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Evaluating tumor evolution and mechanisms of resistance in osteosarcoma

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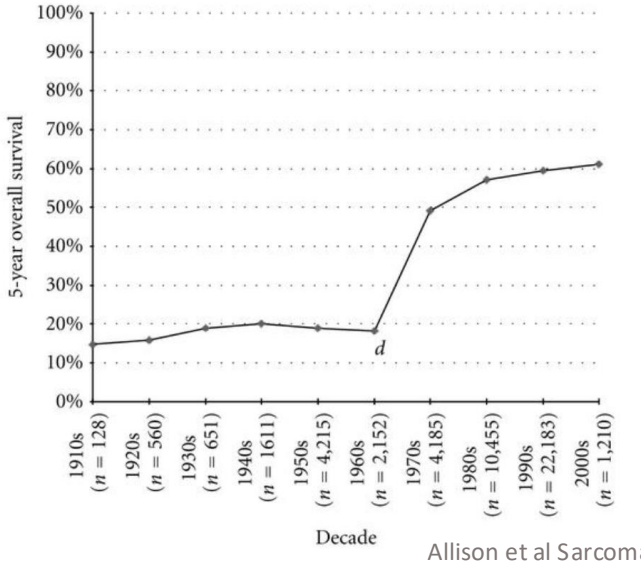
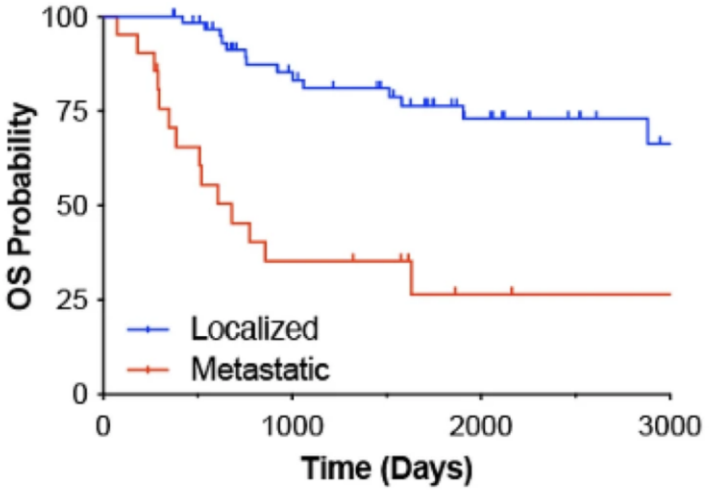
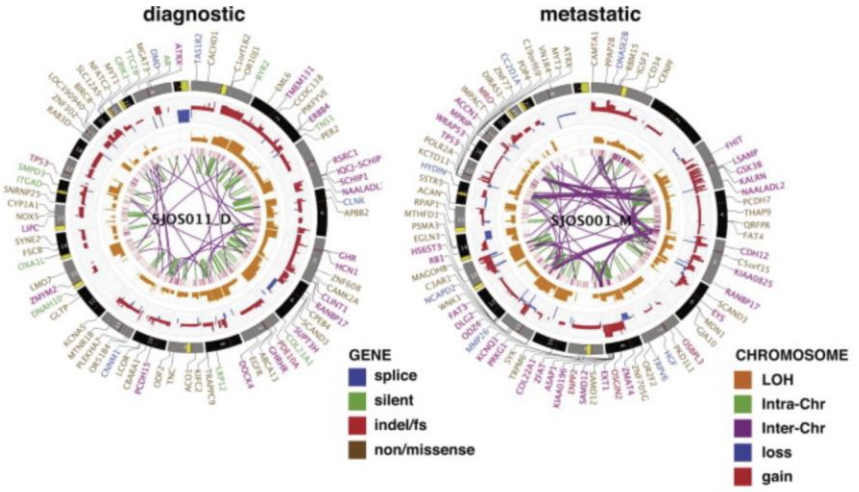
Genomic Instability and Heterogeneity in Osteosarcoma



