What does not kill cancer can make it stronger:
Dynamical modeling of drug-induced cell-state switching

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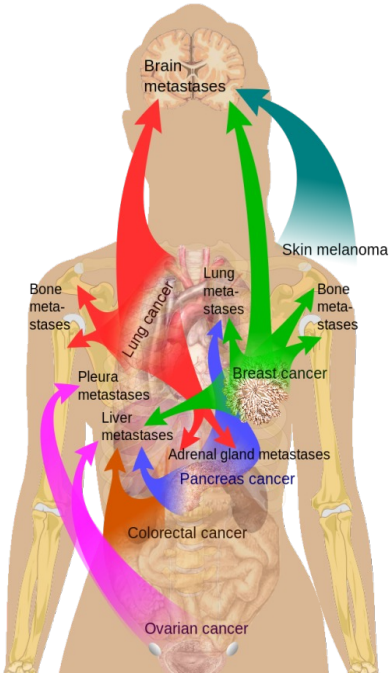
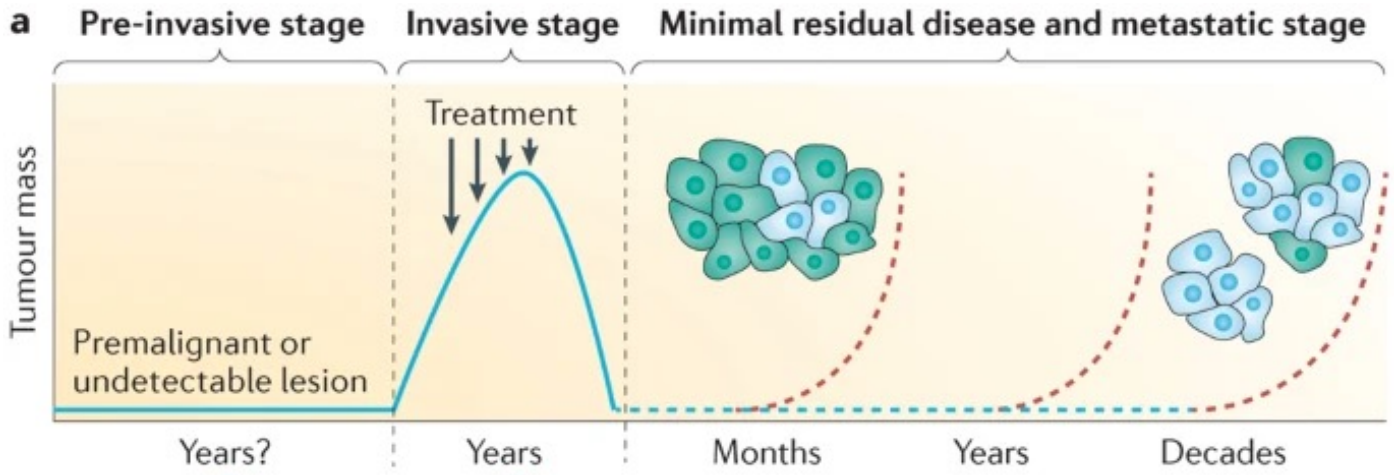
Cancer treatment: current strategies and challenges

- Surgery (1850s)
- Radiation therapy (1900s)
- Chemotherapy (1940s)
- Targeted therapy (1980s)
- Immunotherapy (2010s)

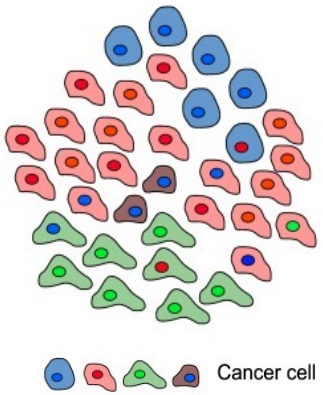
Can we have ‘magic bullets’?





Sosa *et al.* Nat Rev Cancer 2020

Tacit assumptions in current therapeutic strategies



4 types of cancer cells

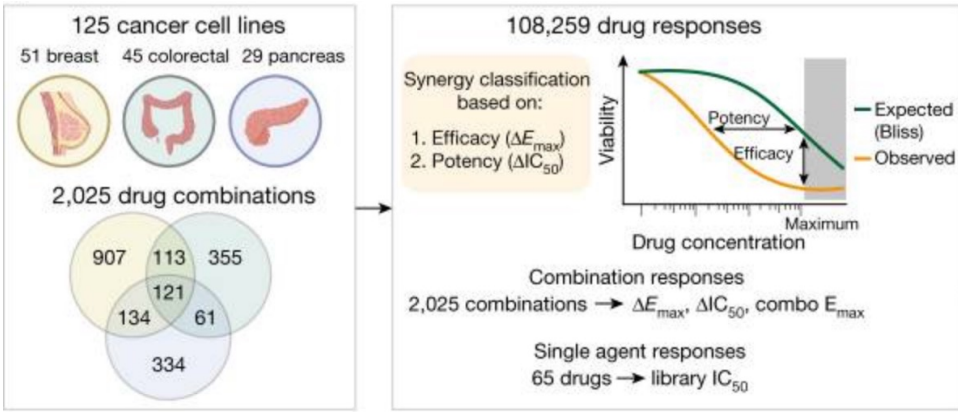
4 different drugs, each killing one cell type

- Each red cell will respond identically to concentration X of drug A and die. (Missing: Phenotypic heterogeneity)
- No drug can induce switch from a red cell to a blue cell. (Missing: Phenotypic plasticity)
- No cell cooperates with other cells during stress/drug. (Missing: Cancer as an ecosystem)

Cancer is a dynamic, complex, adaptive system and needs to be understood such.

Hinohara & Polyak, Trends Cell Biol 2019

‘Trial-n-error’ drug combinations are rarely effective



“Overall, **5.2%** of the 108,259 combination–cell line pairs showed synergy, with the highest rate in pancreas (7.2%), then colon (5.4%) and breast (4.4%).”

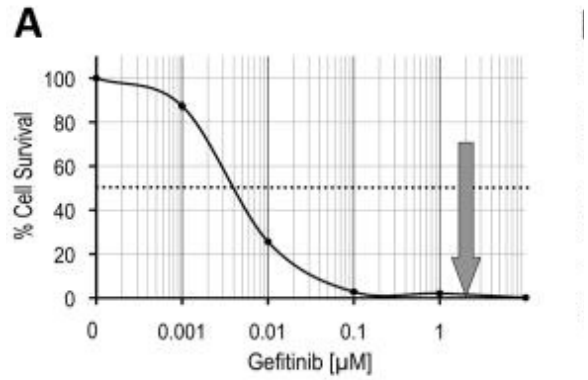
Imagine that your car breaks “worked” only in 5% cases

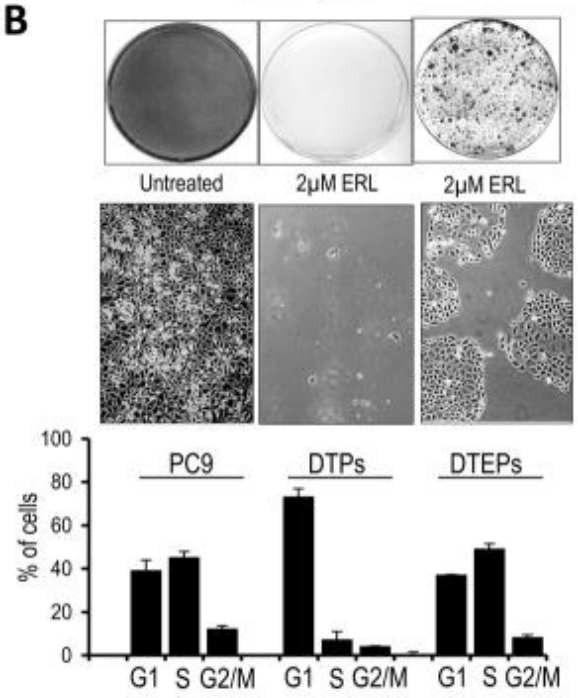
and you **did not** know which 5% cases

Can mechanism-based mathematical models help identify rational drug combinations that are more effective?

