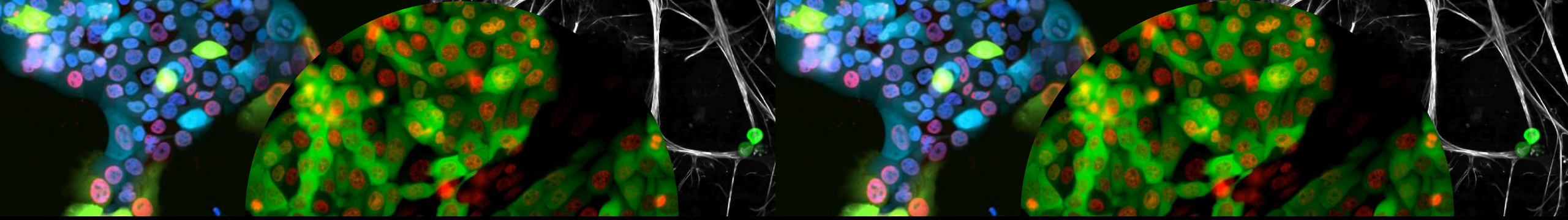
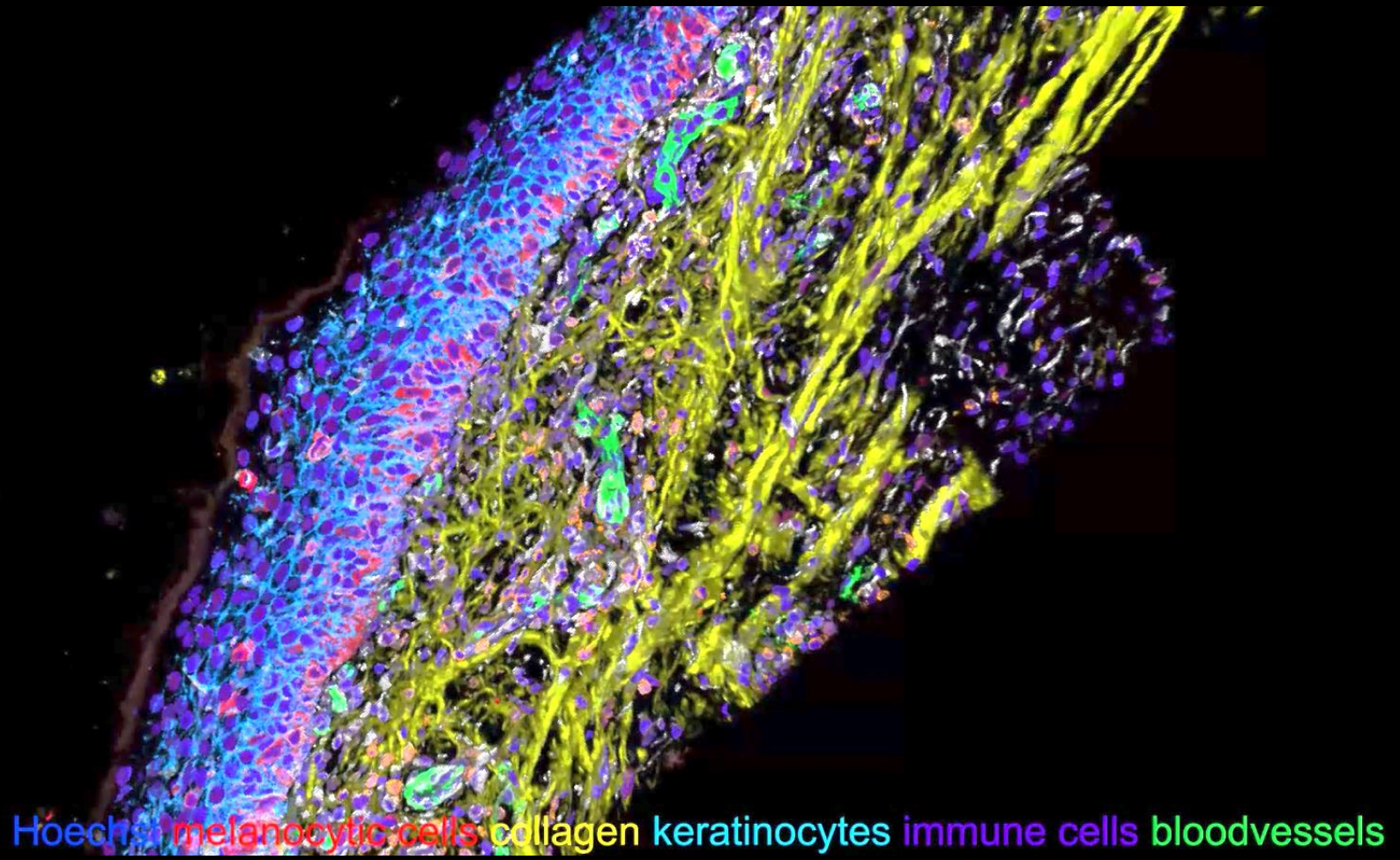