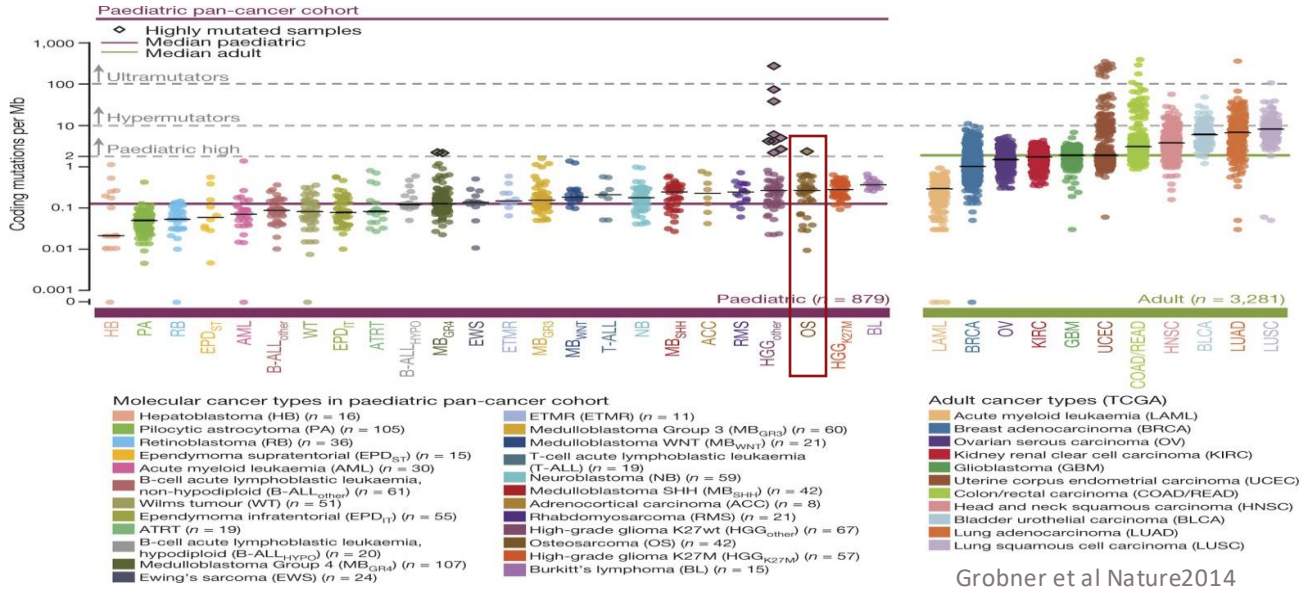
Allison et al Sarcoma 2012



Patel et al Sci Rep 2024



Chen et al Cell Rep 2014



Grobner et al Nature2014

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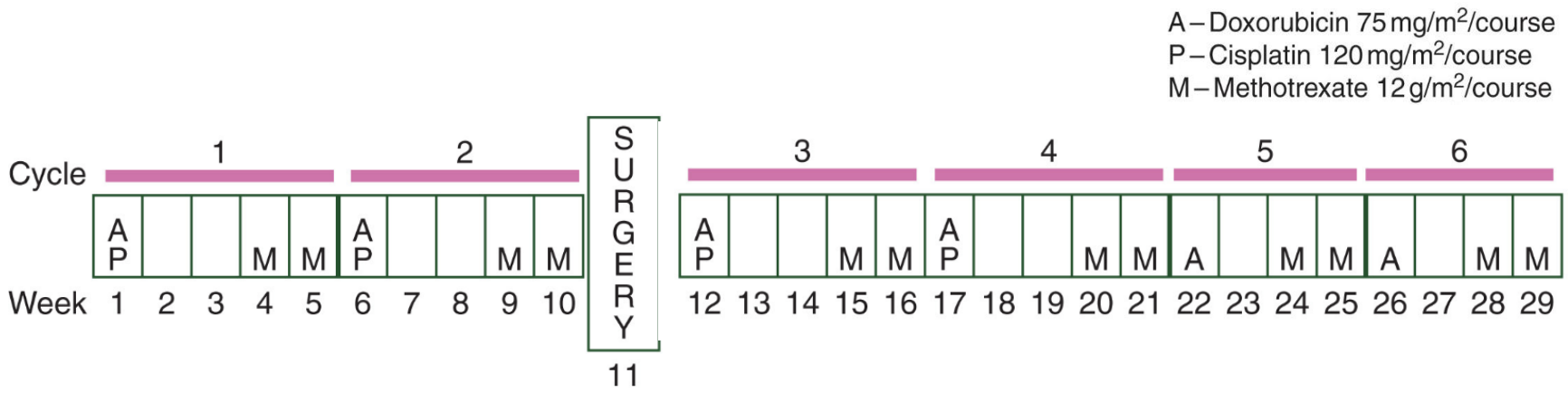
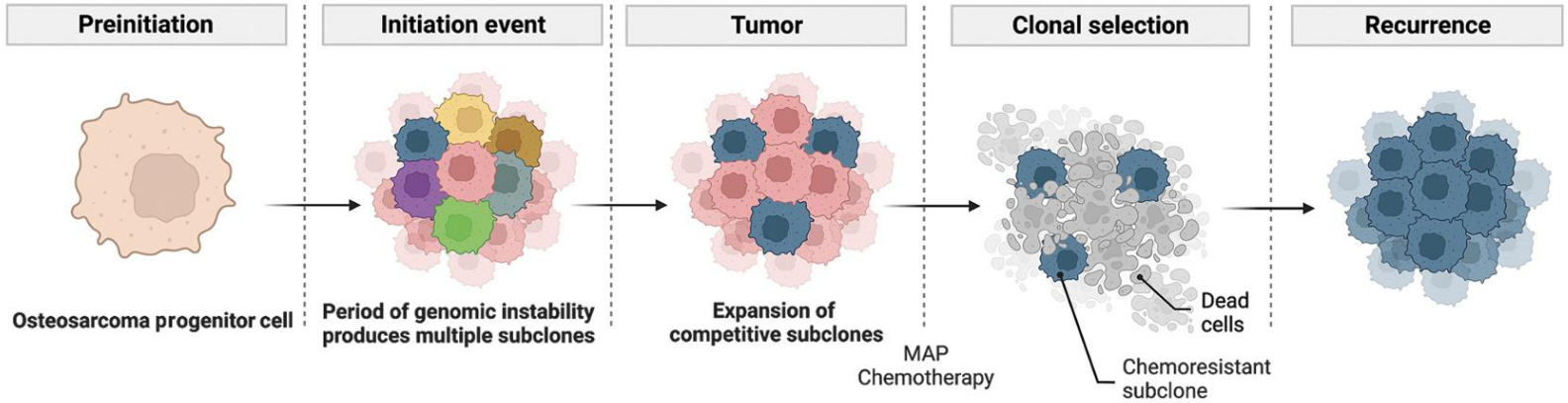
Clonal evolution in resistant osteosarcoma

