SHALEKLAB
from cells to systems

Does Cancer Cell State Matter?

Moving from DNA genotype to RNA phenotype-directed therapies in cancer

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2024 National Cancer Advisory Board and Board of Scientific Advisors for the NCI

Disclosures

I have the following financial relationships to disclose:

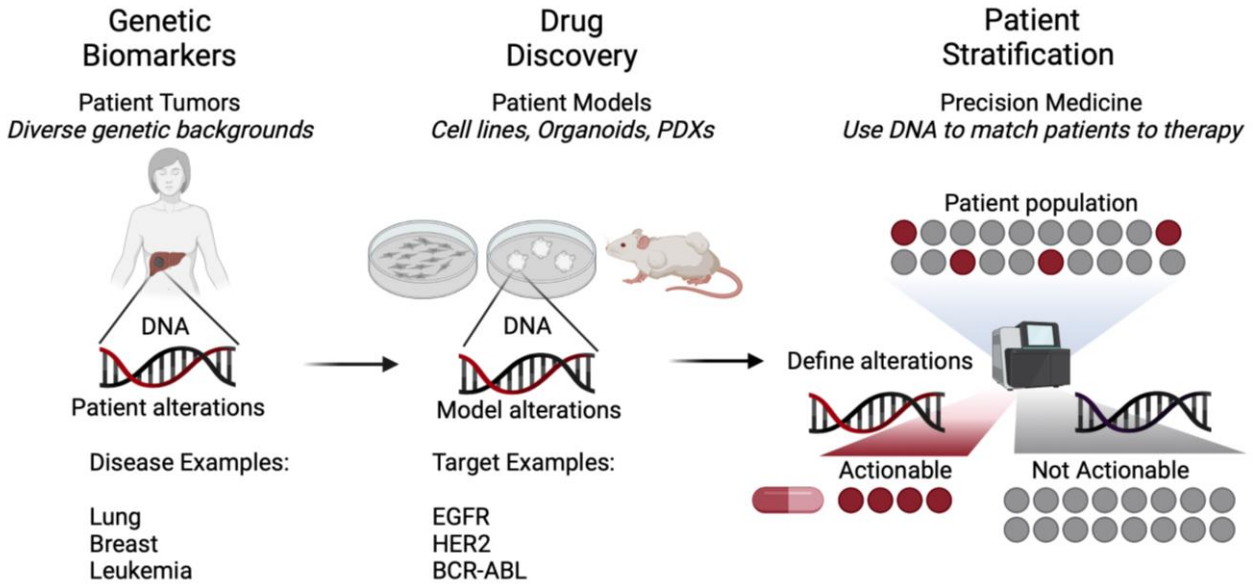
Consultant for: Honeycomb Biotechnologies, Cellarity, Ochre Bio, Bio-Rad, FL86, Relation Therapeutics, IntrECate Biotherapeutics, Passkey Therapeutics, Fog Pharma, and Dahlia Biosciences

Stockholder in: Honeycomb Biotechnologies, Cellarity, Ochre Bio, Relation Therapeutics, IntrECate Biotherapeutics, Santa Ana Bio, Passkey Therapeutics, and Dahlia Biosciences

Funding: See acknowledgements

Matching Patients With Effective Therapies

DNA mutations are the cornerstone of precision medicine



How Have We Done?

Low rates of response

Actionable Not Actionable

~40% patients have actionable alteration

~<5% of patients have responses

Why does the current pipeline fail?

Major Failure Modes

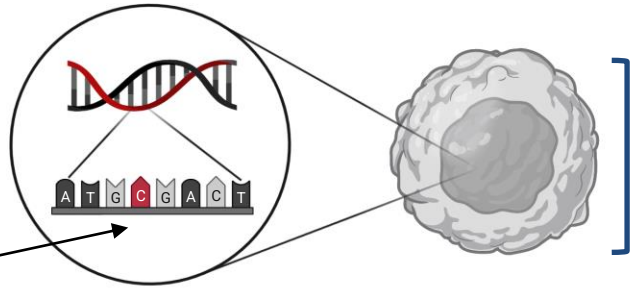
1. The majority of cancer patients don't harbor "actionable" alterations.
2. Effects are often short-lived due to poor response and/or development of resistance.
3. **Assumes DNA alterations are responsible for altered cell function and drug response.**

NCI—MATCH Trial; Le Tourneau et al, *J Natl Cancer Inst* (2015); Massard et al, *Cancer Discov* (2017); Sicklick et al, *Nature Med* (2019); Middleton et al, *Nature* (2020); Letai et al, *Cancer Cell* (2021); van Tilburg et al, *Cancer Discov* (2021)