Dynamic tissue models reveal targetable mechanisms of single cell drug resistance in complex tumor ecosystems

Alexander Davies, DVM, PhD
Division of Oncological Sciences / CEDAR
Knight Cancer Institute, OHSU

FACTOR 2025

Tumor ecosystem complexity



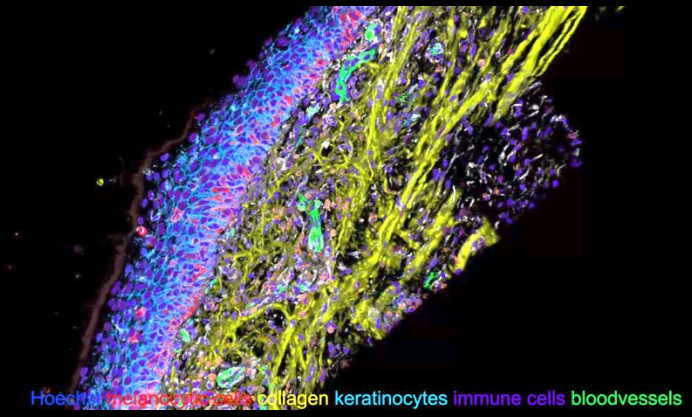
Tissue and immune cells
Extracellular matrix (structure)
Vessels (nutrients/ oxygen)
Signals (stop/go)
Systemic signals (e.g. insulin)

