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.

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

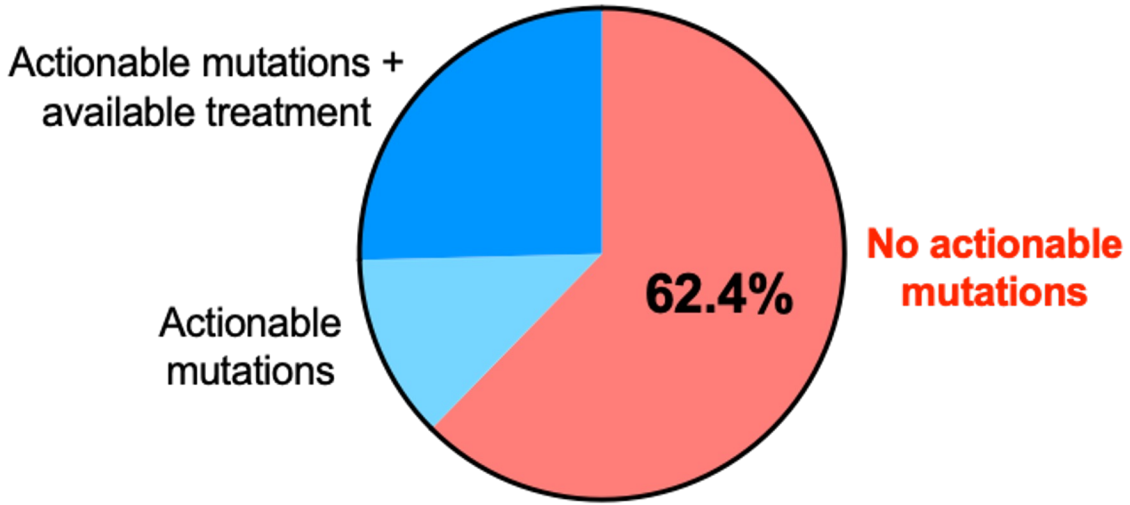
Jason Sheltzer, PhD. PI at Yale. Co-founder of Meliora Therapeutics, SAB at Tyra Biosciences and BioIO.

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

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

Alison Taylor, PhD. PI at Columbia.

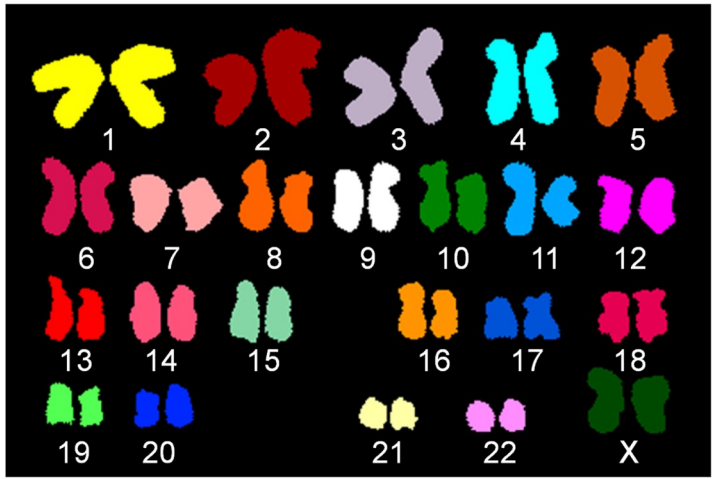
Most cancer patients cannot currently be treated with a targeted therapy



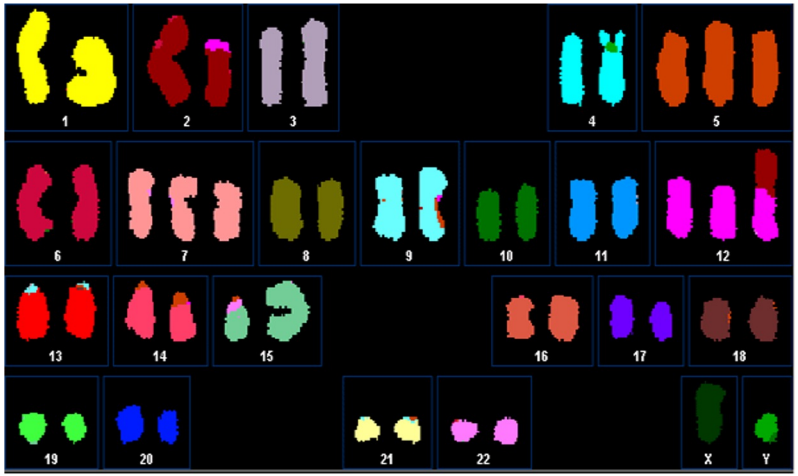
Flaherty et al., JCO 2020

90% of cancers have massive chromosome copy number changes - a condition called aneuploidy