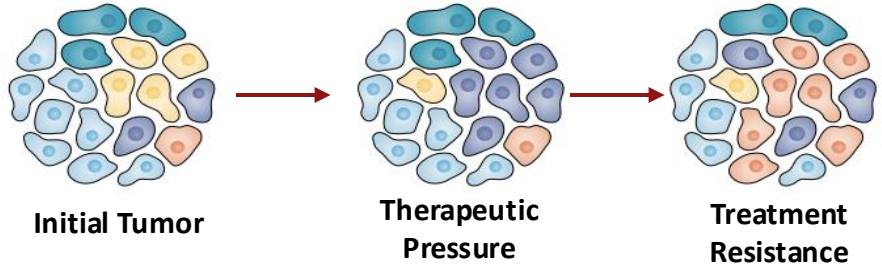


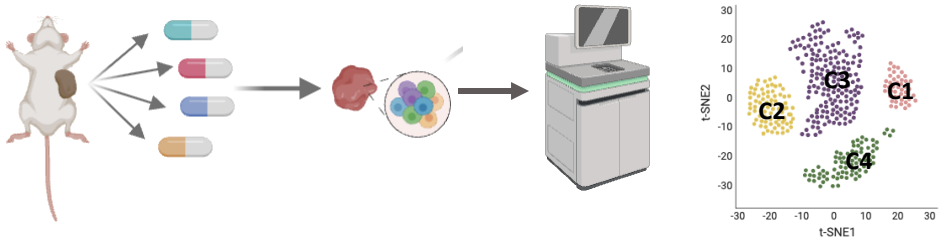


Michael Kinnaman

Kinnaman et al Cancer Res 2023

Single-cell RNAseq

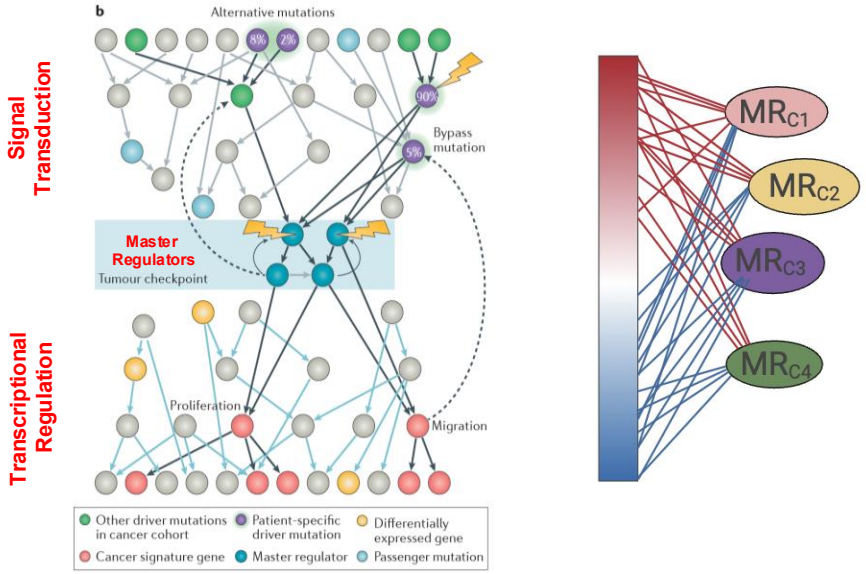




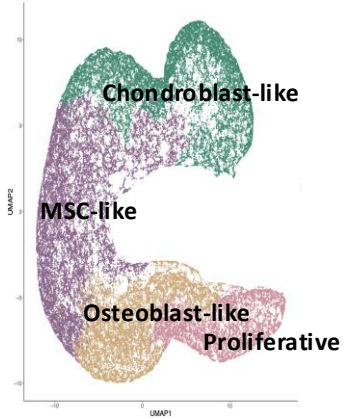
Identify and target Master Regulators of Therapy Resistant States