Single cell behavior

Tissue-scale behavior

Yapp et al., bioRxiv 2024

Tumor ecosystem complexity

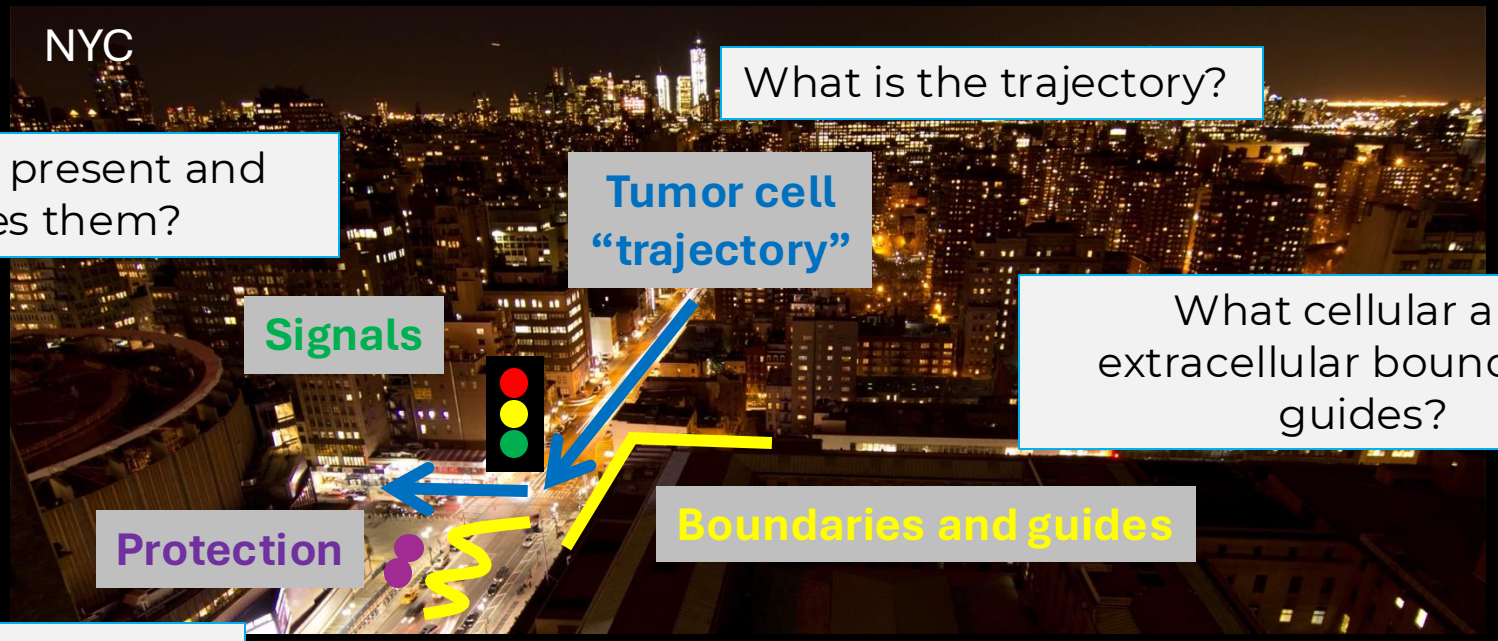


Yapp et al., bioRxiv 2024

Courtesy of Mitch Martinez

Tissues, like cities, are complex and dynamic ecosystems where the behaviors of individuals are modulated by their interactions with the whole… in space *and* time.

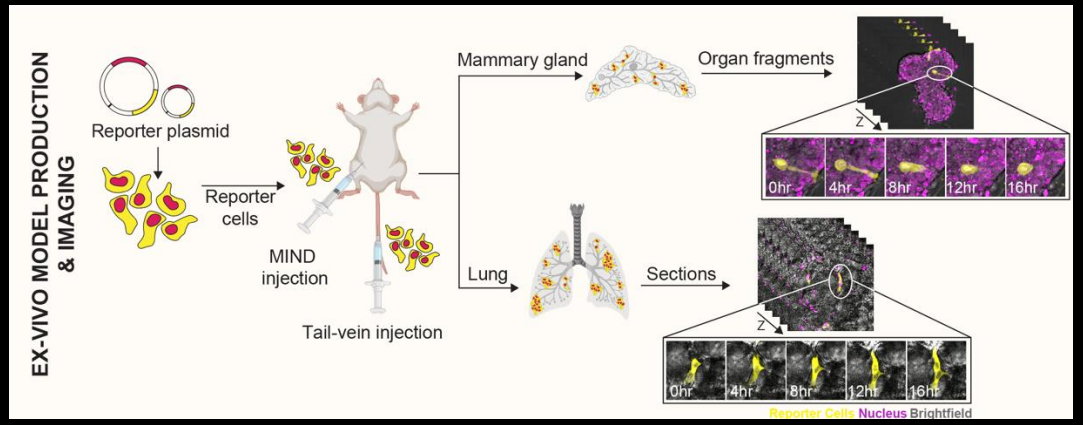
By understanding tumor and ecosystem dynamics we can devise better strategies to improve outcomes



Courtesy of Mitch Martinez

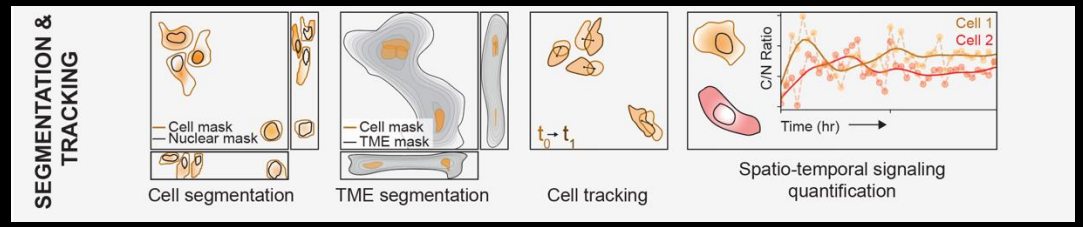
How do these factors converge to dictate drug response –who, what, when, why, how?