Mutations Occur In Cells

Cancer is more than altered DNA

Cancer **mutations** vs. Cancer **cells**

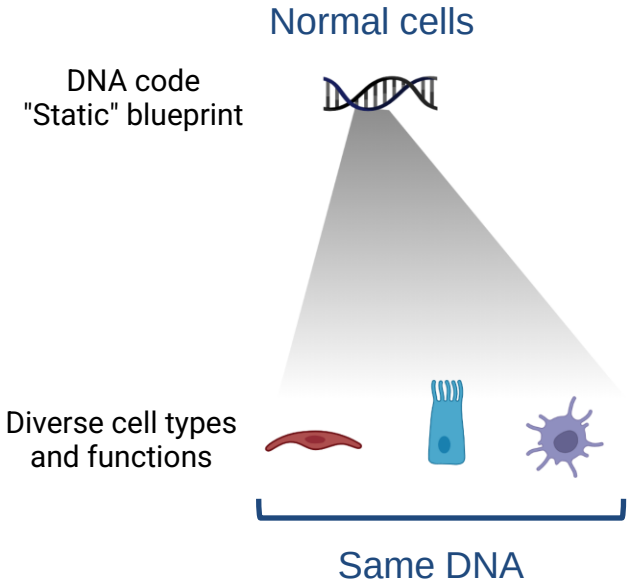


We currently target based on *mutation*

We need to target *cells*

What Is A Cell?

Cellular identity and function are integrative properties



What Is A Cell?

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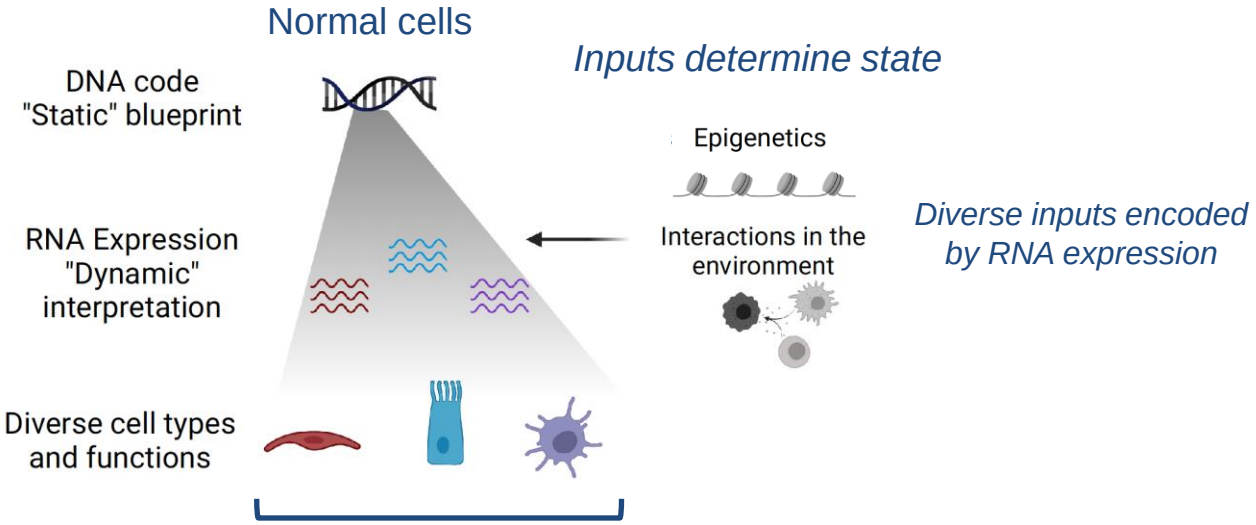
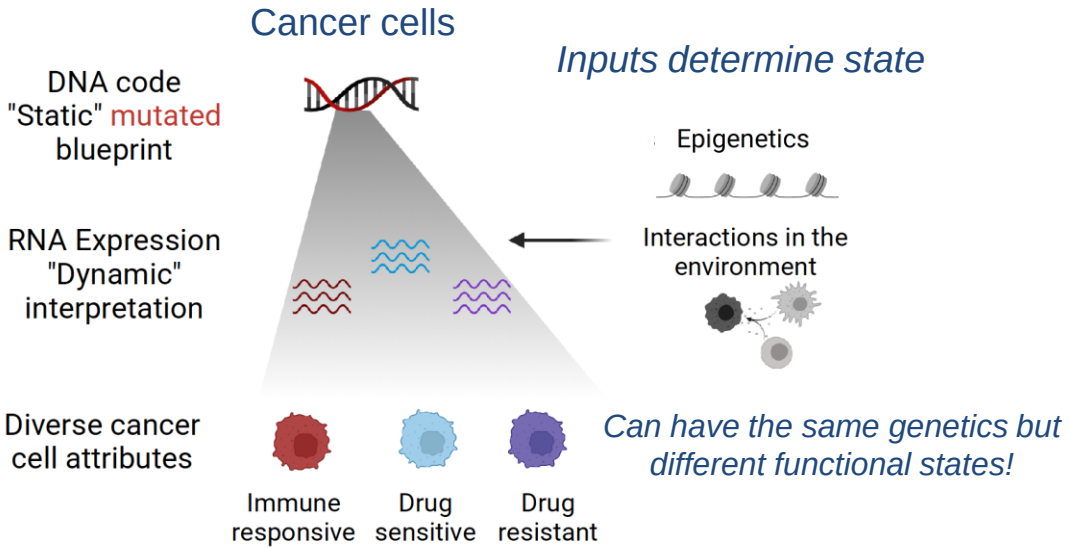