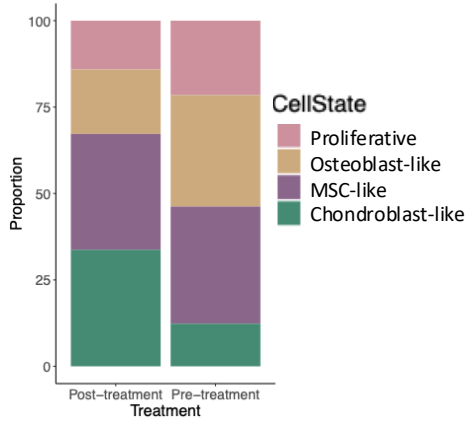
'Bottle-neck' analysis

Tumor Bottleneck Hypothesis



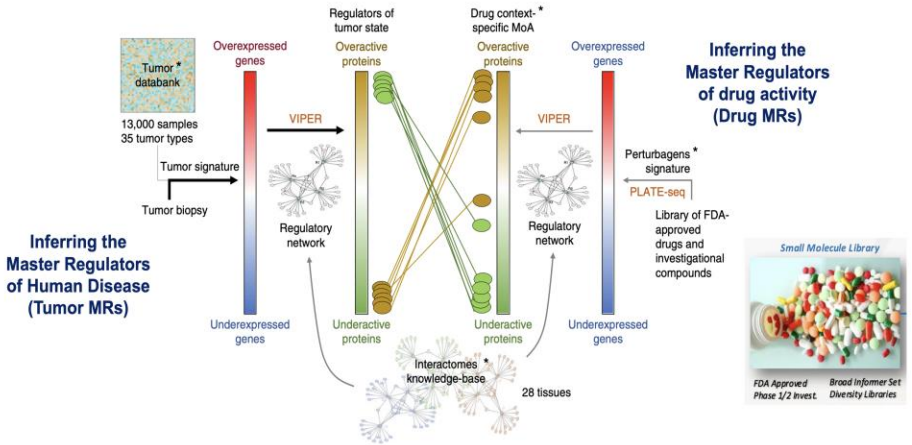
Single cell RNA-seq of pre- vs. post-treatment tumors identifies cell state-specific depletion





	Chondroblast-like	Fibroblast-like	Osteoblast-like	Proliferative
SHH	350	230	114	72
ERBB3	350	196	98	63
CDK7	0	0	176	232
HDAC3	0	0	65	244
FGFR1	0	51	153	104
EDNRA	53	118	93	20
STAT3	0	0	76	139
MS4A2	110	58	22	10
CYSLTR1	82	41	10	0
CXCR2	70	40	15	4
AXL	32	63	19	0
SSTR2	55	33	8	7
ITGA2B	50	26	11	4
LCK	59	23	1	0
PRKCA	0	0	56	27
PGR	46	26	6	2
TERT	42	20	10	7
FGF2	40	21	6	2
BIRC3	36	21	5	0
PDGFRB	15	29	10	0
JAK3	28	11	0	0
ITGB3	23	12	0	0
TLR7	25	6	0	0
FGFR4	18	6	1	0
AKT1	0	0	0	23
MAP2K2	0	0	0	22

OncoTarget™ and OncoTreat™



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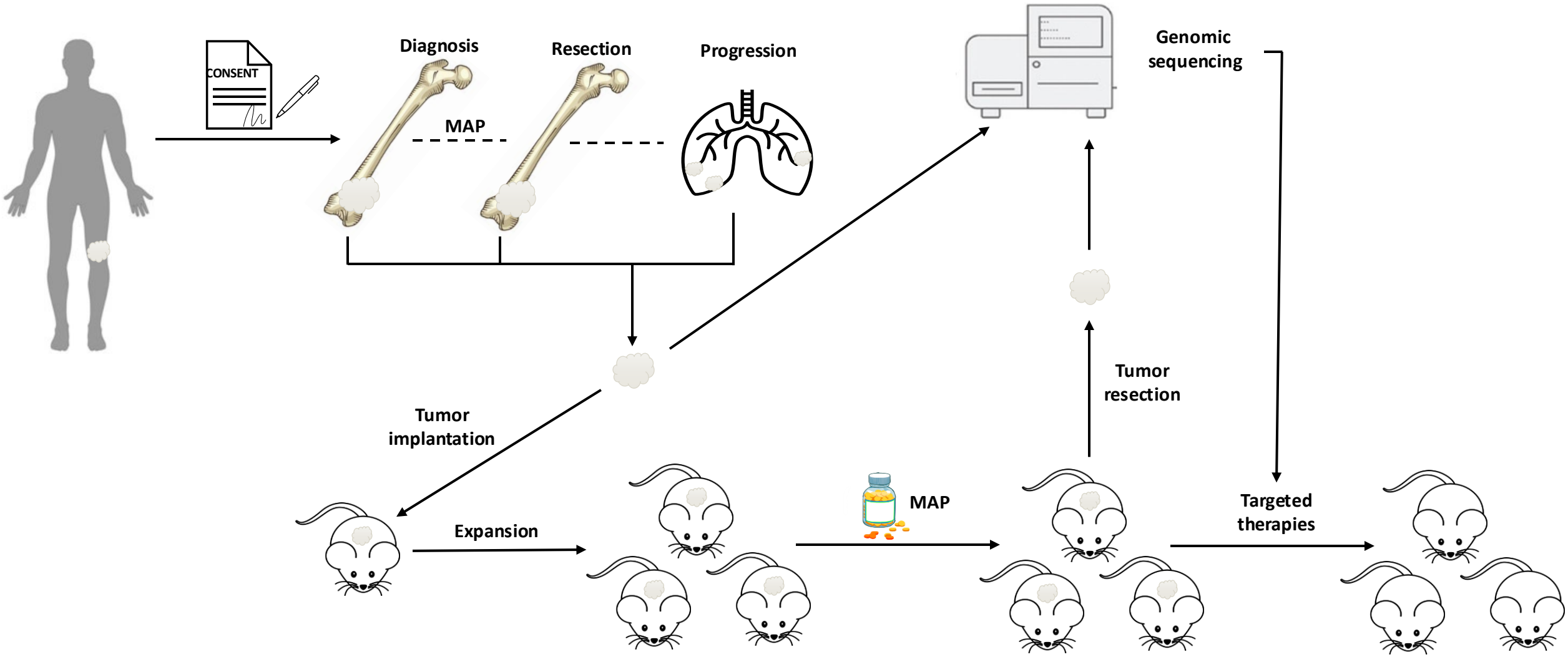
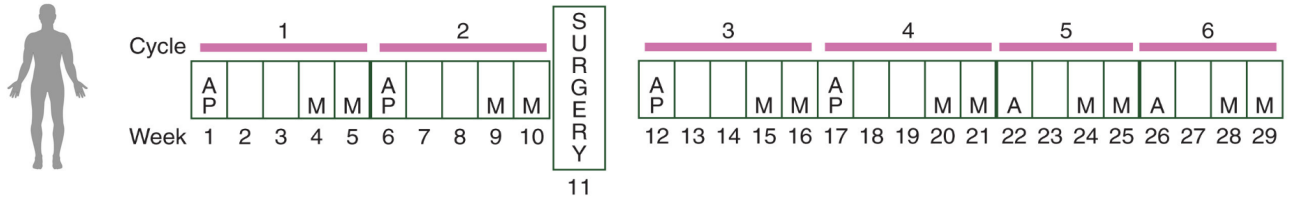
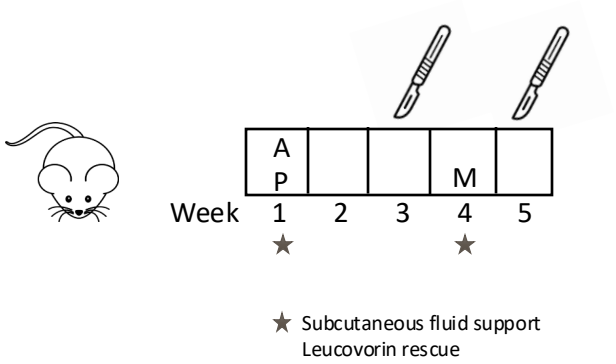
Courtesy of Jovana Pavisic