Normal genome



Cancer genome



Aneuploidy is **ubiquitous** in cancer but **rare** in normal tissue

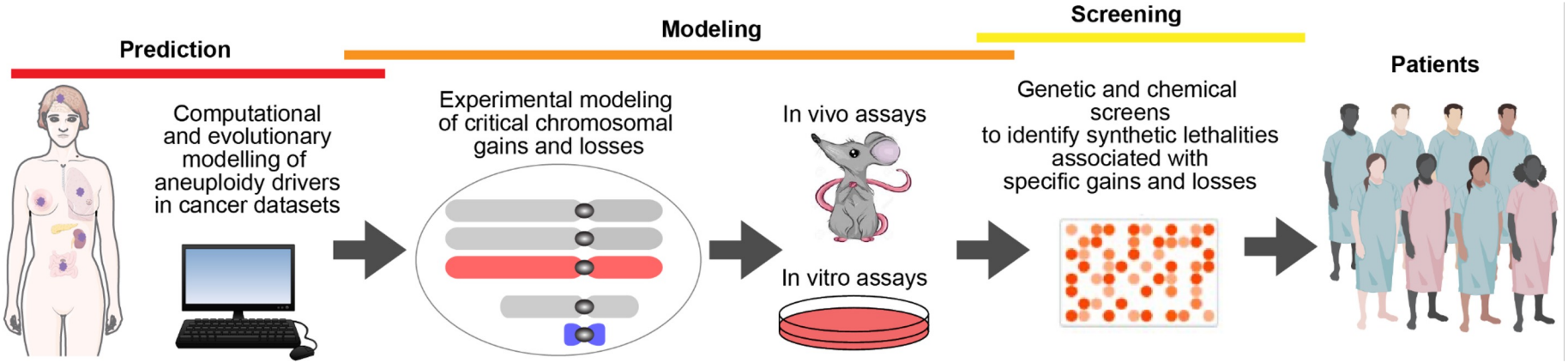
We have made breakthroughs that allow us to model and target aneuploidy for the first time

Davoli Lab, Cell 2023
Beroukhim and Taylor Labs, Nature 2023
Sheltzer Lab, Science 2023

We have developed:

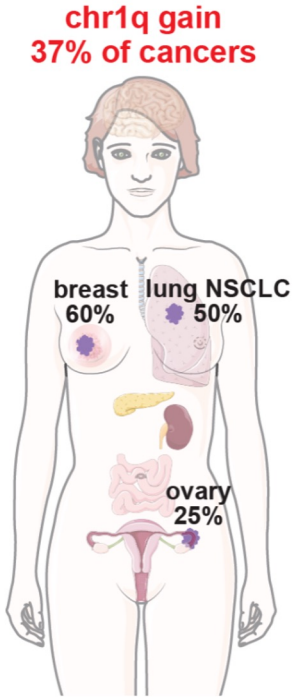
- Tools to generate cell line and organoid models with specific aneuploid chromosomes.
- Computational modeling to uncover the genes that drive high-frequency aneuploidies.
- Experimental and computational techniques to identify tractable therapeutic vulnerabilities in aneuploid cancers.