Serial Imaging of Tumor and microEnvironment (SITE) platform

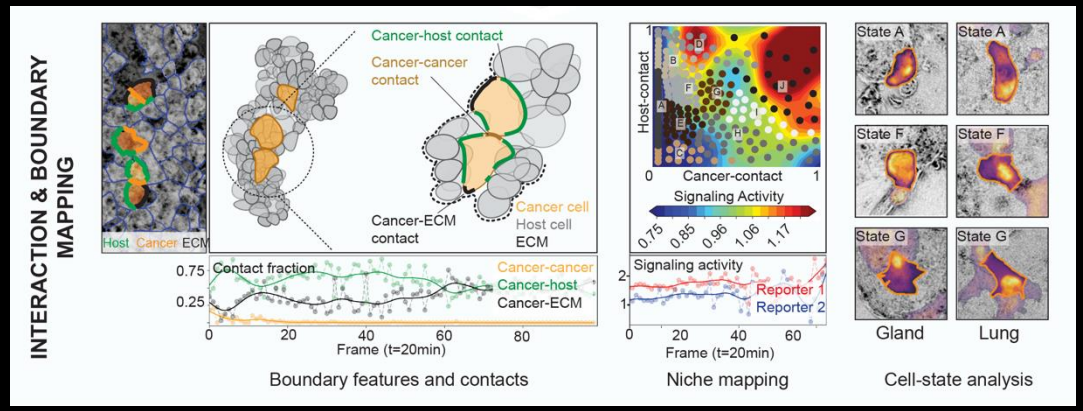


Whole living tissues (build from PuMA, Khanna et al), integration advanced biosensors, and time-lapse live-cell imaging

Single cell resolution and ecosystem mapping over space and time

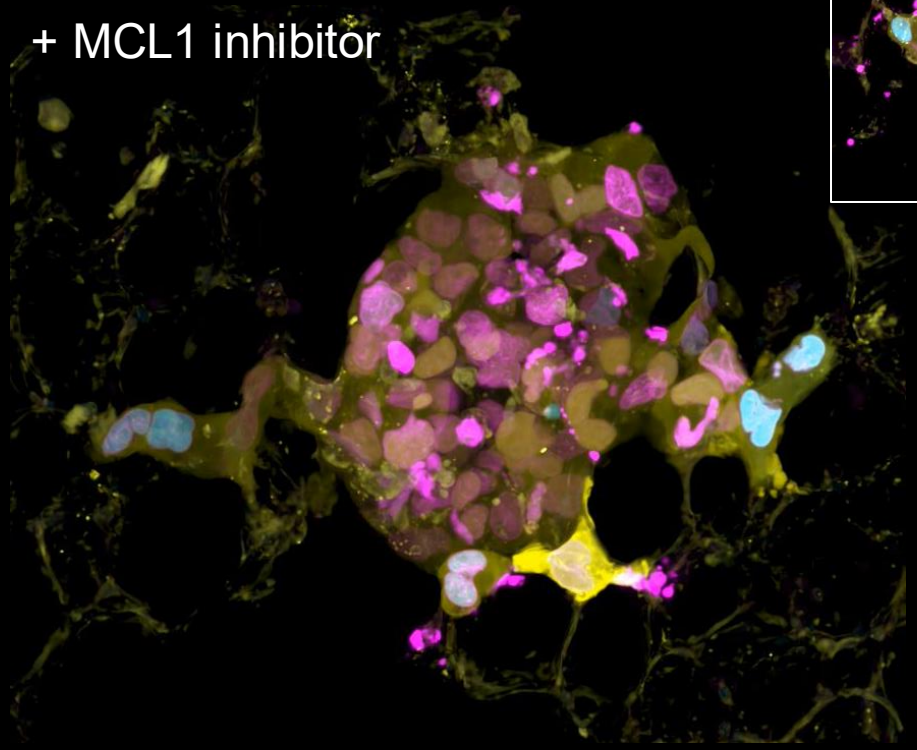


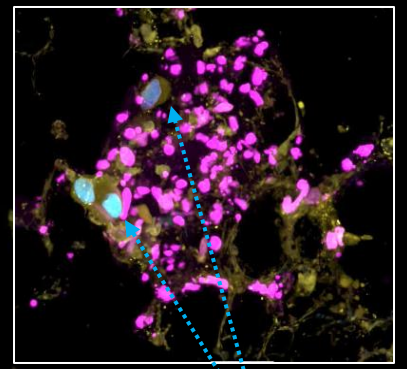
Dynamic tumor-ecosystem interactions, states, and drug response