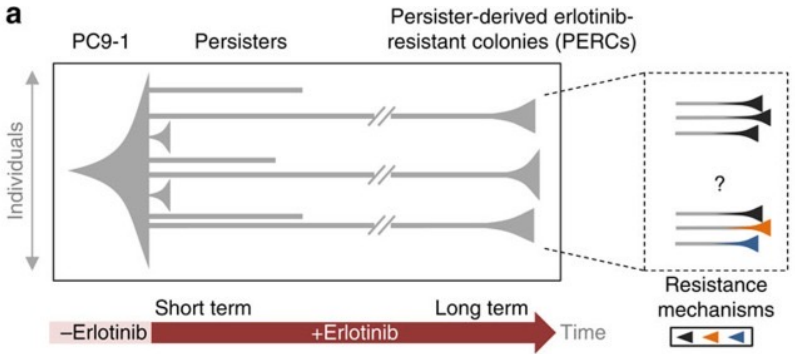
Jaaks *et al.* Nature 2022

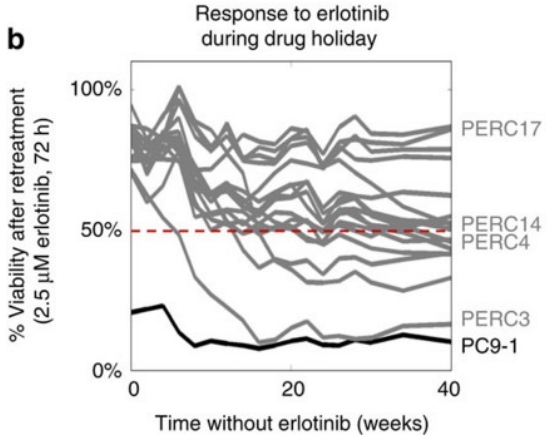
What is the fate of cells that are not killed by the drugs?

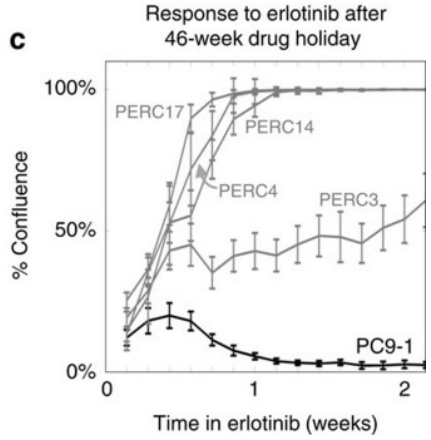




DT(E)Ps = Drug-Tolerant (Expanded) Persisters



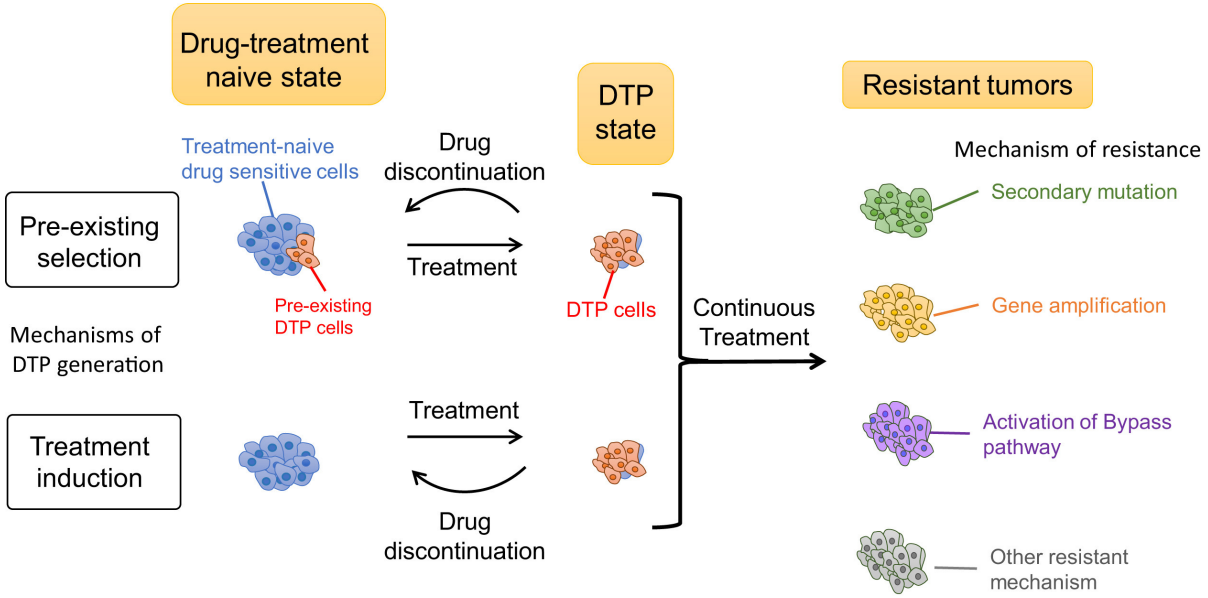


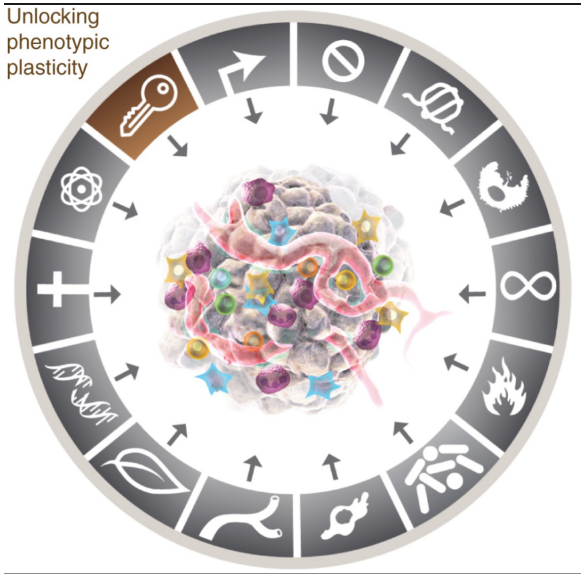


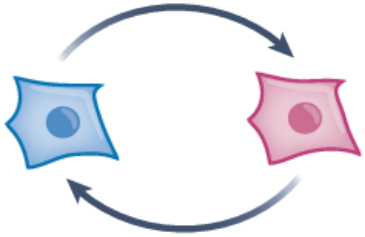
PC9 (lung cancer) cells not killed undergo :
a) rapid non-genetic adaptation
b) slow possible genetic selection/stabilization

Sharma *et al.* Cell 2009; Ramirez *et al.* Nat Comm 2016
Shaffer *et al.* Nature 2017; Shen *et al.* Nat Comm 2019
Rehman *et al.* Cell 2021; Russo *et al.* Nat Genet 2022