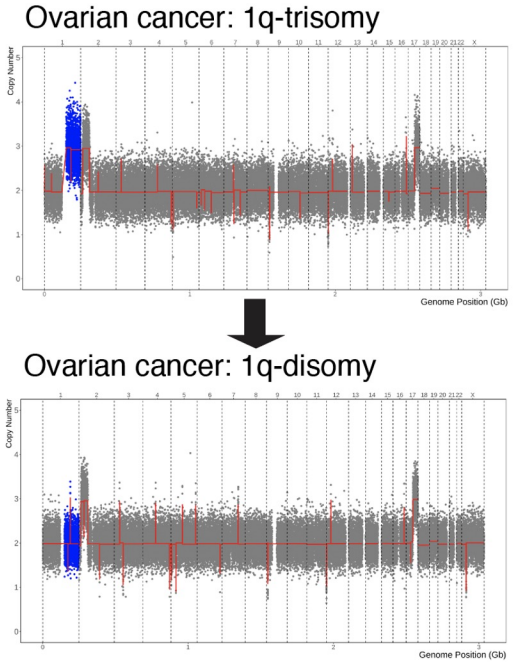
Targeting aneuploidy to tackle undruggable tumors

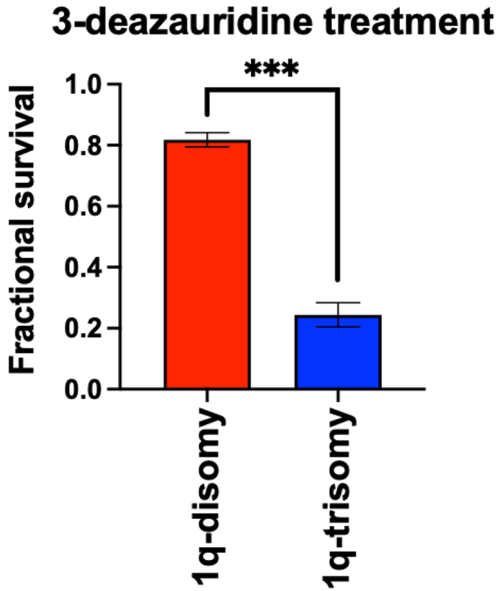


We now have an unprecedented opportunity to develop a coordinated, systematic attack on aneuploidy in cancer

Proof of principle: UCK2 substrates are selectively toxic to cancer cells with a trisomy of Chromosome 1q





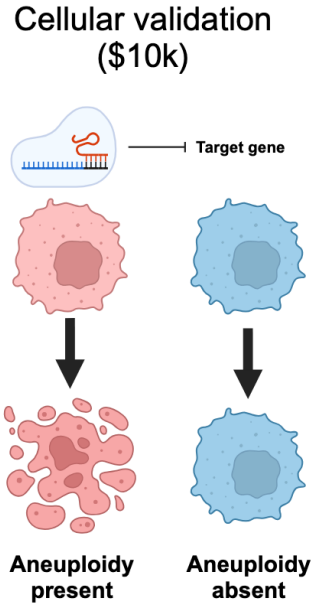


# of US cancer patients per year: **>200,000**

Sheltzer Lab, Science 2023

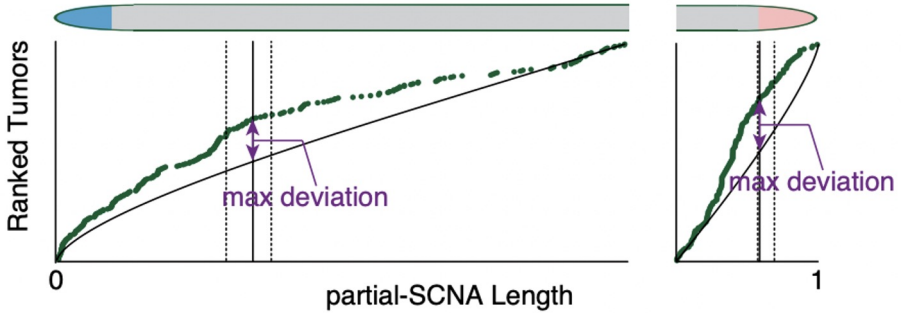
De-risking: genetic validation and generation of a tool compound to target cells with a specific aneuploidy