Shalek et al, *Nature* (2013); Shalek et al, *Nature* (2014); Macosko et al, *Cell* (2015); Gierahn et al, *Nature Meth* (2017); Ordovás-Montañés et al, *Nature* (2018); Hughes et al, *Immunity* (2020); Kazer et al, *Nature Med* (2020); Ziegler et al, *Cell* (2020); Ziegler et al, *Cell* (2021); etc.

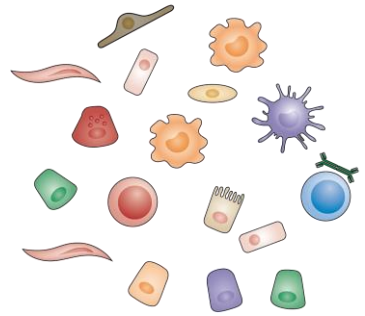
Cancer Cell Function Is Represented By State

Functional disease phenotypes are integrative properties

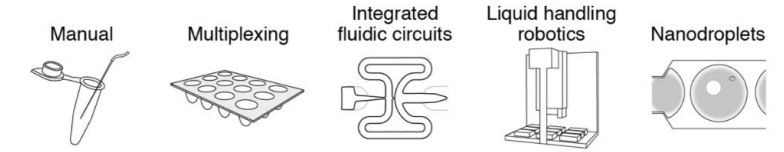


How can we study cell state?

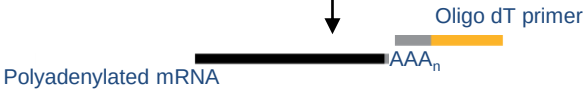
Profiling Cell State



~50,000 cells



Isolate single cells



Capture mRNA

Amplify

Sequence

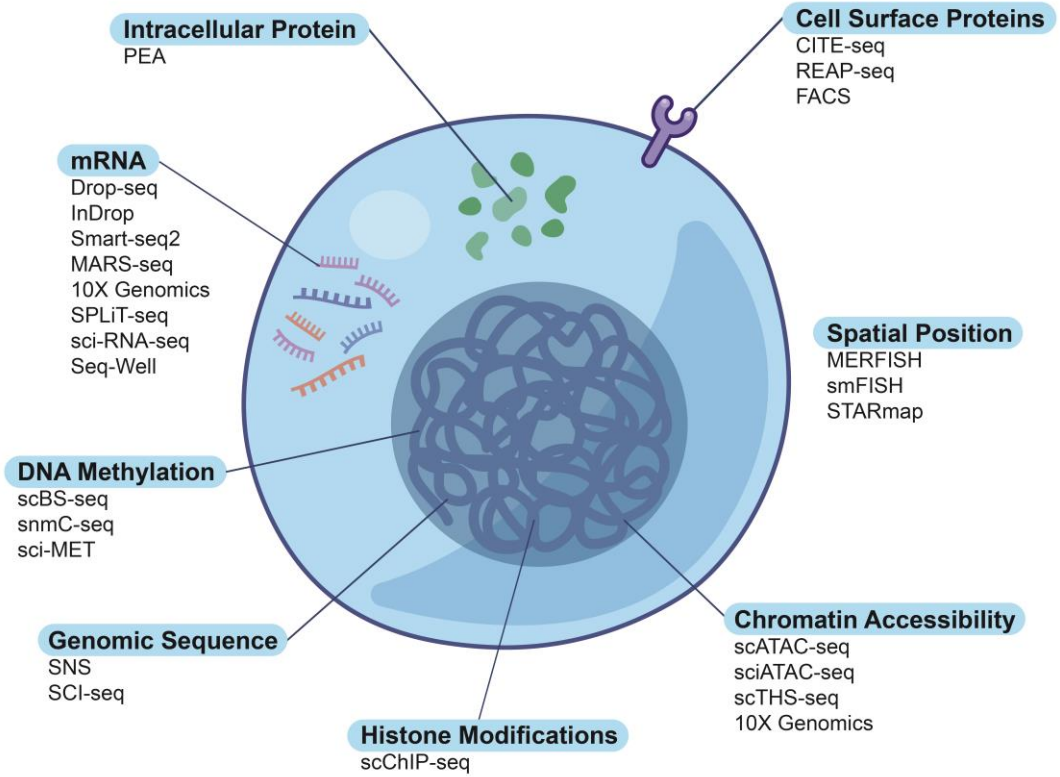
~20,000 genes

~1,000,000,000 data points

Human Cell Atlas White Paper (2017)