Evaluating tumor evolution in osteosarcoma PDX models



Replicating MAP therapy in PDX models



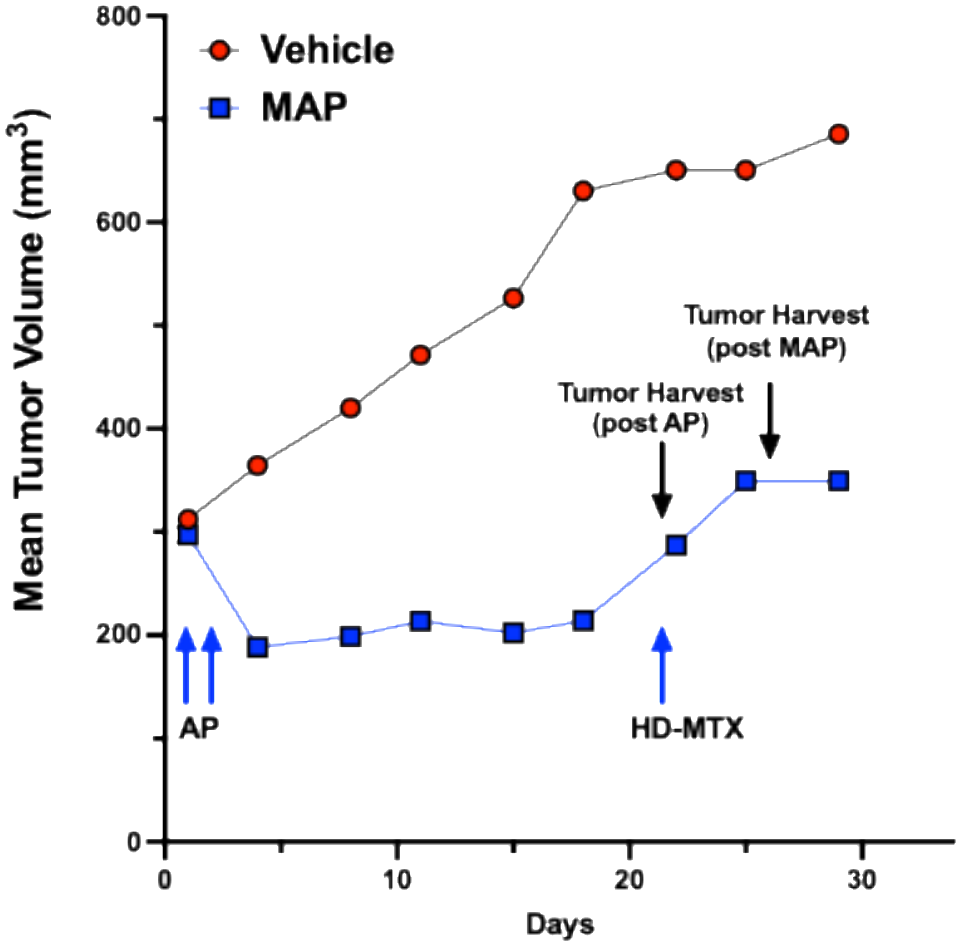


Mouse-equivalent dosing of MAP

Doxorubicin: 37.5 mg/m^2 IV = 6 mg/kg IP (Day 1, 2)

Cisplatin: 60 mg/m^2 IV = 3 mg/kg IP (Day 1,2)