DTPs: an outcome of phenotypic plasticity

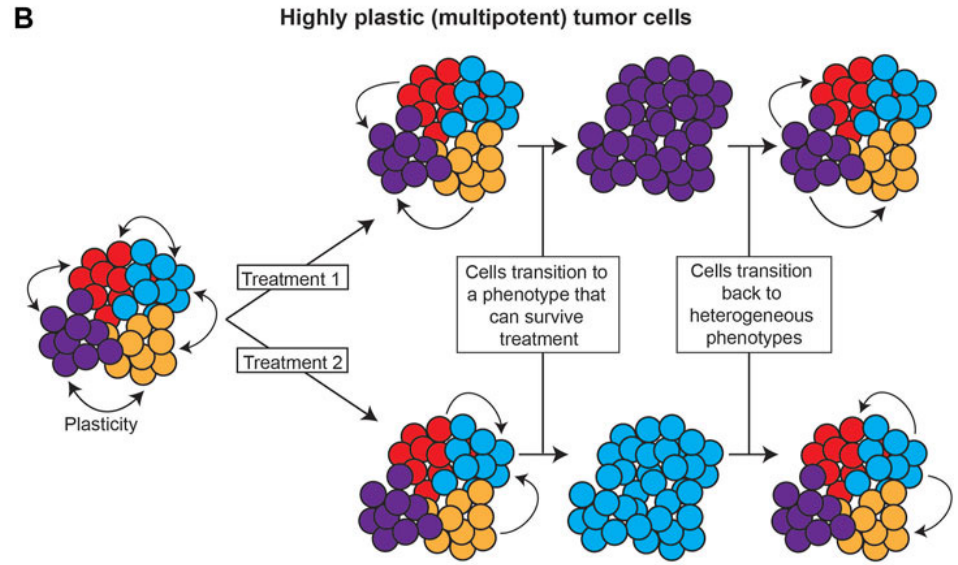






Mikubo *et al.* J Thorac Oncol 2021
Hanahan, Cancer Discov 2022
Pillai, Hojel, Jolly#, Goyal#, Nat Comp Sci 2023

Phenotypic plasticity in drug resistance & metastasis



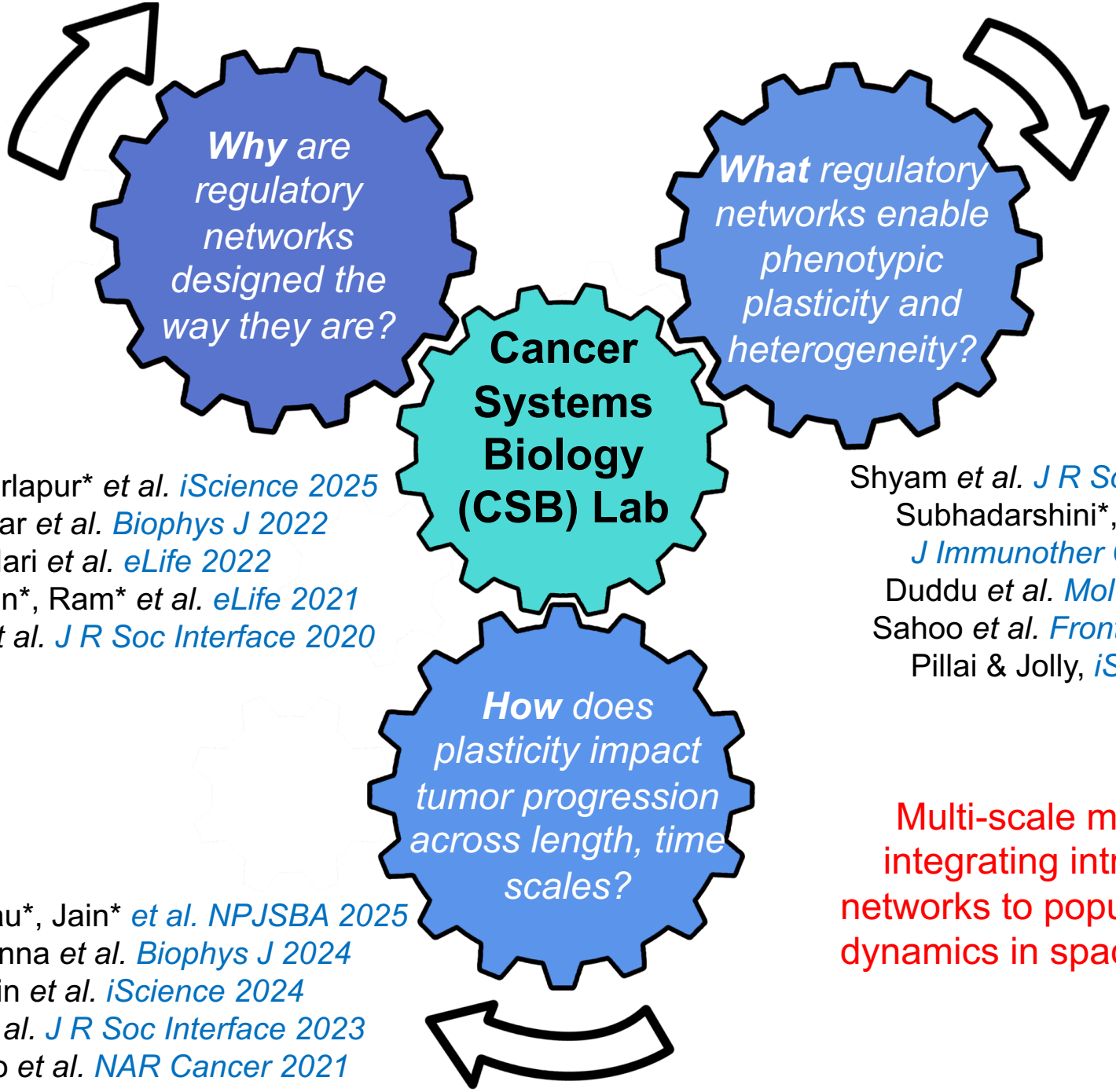
	Genetic mutations	Phenotypic plasticity
Timescale	Slow (months)	Fast (hours)
Reversibility	Irreversible	Reversible (can be transiently heritable)

No unique mutational signatures have been yet identified for metastasis.

Our focus:

- Develop mechanistic models to understand cancer cell-state transitions
- Analyse single-cell omics data to validate mechanistic dynamical models
- Predict therapeutic strategies based on better dynamical understanding

Hanahan, Cancer Discov 2022; Groves *et al.* Front Netw Physiol 2023



Hari*, Harlapur* *et al.* *iScience 2025*
Hebbar *et al.* *Biophys J 2022*
Hari *et al.* *eLife 2022*
Chauhan*, Ram* *et al.* *eLife 2021*
Duddu *et al.* *J R Soc Interface 2020*

