Expanding the universe of cancer therapies by targeting aneuploidy
Our team – experienced biotech veterans and leaders in studying aneuploidy

**Ali Fattaey, PhD.** Formerly the CEO of Metabomed, formerly the CEO of Curis.

**Jason Sheltzer, PhD.** PI at Yale. Co-founder of Meliora Therapeutics, SAB at Tyra Biosciences and BioIO.

**Matthew Meyerson, MD PhD.** PI at Dana-Farber. Co-founder of Foundation Medicine.

**Rameen Beroukhim, MD PhD.** PI at Dana-Farber. SAB at Scorpion Therapeutics.

**Teresa Davoli, PhD.** PI at NYU. SAB at io9.

**Alison Taylor, PhD.** PI at Columbia.
Most cancer patients cannot currently be treated with a targeted therapy.

62.4% of patients have no actionable mutations. Flaherty et al., JCO 2020
90% of cancers have massive chromosome copy number changes - a condition called aneuploidy

Aneuploidy is **ubiquitous** in cancer but **rare** in normal tissue
We have made breakthroughs that allow us to model and target aneuploidy for the first time

We have developed:

- Tools to generate cell line and organoid models with specific aneuploid chromosomes.
- Computational modeling to uncover the genes that drive high-frequency aneuploidies.
- Experimental and computational techniques to identify tractable therapeutic vulnerabilities in aneuploid cancers.

Davoli Lab, Cell 2023
Beroukhim and Taylor Labs, Nature 2023
Sheltzer Lab, Science 2023
We now have an unprecedented opportunity to develop a coordinated, systematic attack on aneuploidy in cancer.
Proof of principle: UCK2 substrates are selectively toxic to cancer cells with a trisomy of Chromosome 1q

# of US cancer patients per year: \( >200,000 \)

Sheltzer Lab, Science 2023
De-risking: genetic validation and generation of a tool compound to target cells with a specific aneuploidy

- We identified a druggable dependency that exhibits a 95% correlation with a specific aneuploidy.
- This aneuploidy is present in ~9% of all cancers.
1q-trisomy tumor

1q-disomy tumor

Happy to answer any questions!
“Aneuploidy addictions” - an evolutionary trap for drug resistance

- Certain aneuploidies are required for tumor formation.

- Therapies could select against specific aneuploidies - but the resulting aneuploidy-loss cells will have lower tumor-forming potential!

- This creates an evolutionary trap, pushing cells toward a non-malignant state.
“Aneuploidy addictions” - an evolutionary trap for drug resistance
Aneuploidies: the most common genetic events in cancer

Shih et al., *Nature* 2023
Proof of principle - 7p gains

Target Market Size

- chr7p gain
  - brain 75%
  - melanoma 50%
  - lung 40%
  - colorectum 50%

Colon cancer line - trisomy 7p

Colon cancer line - disomy 7p

Inhibitor of Gene X

Isogenic colon cancer lines

Panel of Colon cancer Cell lines
Chemical screen top hit in same pathway