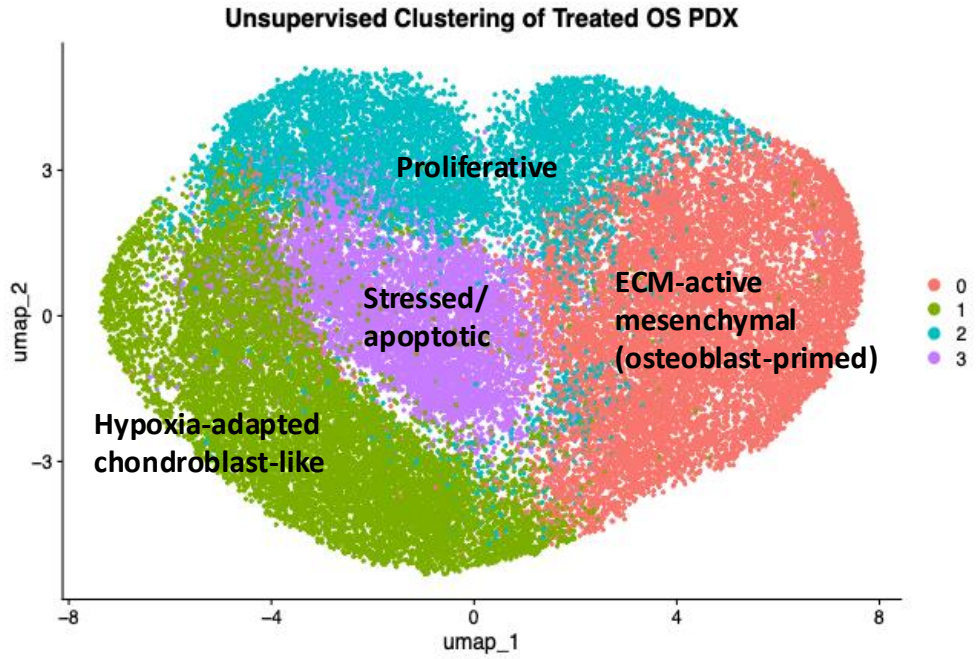
HD-Methotrexate: 12000 mg/m^2 IV = 225 mg/kg IP (Day 22) with Leucovorin rescue

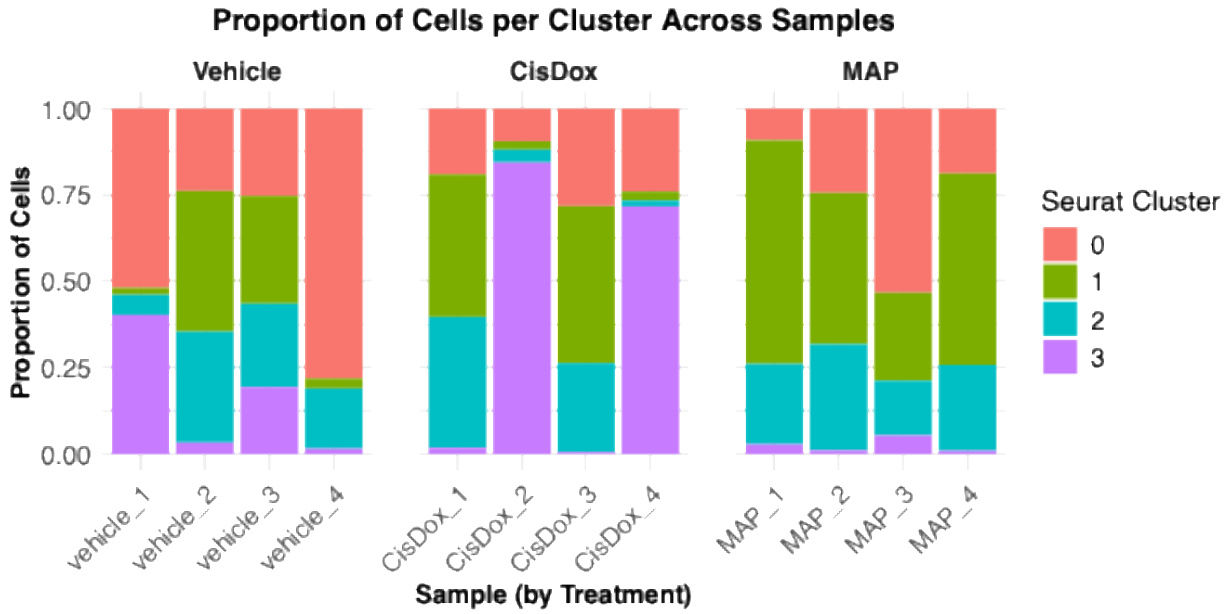


Kristen Victor
Daoqi You

Gene expression analysis of treated OS PDX snRNA-seq

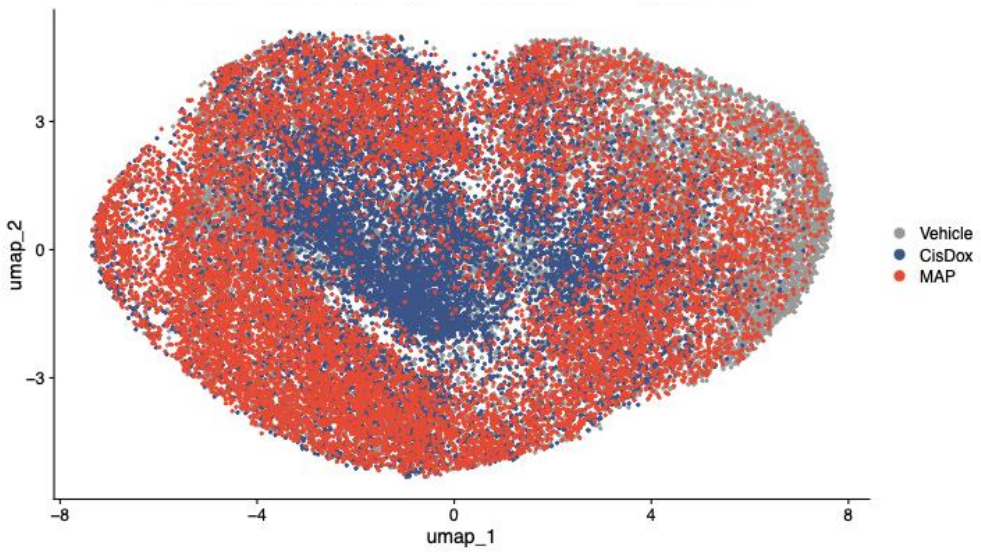
- snRNA-seq for 264,401 high-quality tumor nuclei across 12 samples (n = 4 / treatment arm)