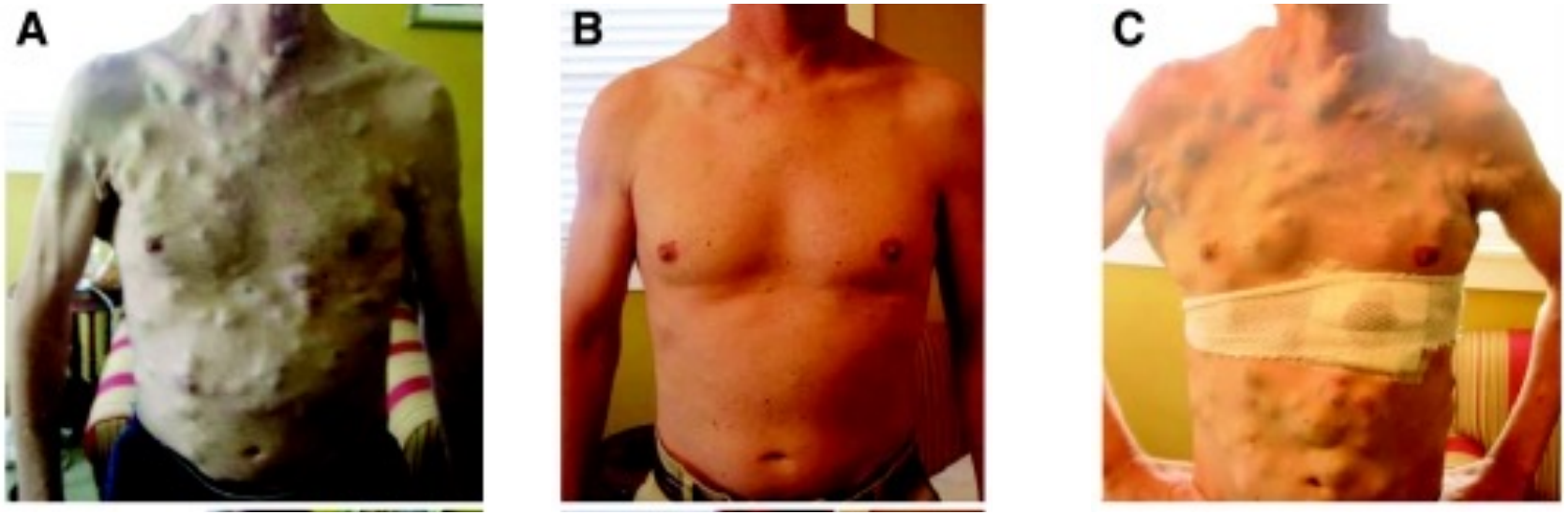
Shyam *et al.* *J R Soc Interface 2023*
Subhadarshini*, Sahoo* *et al.* *J Immunother Cancer 2023*
Duddu *et al.* *Mol Biol Cell 2022*
Sahoo *et al.* *Front Immunol 2021*
Pillai & Jolly, *iScience 2021*

Guilberteau*, Jain* *et al. NPJSBA 2025*
Prasanna *et al.* *Biophys J 2024*
Jain *et al.* *iScience 2024*
Jain *et al.* *J R Soc Interface 2023*
Sahoo *et al.* *NAR Cancer 2021*

Multi-scale modeling: integrating intracellular networks to population level dynamics in space and time

Case study 1: Minimal residual disease in melanoma

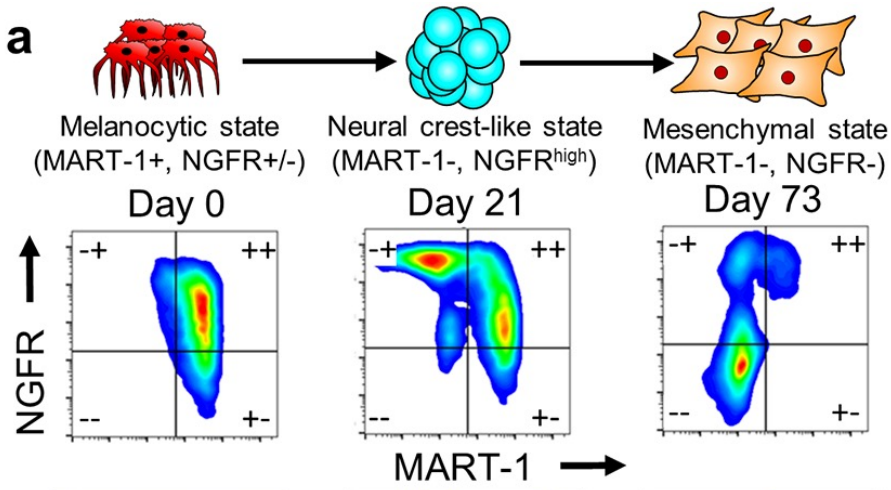
- 70% of all melanomas contain mutations in RAS-RAF pathway
- Targeted therapy includes BRAF inhibitors – Vemurafenib
- Only 29% 5-year survival rate post metastasis



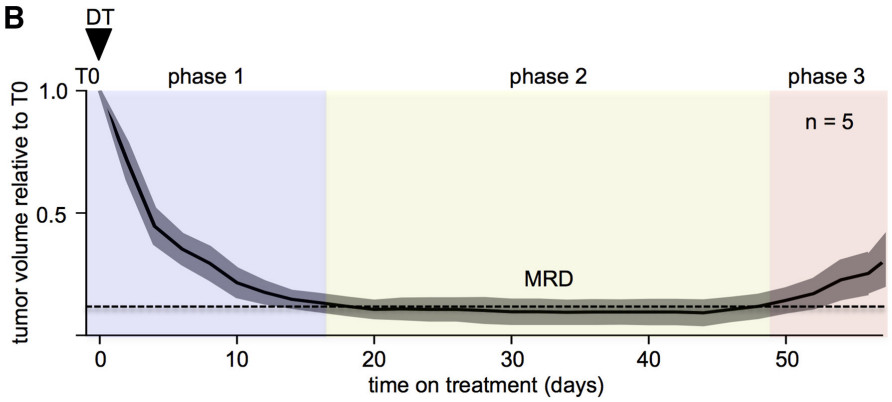
Pre-treatment | 15 weeks after therapy | 23 weeks after therapy

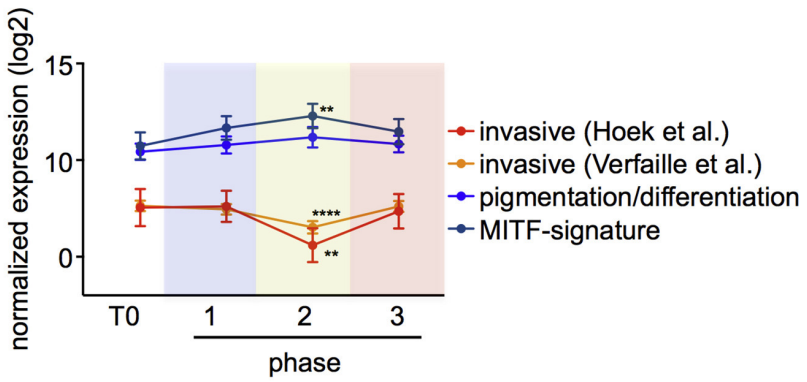
Rambow *et al*. Cell 2018; Wagle *et al.* J Clin Oncol 2011

