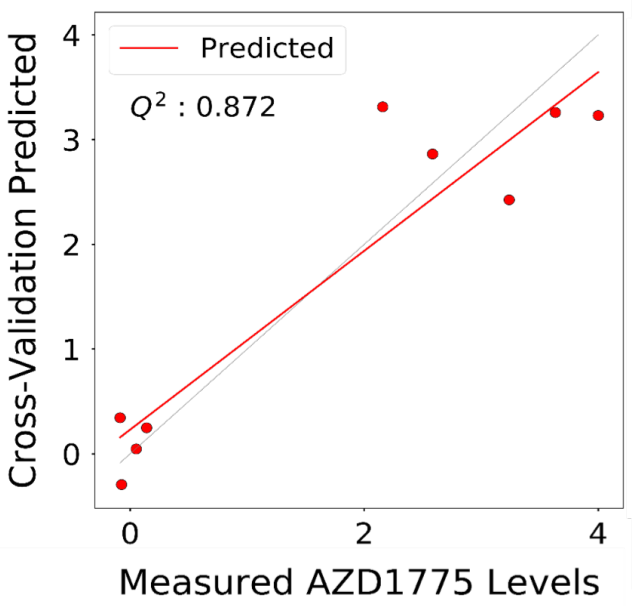


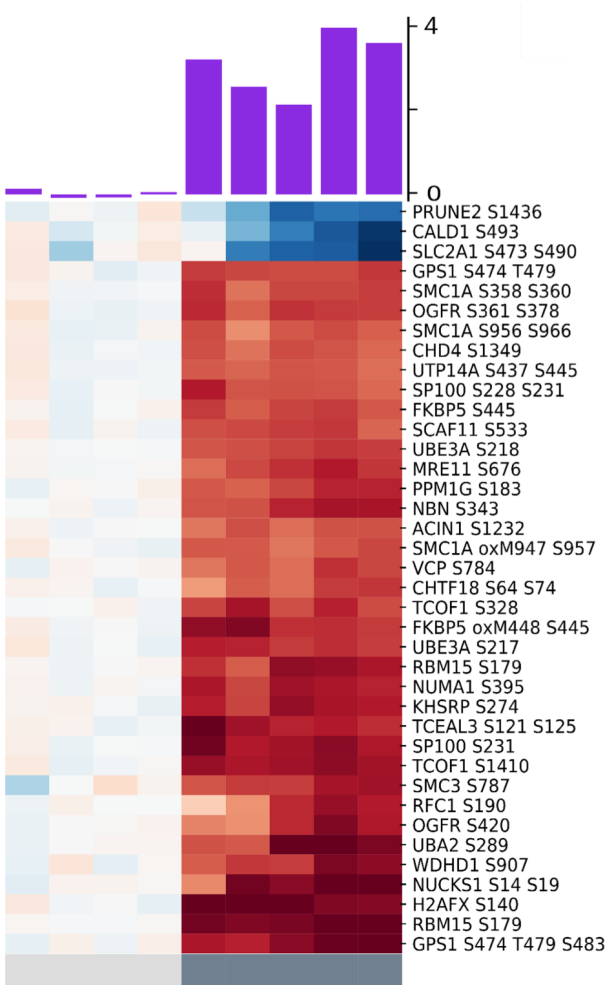
Data integration: Partial least-squares regression (PLSR) model to connect GBM12 phosphoproteomic and drug levels