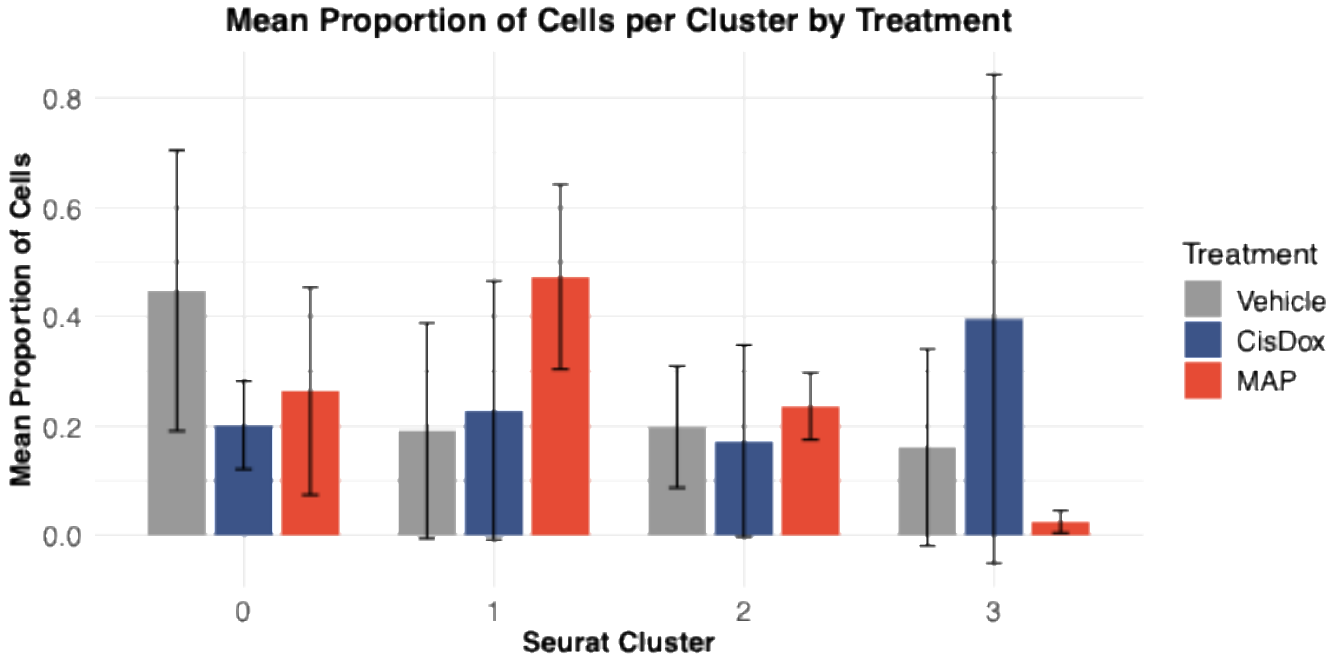




- Subpopulation proportions vary between replicates, emphasizing the need for multiple biological replicates to capture true treatment effects