Drug-induced phenotypic transitions in melanoma



Response of $BRAF^{V600E}$ mutant cell line to BRAF inhibition

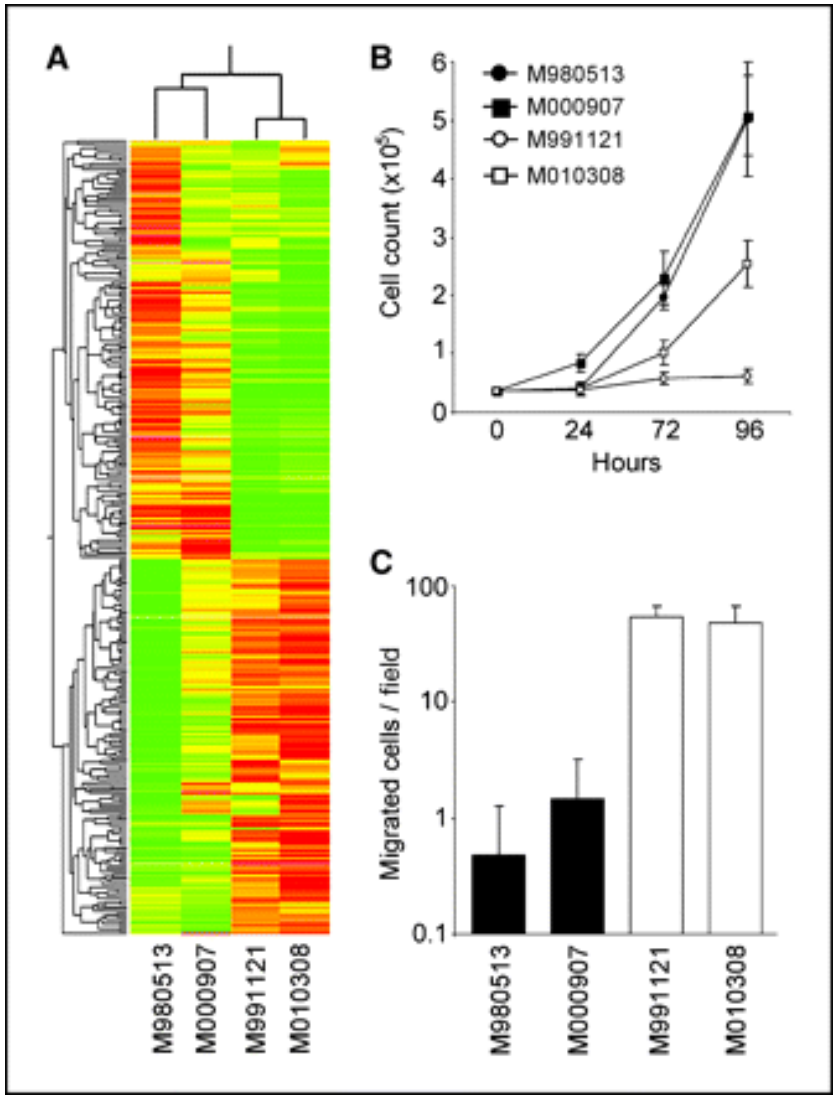


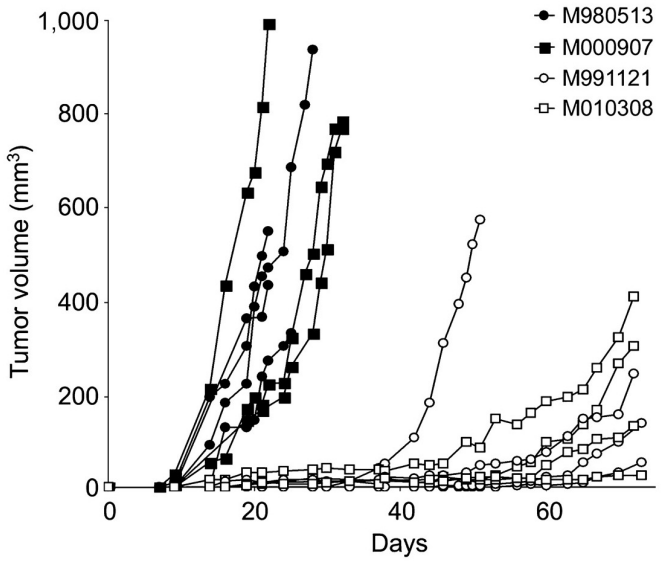


Response of $BRAF^{V600E}$ PDX model to BRAF inhibition

Rambow *et al*. Cell 2018; Su *et al.* PNAS 2017; Su *et al*. PLoS Comp Biol 2019

Phenotypic plasticity in melanoma drives heterogeneity



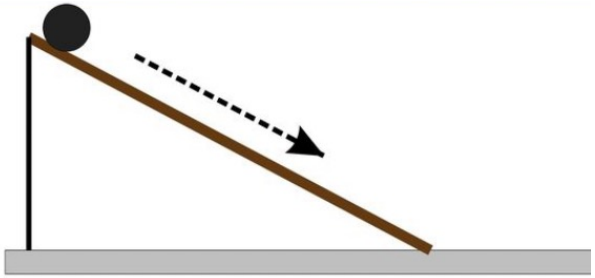


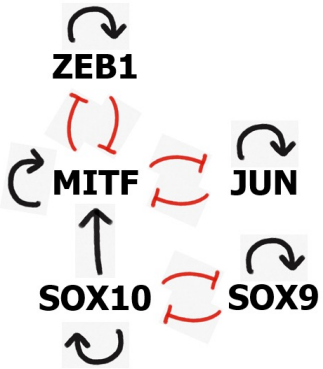
- Both “proliferative” and “invasive” cells grew tumors *in vivo* (PDX).
- Tumors grown *in vivo* from either population contained both “proliferative” and ”invasive” cells.

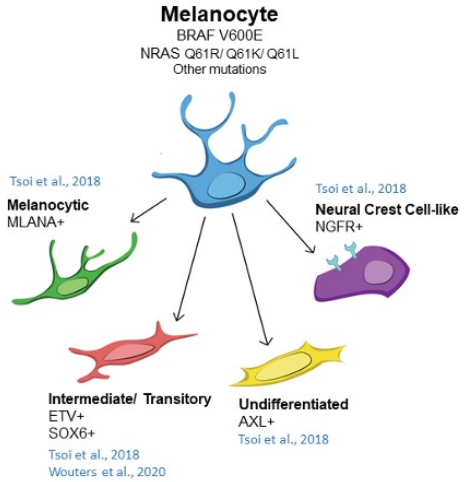
Hoek *et al.* Cancer Res 2008

An Occam's razor (minimalistic) approach

Can we identify a ***minimal*** network that can explain phenotypic switching in melanoma?





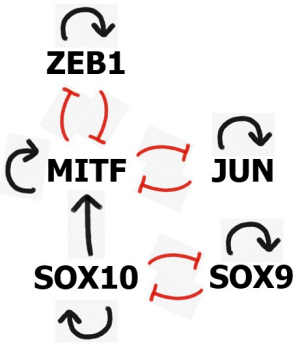


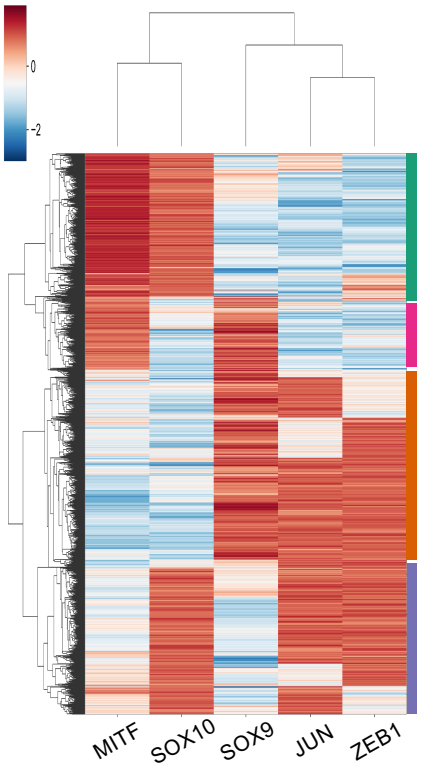
Sarthak Sahoo
(PhD, IISc)