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

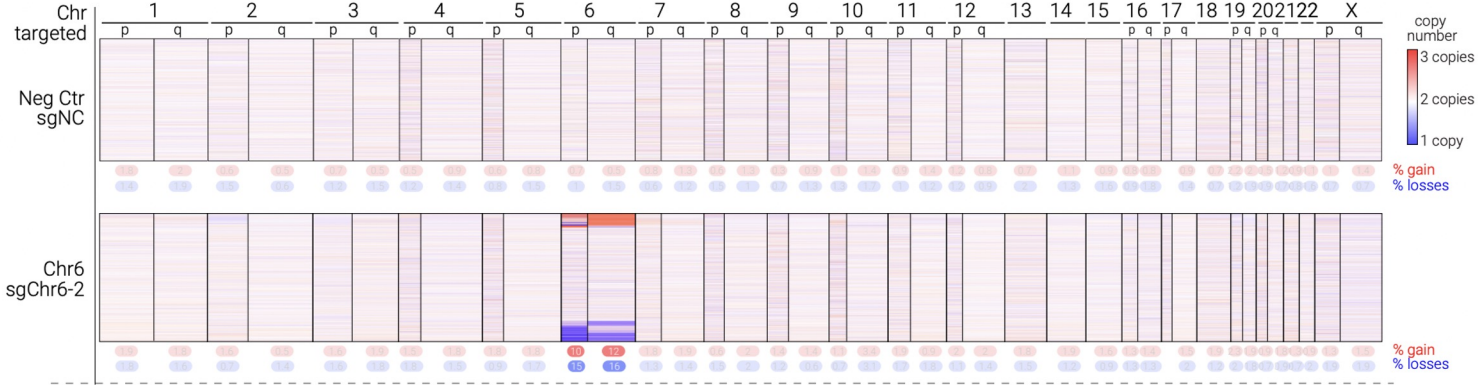


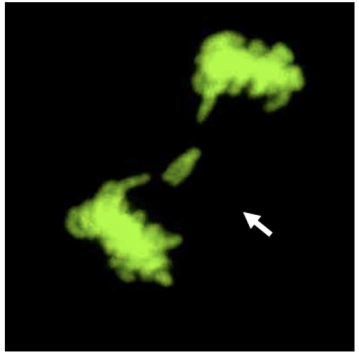
1q-trisomy tumor

1q-disomy tumor



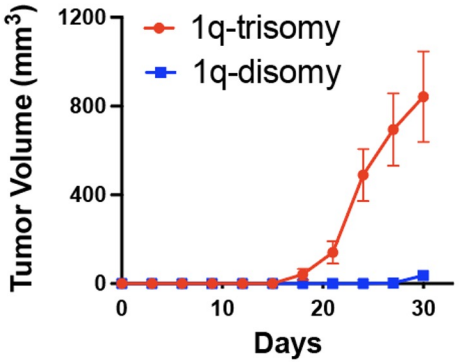
Happy to answer any questions!

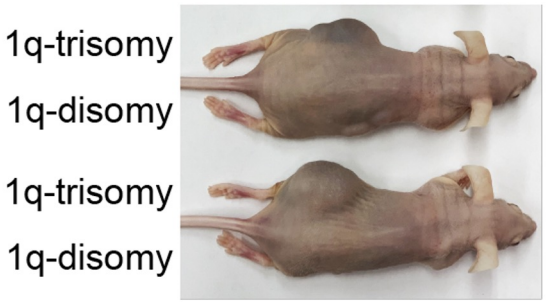




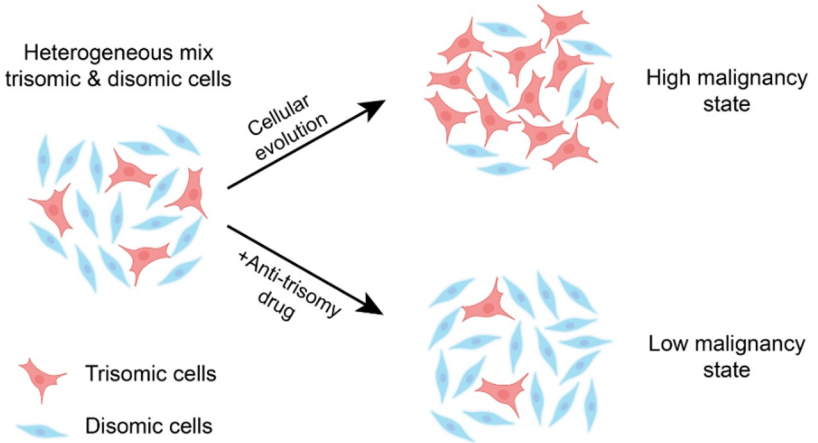
“Aneuploidy addictions” - an evolutionary trap for drug resistance