Shalek et al, *Nature* (2013); Shalek et al, *Nature* (2014); Macosko et al, *Cell* (2015); Tirosh et al, *Science* (2016)

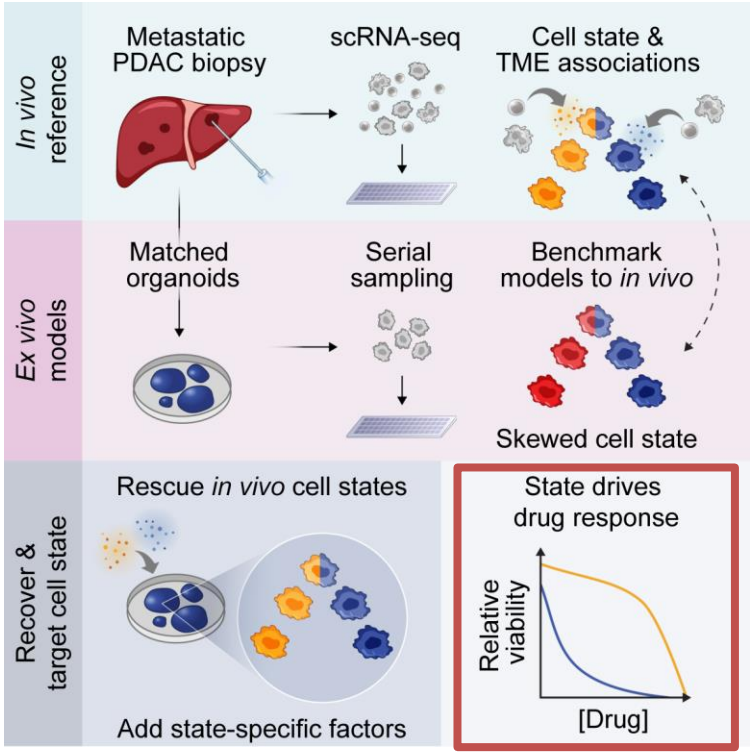
Capturing Different Molecular Features



Adapted from: Stuart et al, *Nat Rev Genet* (2019)

A Integrate Pipeline To Define & Model Cell States

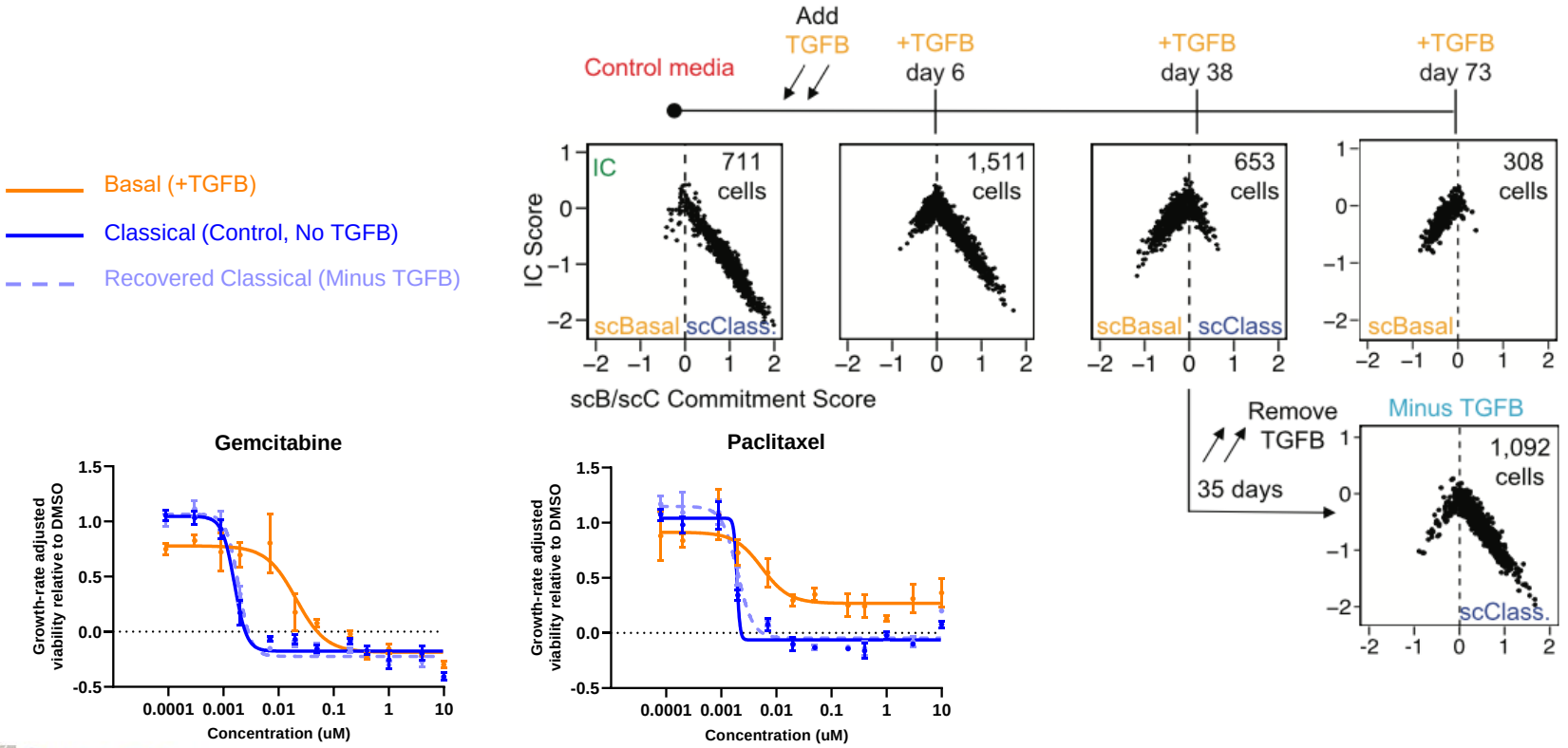
Proof of concept in Pancreatic Cancer (PDAC)