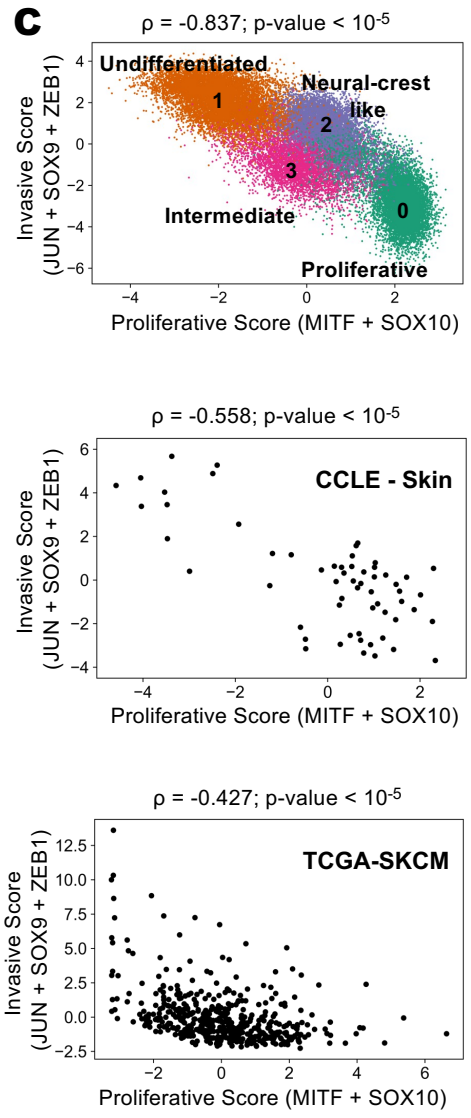
Seemadri Subhadarshini
(PhD, IISc)

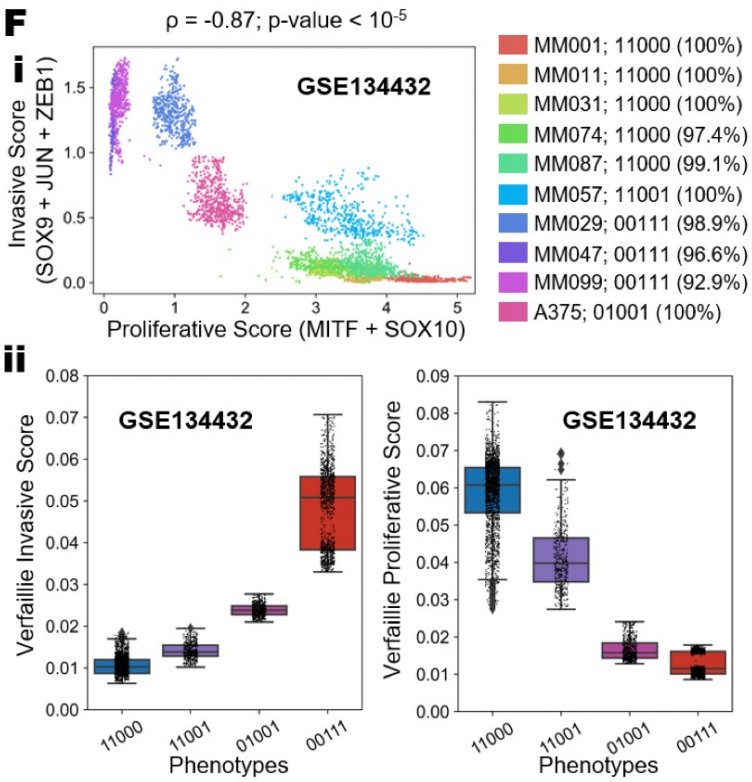
(**Mechanism-based approach**: from regulatory network to transcriptomic data)

A minimal network captures proliferative-invasive transition









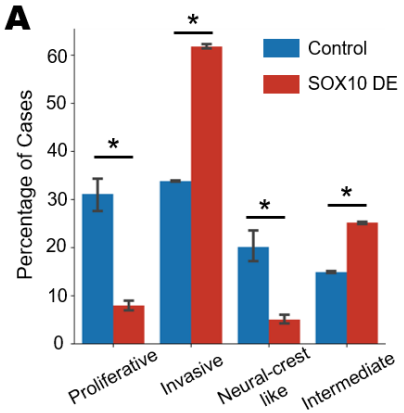
Minimal (5-dimension) network explains patterns observed in ~1000 gene-signature ensemble

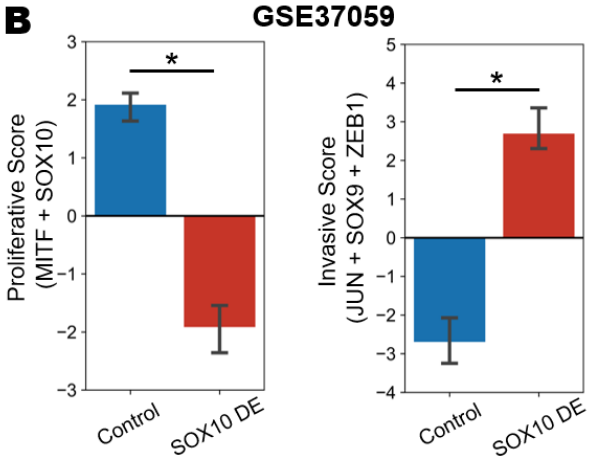
Subhadarshini*, Sahoo* *et al.* J Immunother Cancer 2023

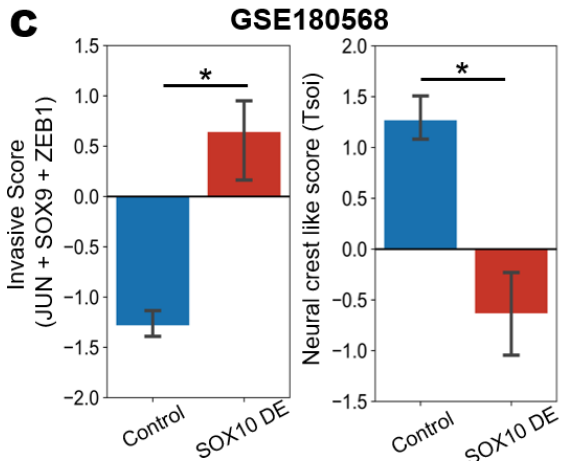
In silico recapitulation of SOX10 KD dynamics *in vitro*