Murthy et al., BioRxiv 2025 (pre-print)

SITE models reveal ecosystem-level interactions underlying single cell drug response variation ex vivo





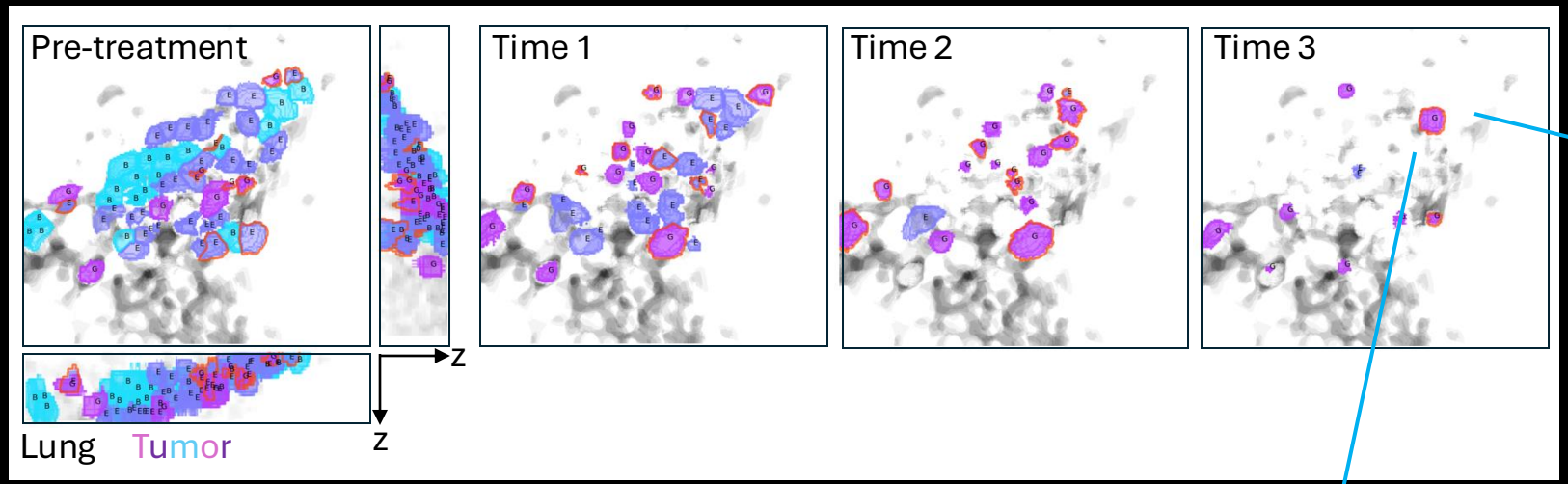
Why do these cells evade treatment?

Signaling (ERK)
Transcription (Fra-1)
Nucleus (Histone H2B)

Makkawi et al. (in preparation)

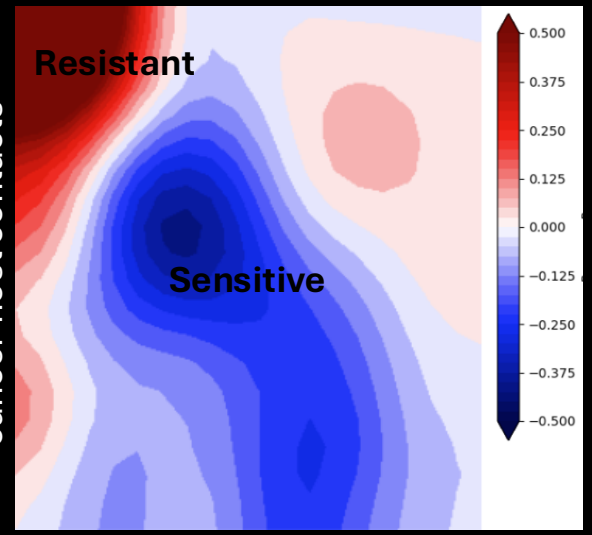
Tumor and host interactions are coordinately associated with drug resistance behavior