Raghavan et al, *Cell* (2021)

Are There Functional Consequences To Changing State?

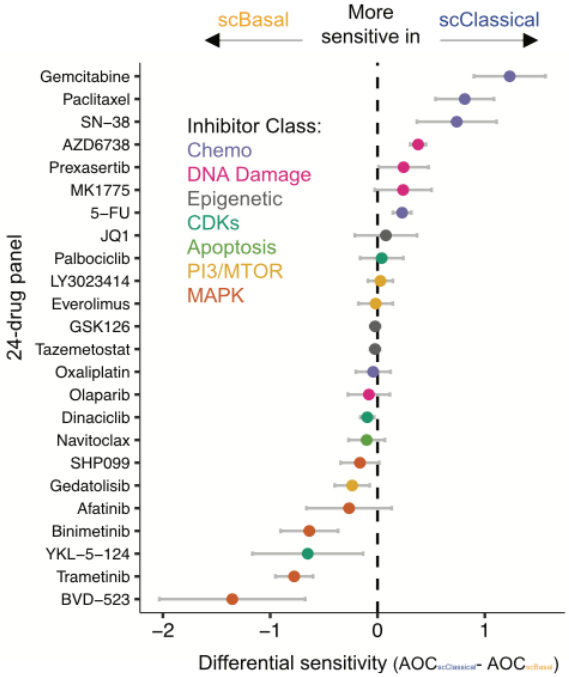
Drug response shifts are reversible



Raghavan et al, *Cell* (2021)

Functional Consequences To State Change - State Specific Screening?

Classes of drugs are differentially sensitive within an isogenic patient model



- The "scClassical" state is more sensitive to chemotherapeutic agents
- The "scBasal" state of the same model is more sensitive to MAPK pathway inhibitors (MEK and ERK inhibitors)
- ***We are missing critical features relevant to drug response by not preserving cell state in cancer!***

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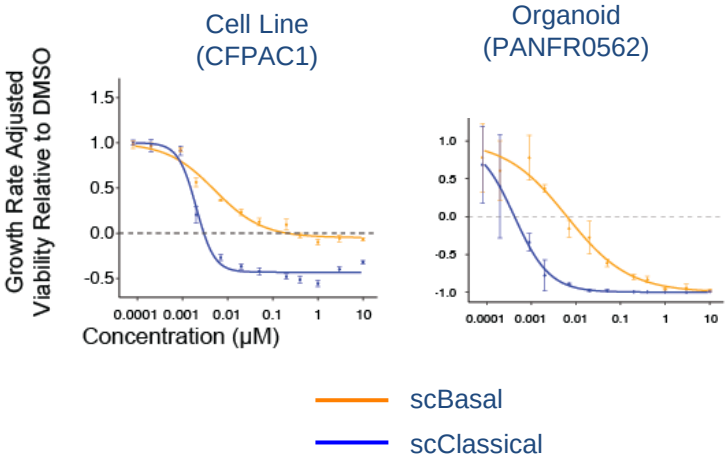
Raghavan et al, *Cell* (2021)

How Does This Align With Clinical Observations?