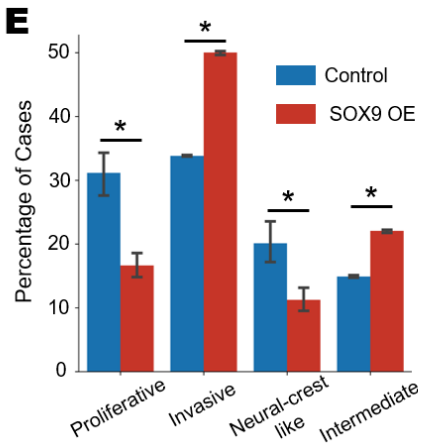
In silico
model prediction

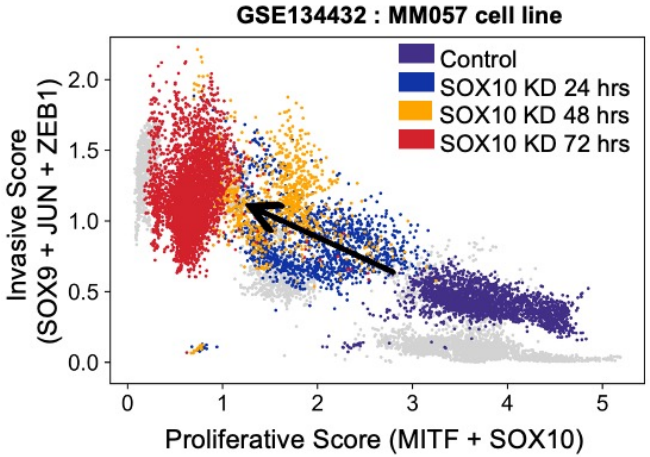
In vitro
experimental validation

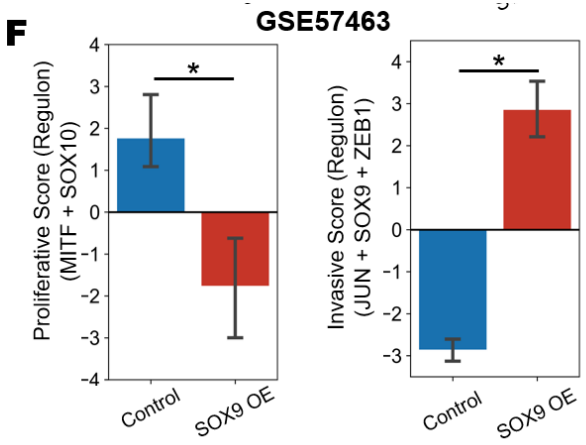










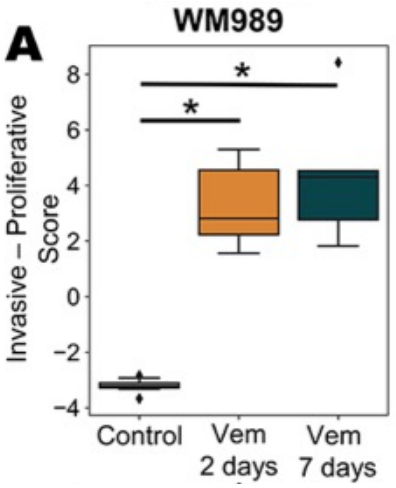


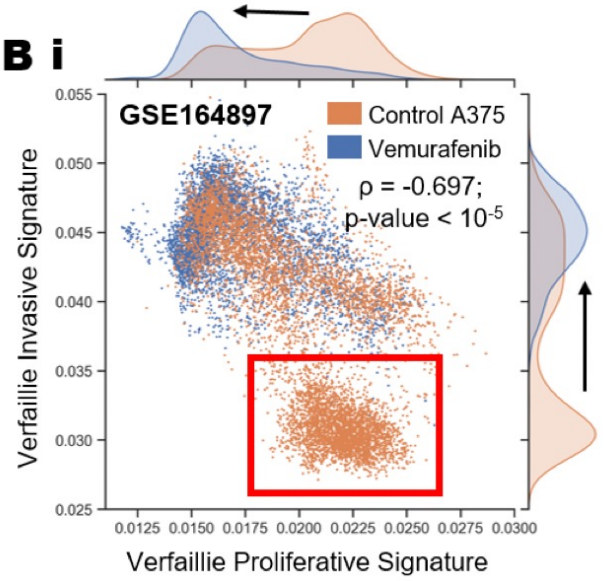
Subhadarshini*, Sahoo* *et al.* J Immunother Cancer 2023

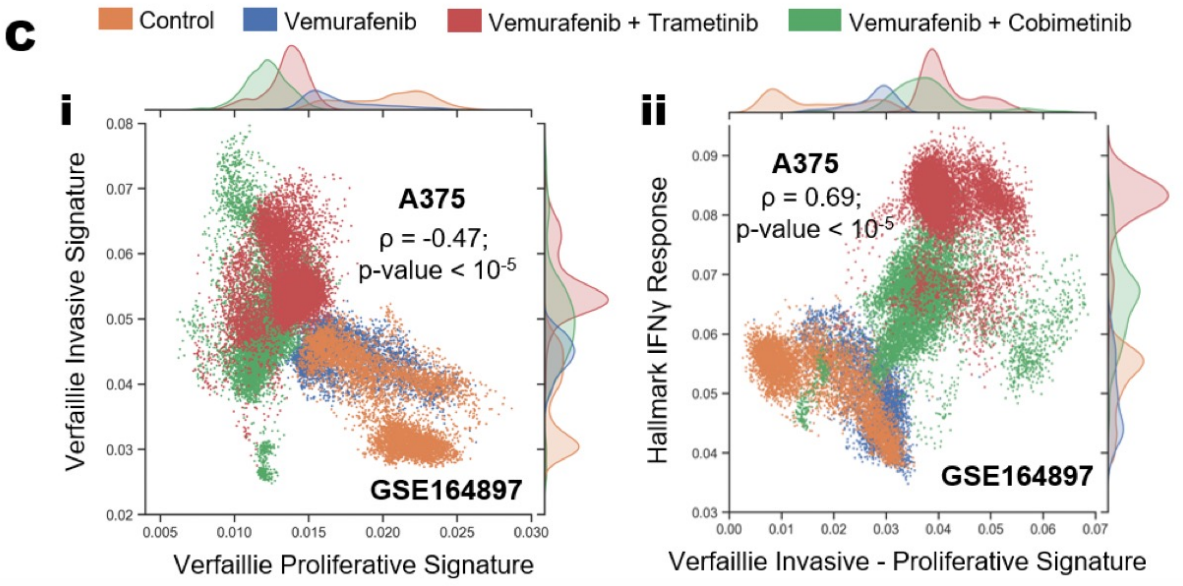
scRNA-seq data analysis reveals drug-induced plasticity

Pre-existing heterogeneity in A375 (scRNA-seq): induction or selection?