Gene expression analysis of treated OS PDX snRNA-seq



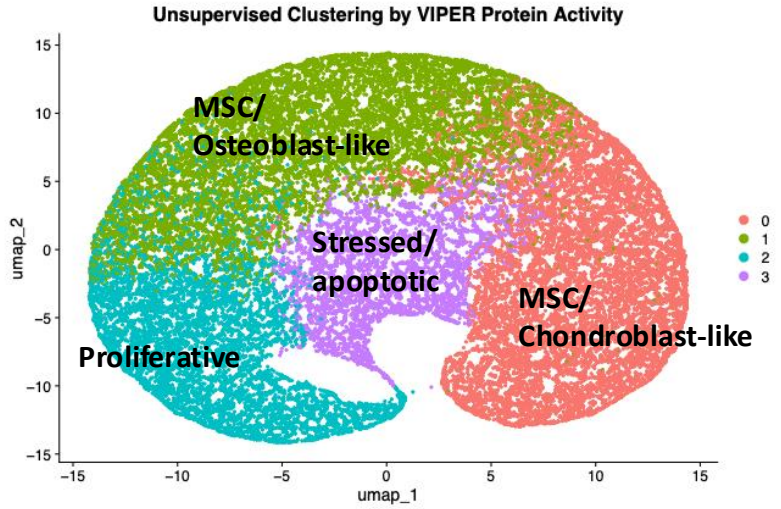


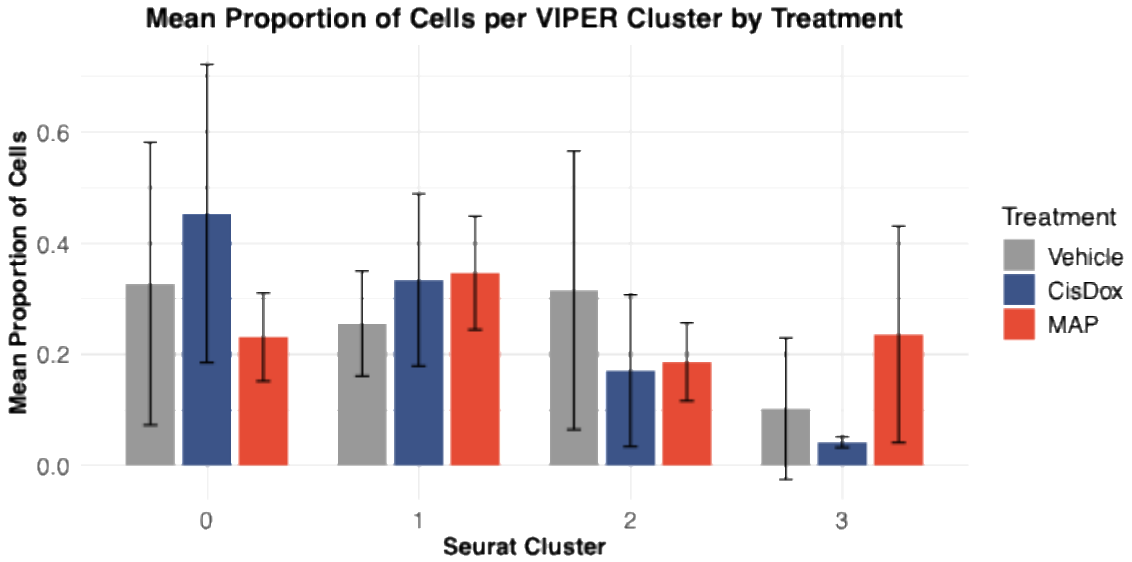
- Chemotherapy treatment alters cell state composition
- Depletion of ECM-active mesenchymal (osteoblast-primed) C0 cells and expansion of Hypoxia-adapted chondroblast-like C1 cells post MAP chemotherapy
- Stressed/apoptotic cells most enriched after Cisplatin/Doxorubicin, consistent with predominant cell death occurring with these drugs

Jovana Pavisic

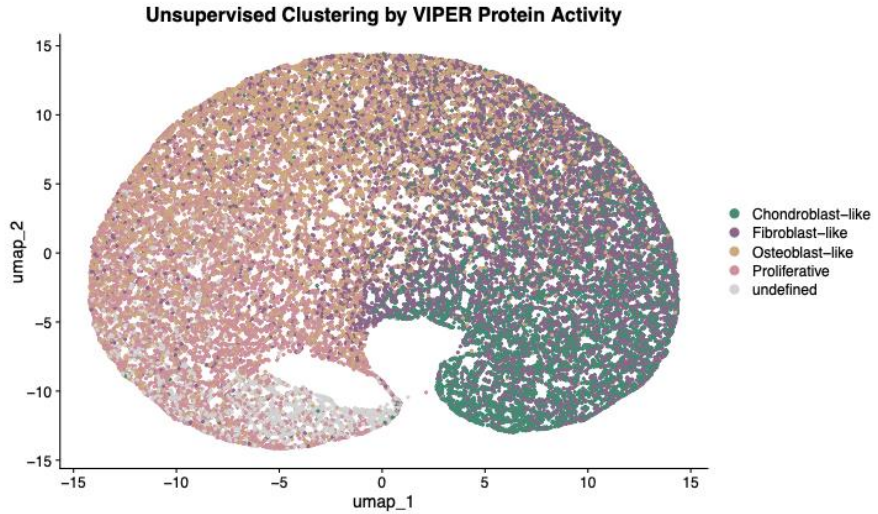
VIPER-inferred protein activity analysis of treated OS PDX snRNA-seq

- Transform gene expression profiles to activity profiles for ~3,000 transcriptional regulators





Patient heterogeneity recapitulated in the PDX



	PDX_MSCChondro	PDX_MSCOsteo	PDX_Proliferative	PDX_Dying
FLT1	350	350	149	350
IL6R	350	350	129	350
KDR	350	350	127	350
AXL	350	350	61	350
LYN	350	350	39	248
PDGFRB	350	155	23	130
F2R	350	113	26	105
CXCR4	127	110	15	59
HSP90AA1	7	21	76	0
EDNRA	19	13	17	19
HDAC7	0	0	54	0
RARA	8	3	0	8
HDAC3	0	0	0	4

OncoTarget of treated versus vehicle tumor cells can identify cell state-specific therapeutic vulnerabilities activated post chemotherapy for therapeutic translation

Jovana Pavisic

Ongoing research and future directions

- Complete MAP treatment of PDX models (n=5 discrete models)
- Analyze single cell data to characterize cell state-specific evolution in response to chemotherapy treatment
- Utilize regulatory network analysis to identify and target MRs of chemotherapy-resistant disease
- Perform *in vivo* validation of MR predictions

A special thank you to #BecauseOfAva, the Levin family, and all of the OsteoWarriors and OsteoAngels!

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Thank You!