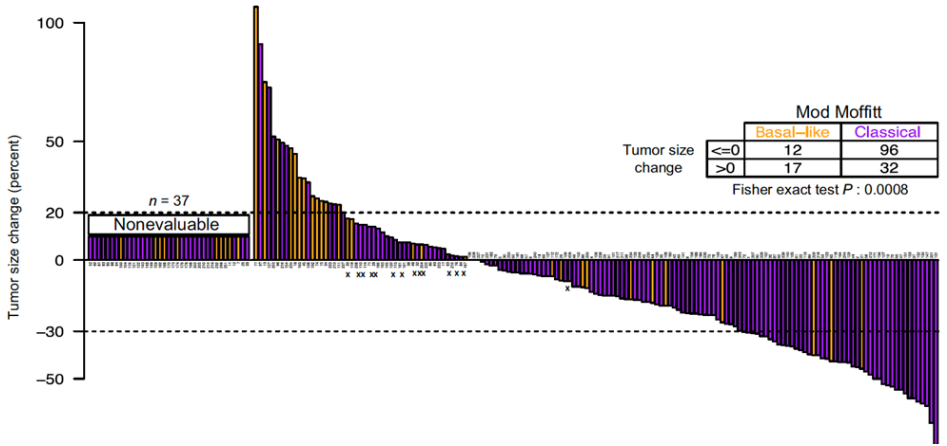
State-aligned **models** response to chemotherapy

Isogenic models cell lines and organoids

SN-38 (active irinotecan)



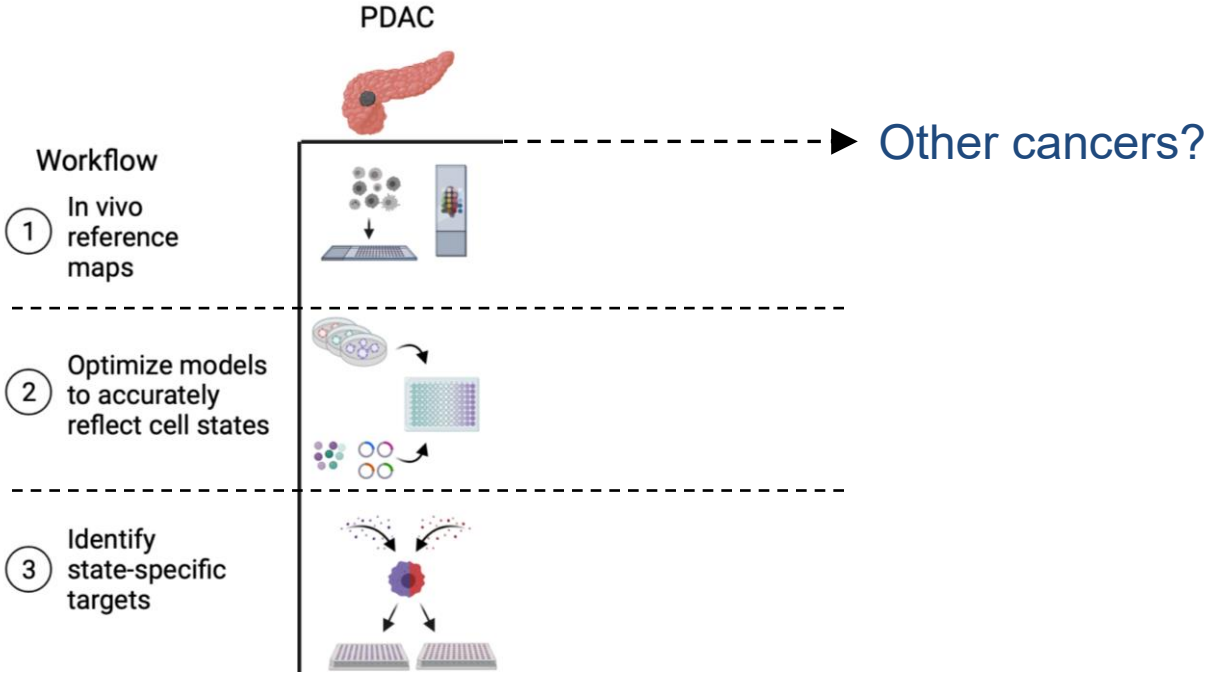
State-stratified **patient** response to chemotherapy



O'Kane et al, *Clin Cancer Res* (2020)