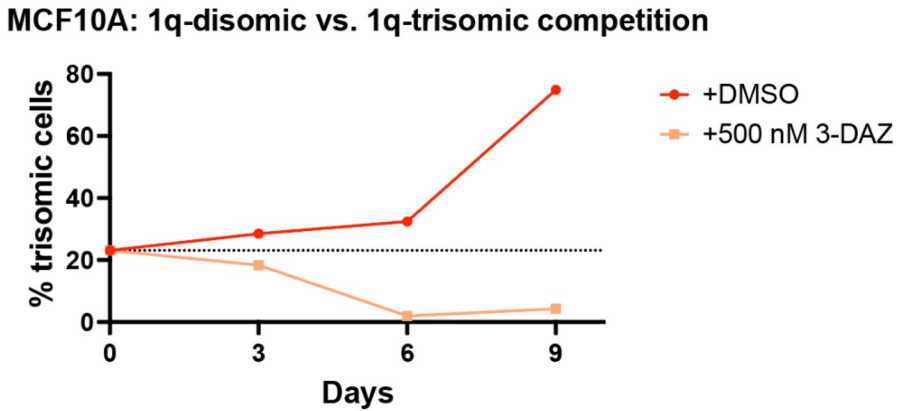
- Certain aneuploidies are required for tumor formation.
- Therapies could select against specific aneuploidies - but the resulting aneuploidy-loss cells will have lower tumor-forming potential!
- This creates an evolutionary trap, pushing cells toward a non-malignant state.





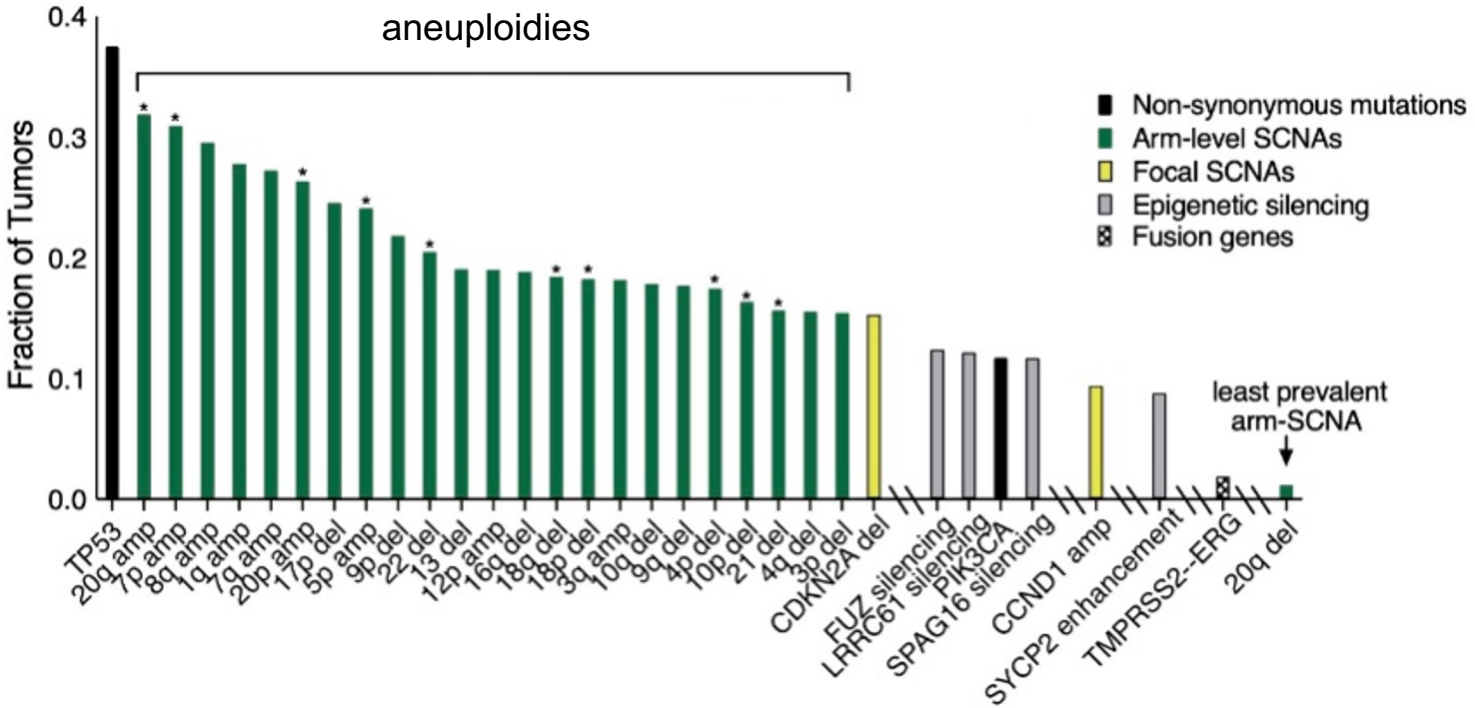
“Aneuploidy addictions” - an evolutionary trap for drug resistance