Single cell drug response over time



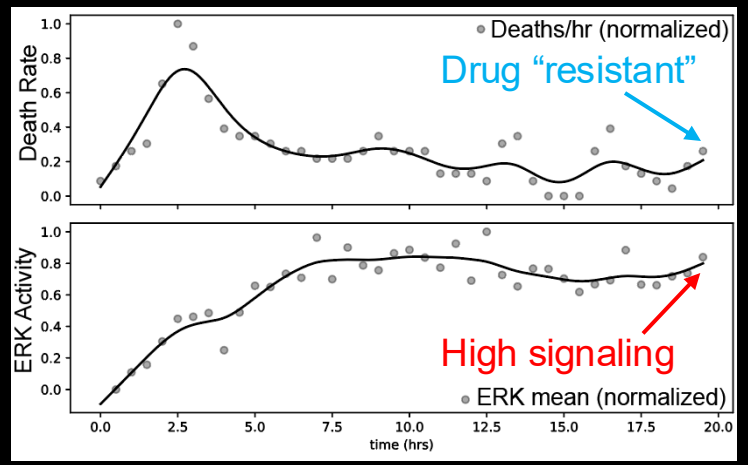
Spatial positioning and interactions

Probability of resistance



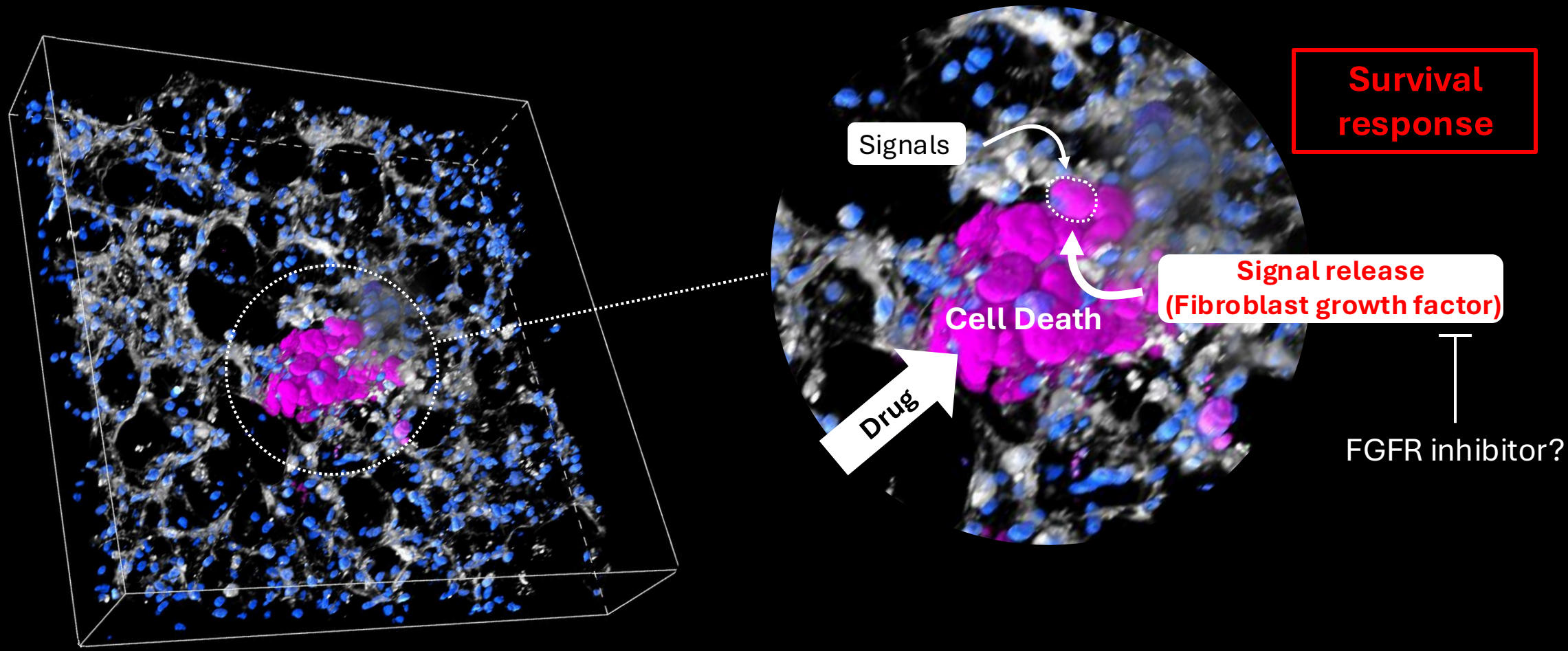
Signaling and drug response

Temporal death-signaling relationship



Makkawi et al. (in preparation)