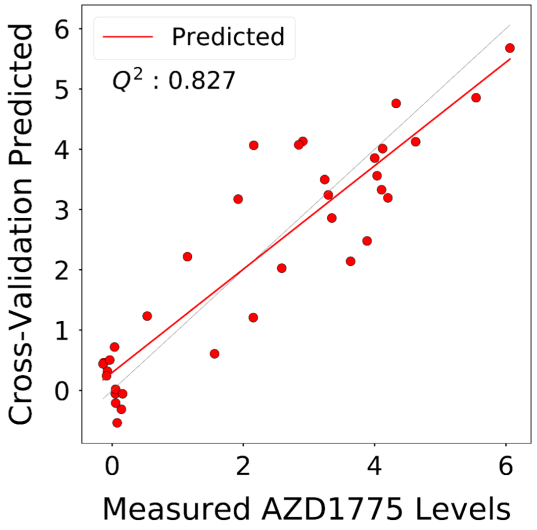


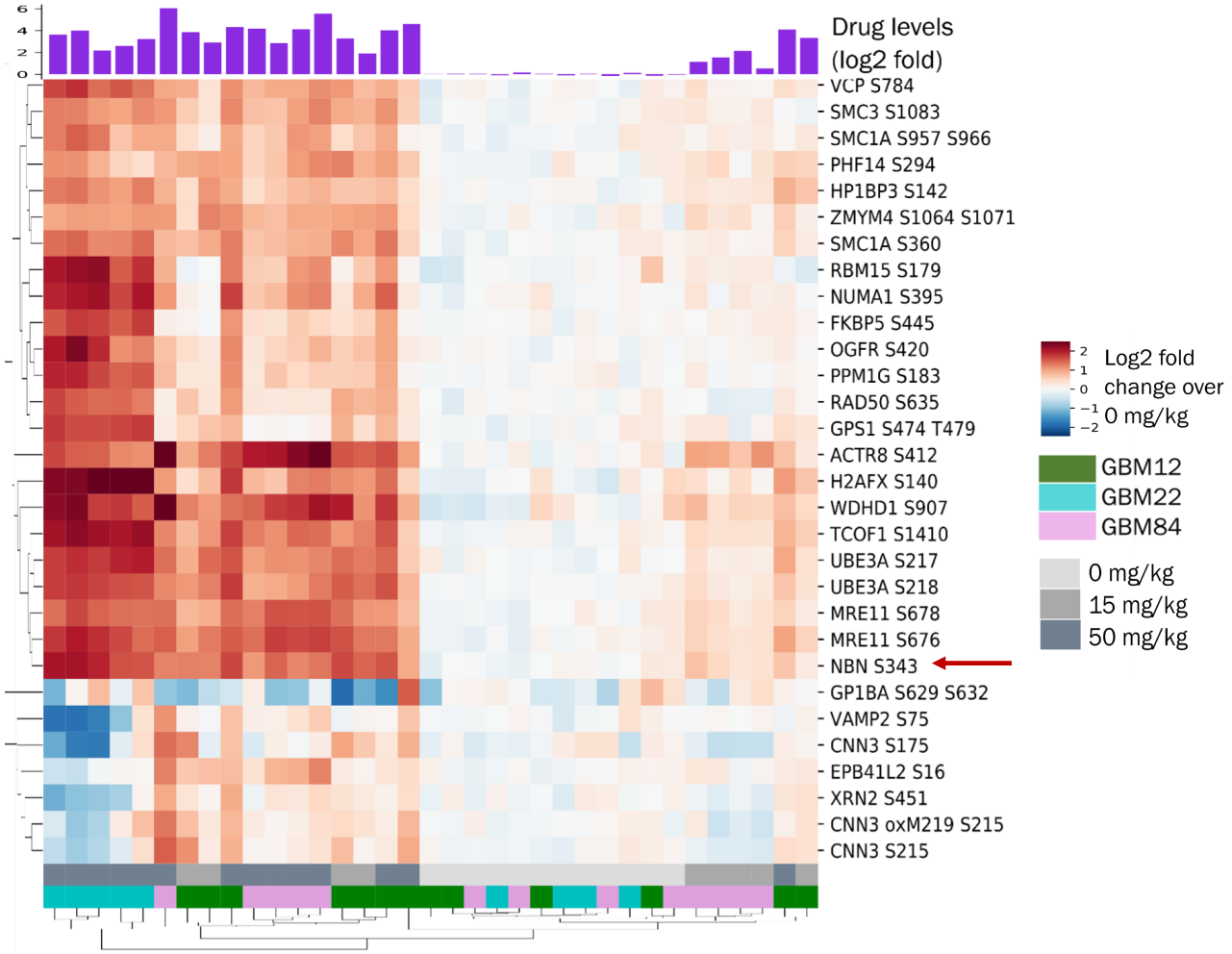
Data integration: Partial least-squares regression (PLSR) model to connect GBM22 phosphoproteomic and drug levels