Sheltzer Lab, Science 2023

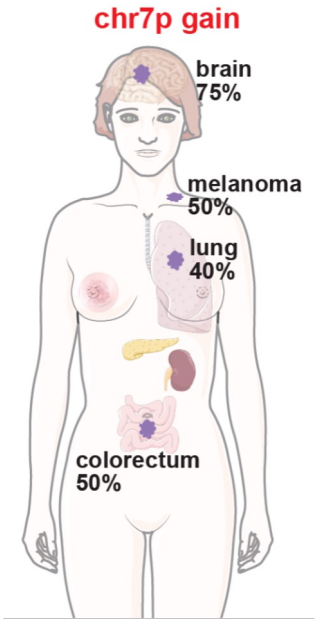
Aneuploidies: the most common genetic events in cancer



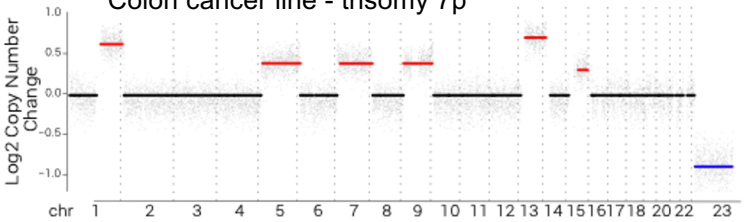
Shih et al., *Nature* 2023

Proof of principle - 7p gains

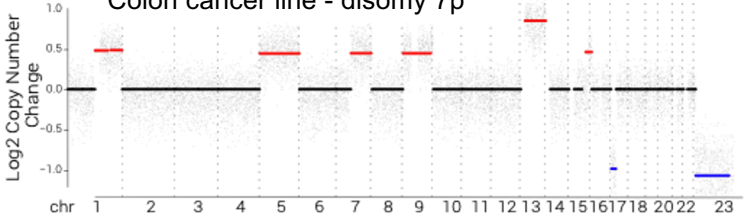
Target Market Size



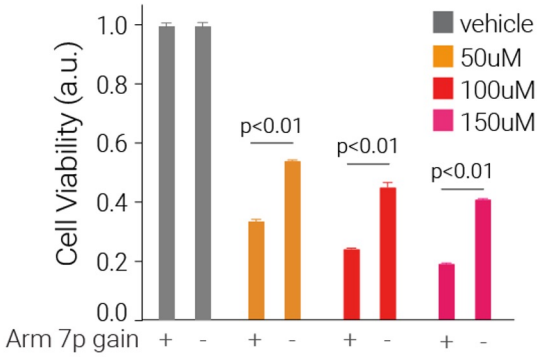
Colon cancer line - trisomy 7p



Colon cancer line - disomy 7p

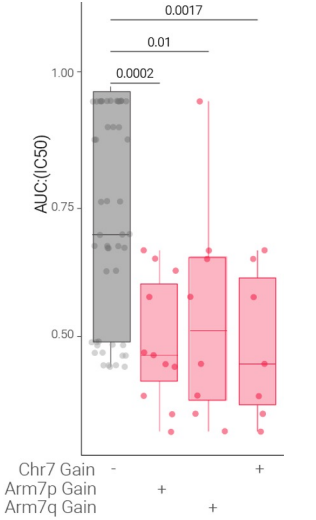


Inhibitor of Gene X



Isogenic colon cancer lines

Inhibitor of Gene X



Panel of Colon cancer Cell lines

Chemical screen top hit in same pathway