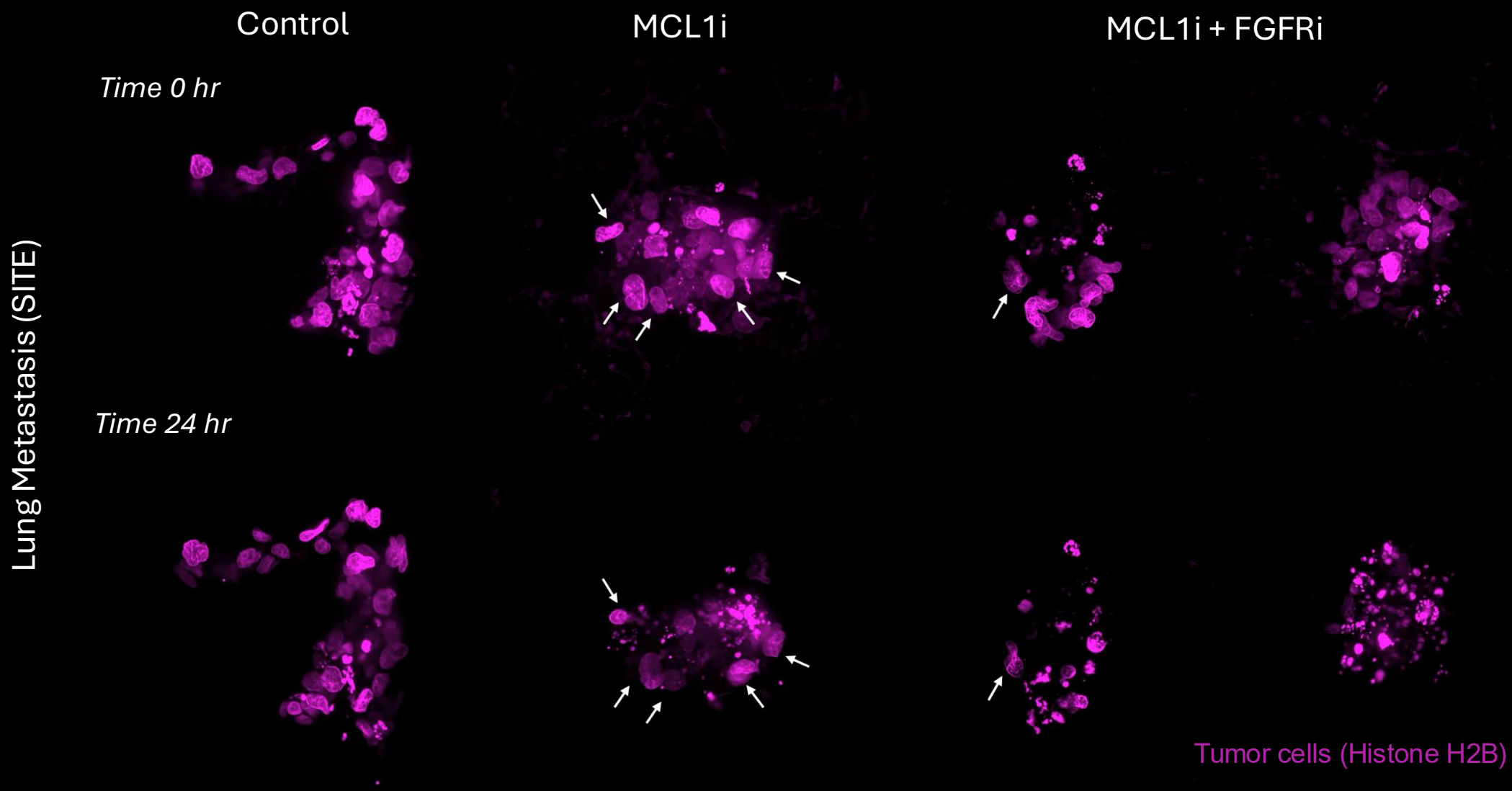
Drug-induced signaling within the tumor ecosystem enhances survival