Extending The Approach

Cross-cancer effort to target cell state

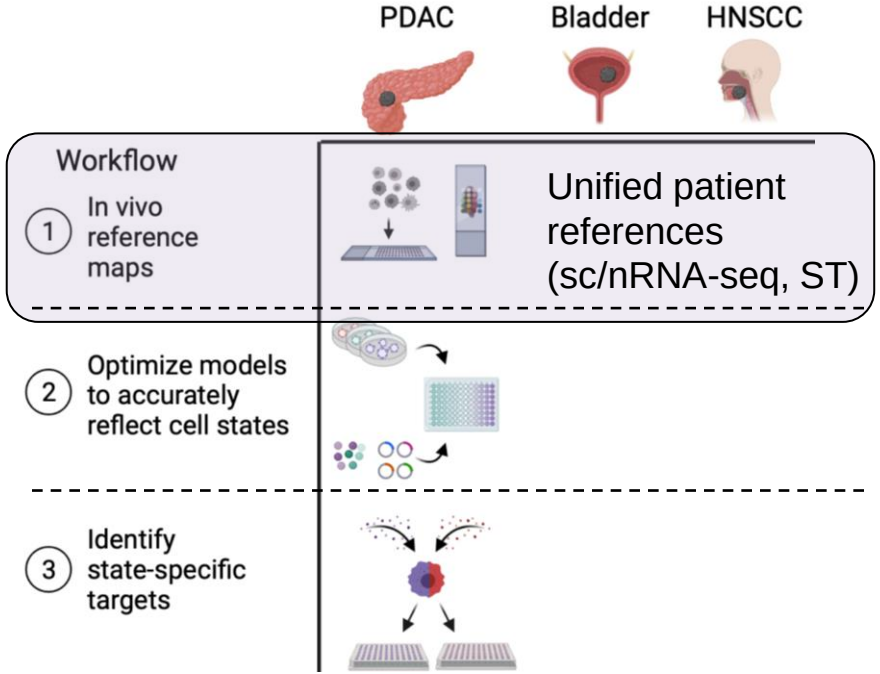


Extending The Approach


Andrew Navia

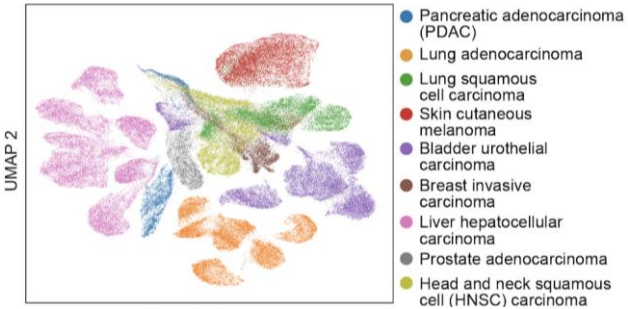

Mifrah Hayath

Cross-cancer effort to target cell state



TCGA snRNA-seq (w/ NCI)