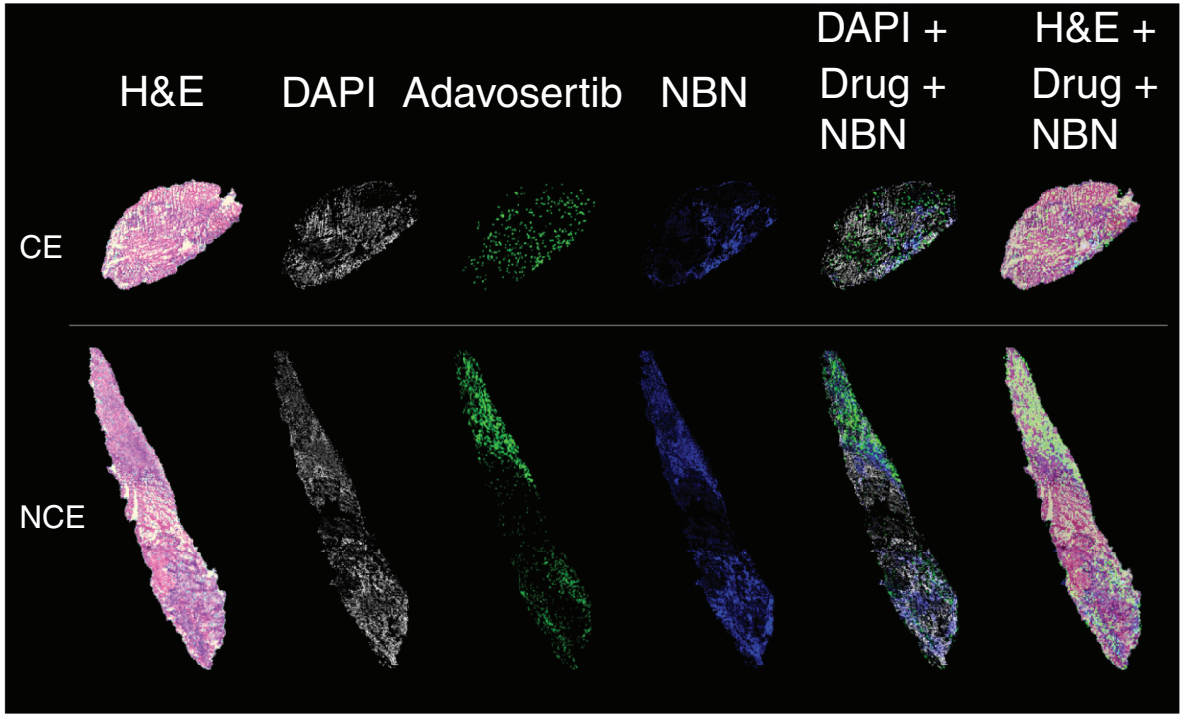


‘Cross-model’ model: integrating AZD1775 drug level and phosphorylation data across 45 flank tumors





Extension to clinical trial tissue specimens: Phospho-Nibrin directly correlates with adavosertib drug distribution in GBM tumor tissue



CE = contrast enhancing (tumor core)
NCE = non-contrast enhancing (tumor rim)

Neuro-Oncology
24(1), 64–77, 2022 | https://doi.org/10.1093/neuonc/noab197 | Advance Access date 12 August 2021

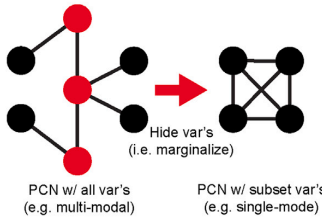
Multimodal platform for assessing drug distribution and response in clinical trials

Begoña G. C. Lopez,† Ishwar N. Kohale,† Ziming Du,† Ilya Korsunsky, Walid M. Abdelmoula, Yang Dai, Sylwia A. Stopka, Giorgio Gaglia, Elizabeth C. Randall, Michael S. Regan, Sankha S. Basu, Amanda R. Clark, Bianca-Maria Marin, Ann C. Mladek, Danielle M. Burgenske, Jeffrey N. Agar, Jeffrey G. Supko, Stuart A. Grossman, Louis B. Nabors, Soumya Raychaudhuri, Keith L. Ligon, Patrick Y. Wen, Brian Alexander, Eudocia Q. Lee, Sandro Santagata, Jann Sarkaria, Forest M. White, and Nathalie Y. R. Agar

New directions – using partial correlation network analysis to infer networks and critical nodes from multi-omic data, including phenotypic data

Cell Systems

CellPress
OPEN ACCESS



Article

Markov field network model of multi-modal data predicts effects of immune system perturbations on intravenous BCG vaccination in macaques

Shu Wang,[1,8] Amy J. Myers,[2,8] Edward B. Irvine,[3,4] Chuangqi Wang,[5] Pauline Maiello,[2] Mark A. Rodgers,[2] Jaime Tomko,[2] Kara Kracinovsky,[2] H. Jacob Borish,[2] Michael C. Chao,[4] Douaa Mugahid,[4] Patricia A. Darrah,[6] Robert A. Seder,[6] Mario Roederer,[6] Charles A. Scanga,[2] Philana Ling Lin,[7] Galit Alter,[3] Sarah M. Fortune,[3,4] JoAnne L. Flynn,[2] and Douglas A. Lauffenburger[1,9,*]

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https://doi.org/10.1016/j.cels.2024.10.001