Tumor cells (Histone H2B) Lung tissue Lung Nuclei

Makkawi et al. (in preparation)

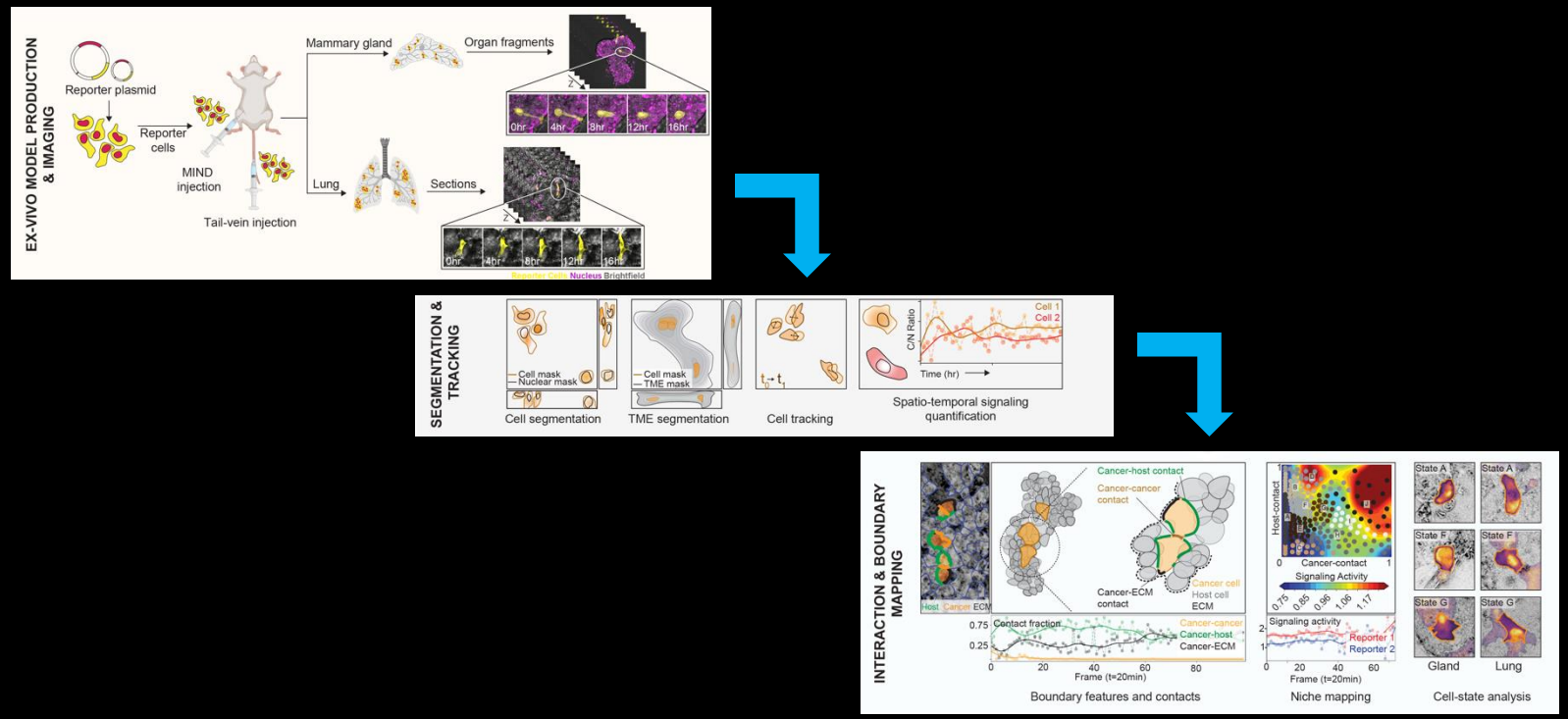
Combinatorial targeting can enhance tumor elimination



Makkawi et al. (in preparation)

SITE models enable detailed exploration of tumor ecosystem biology and drug response

SITE Platform:



The who, what, when, why, how of tumor behavior and drug response

Quantitative single cell resolution with context over time

Modeling of patient-to-patient variability – biology and drug response

Combinatorial therapy with FGFR inhibitors to eliminate persisting cells?

Future: Fully humanized, immune functionalized

Murthy et al., BioRxiv 2025 (pre-print)

Thank you!!!

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Because of Matthew