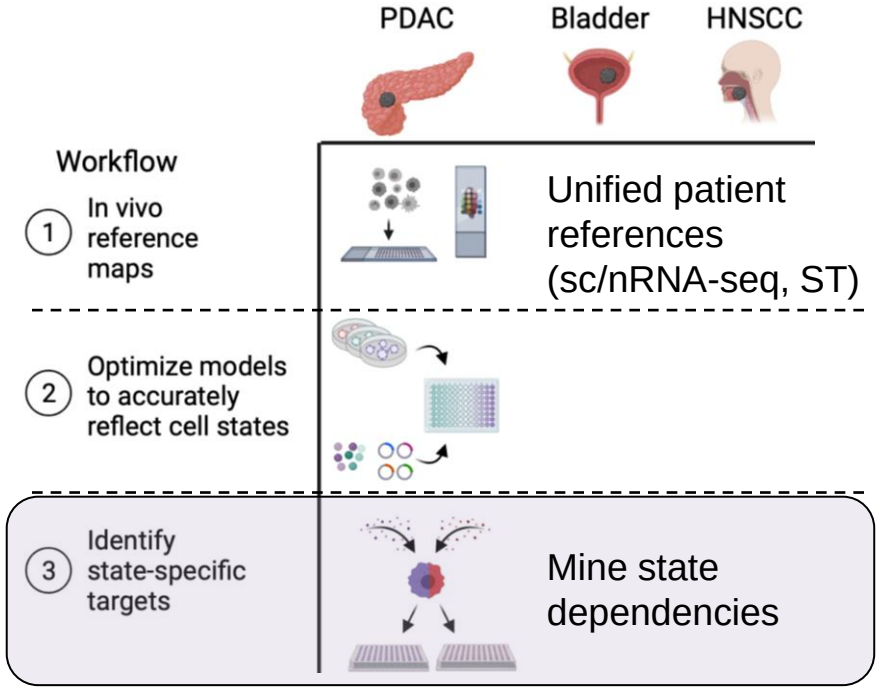
Pan-cancer nuclei UMAP visualization

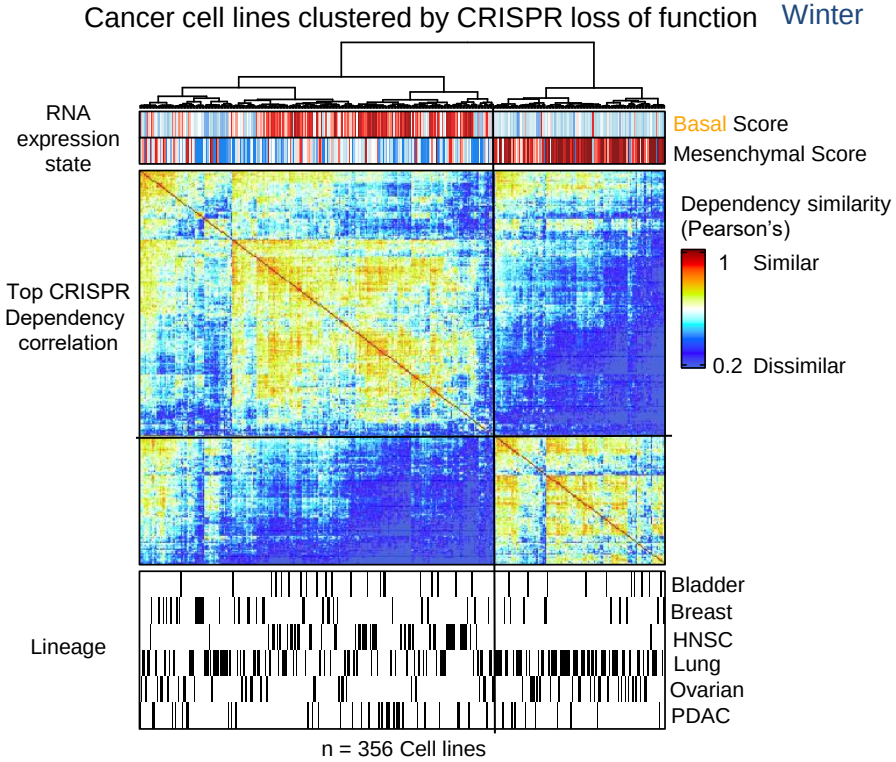


Extending The Approach

Peter Winter

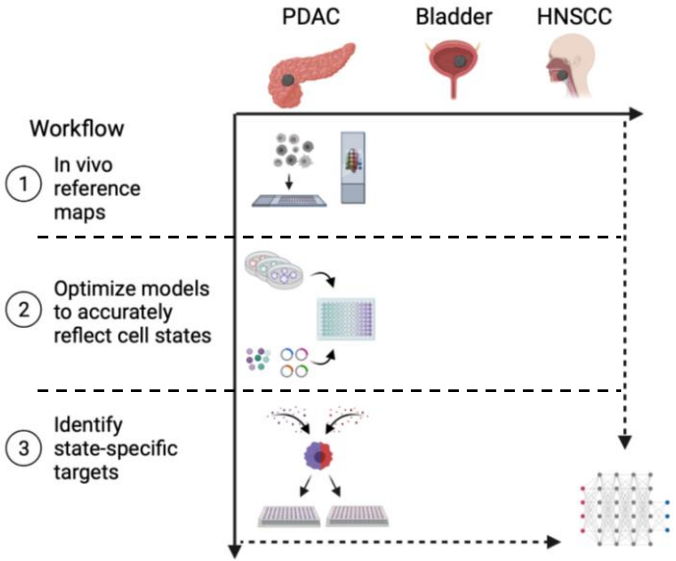
Cross-cancer effort to target cell state





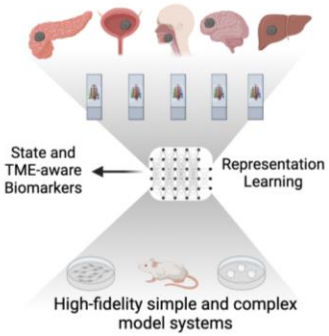
Building A Cell State Discovery Engine To “Complete The Square”

Linking cell state to druggable vulnerabilities across cancers

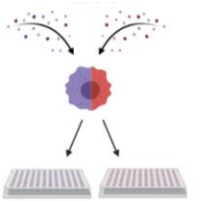


Integrative analysis framework

Learning pan-cancer ecosystems

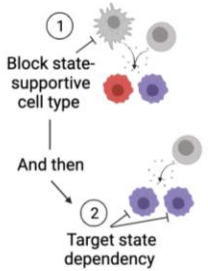


State-specific screening



- Choose correct models
- Model plasticity
- Genetic interaction

Targeting cancer ecosystems



Cell state benchmarking, vetting new biomarkers, pan-cancer and disease-specific target identification

Thank You!!!

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