Combinatorial drug treatment leading to new phenotypes: plasticity





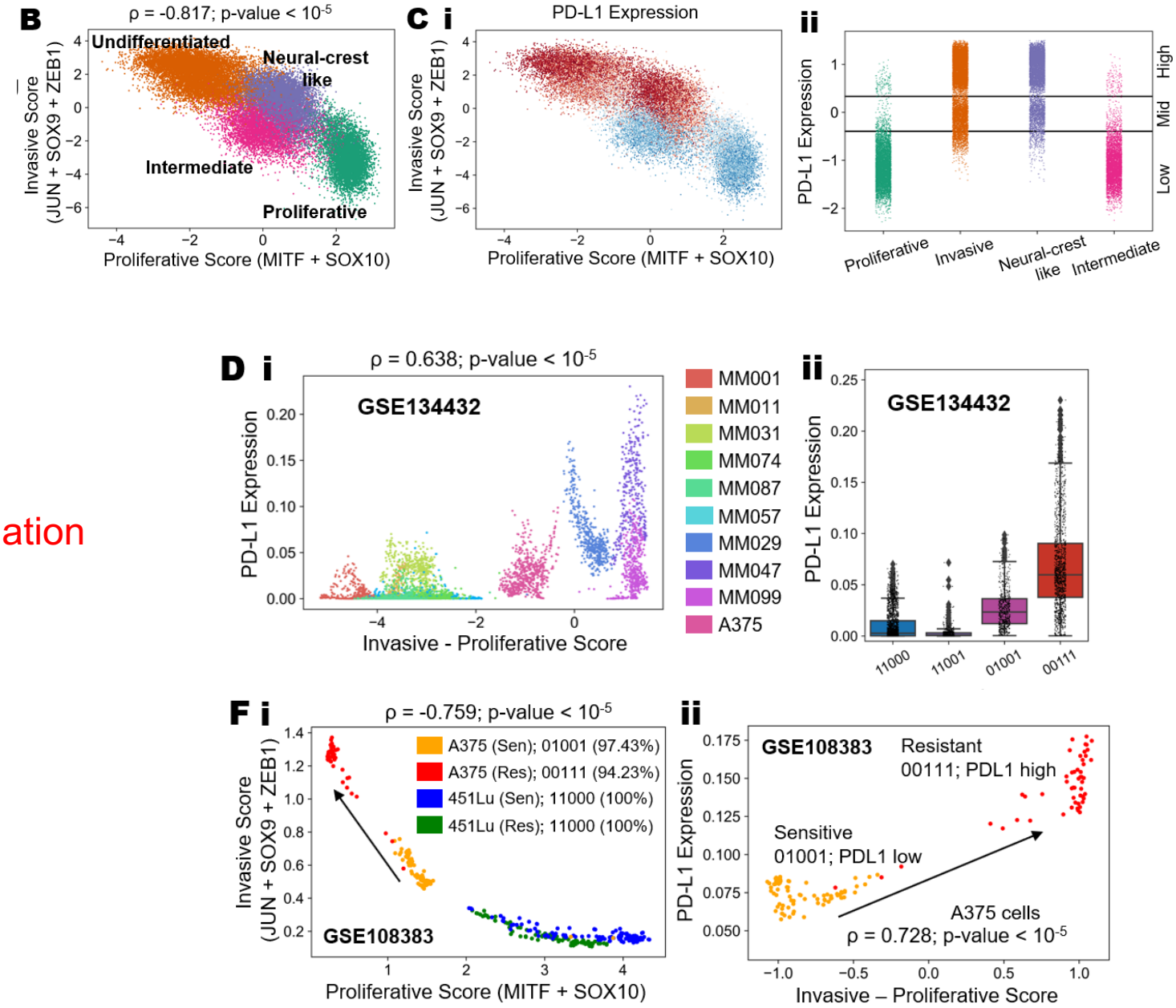


Subhadarshini*, Sahoo* *et al.* J Immunother Cancer 2023

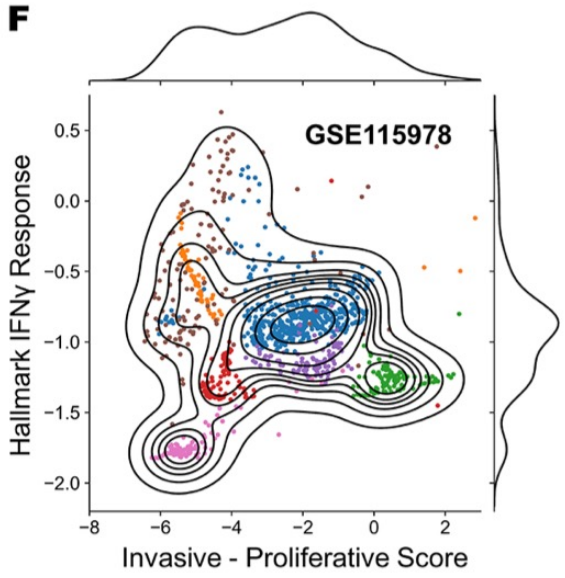
Proliferative-invasive switch associates with increased PD-L1

In silico
model prediction

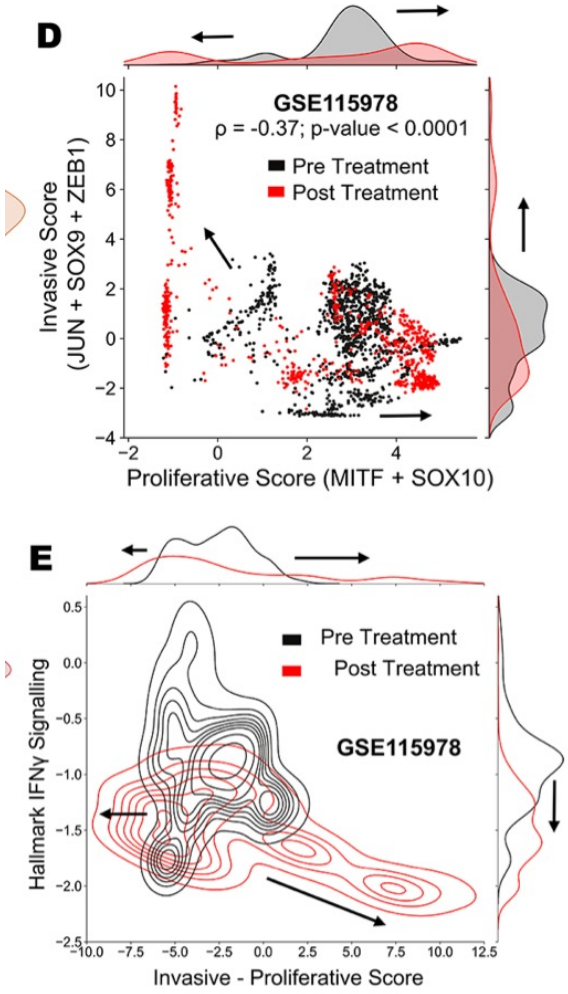
In vitro
experimental validation



Drug-induced plasticity in ICI-treated patient samples



Pre-treatment(immune checkpoint inhibitor (ICI)) heterogeneity in patient tumors

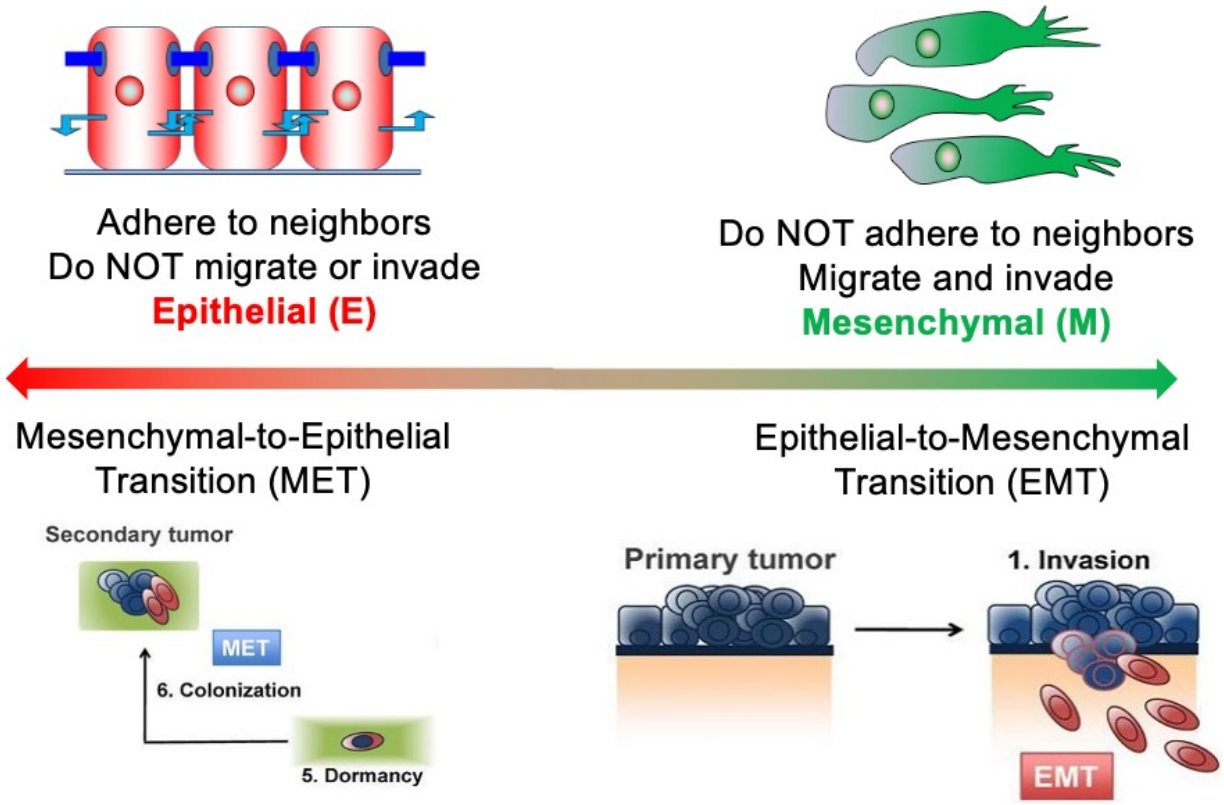


Post-treatment plasticity & heterogeneity in patient tumors

Subhadarshini*, Sahoo* *et al.* J Immunother Cancer 2023

Case study 2: Tamoxifen resistance in ER+ breast cancer

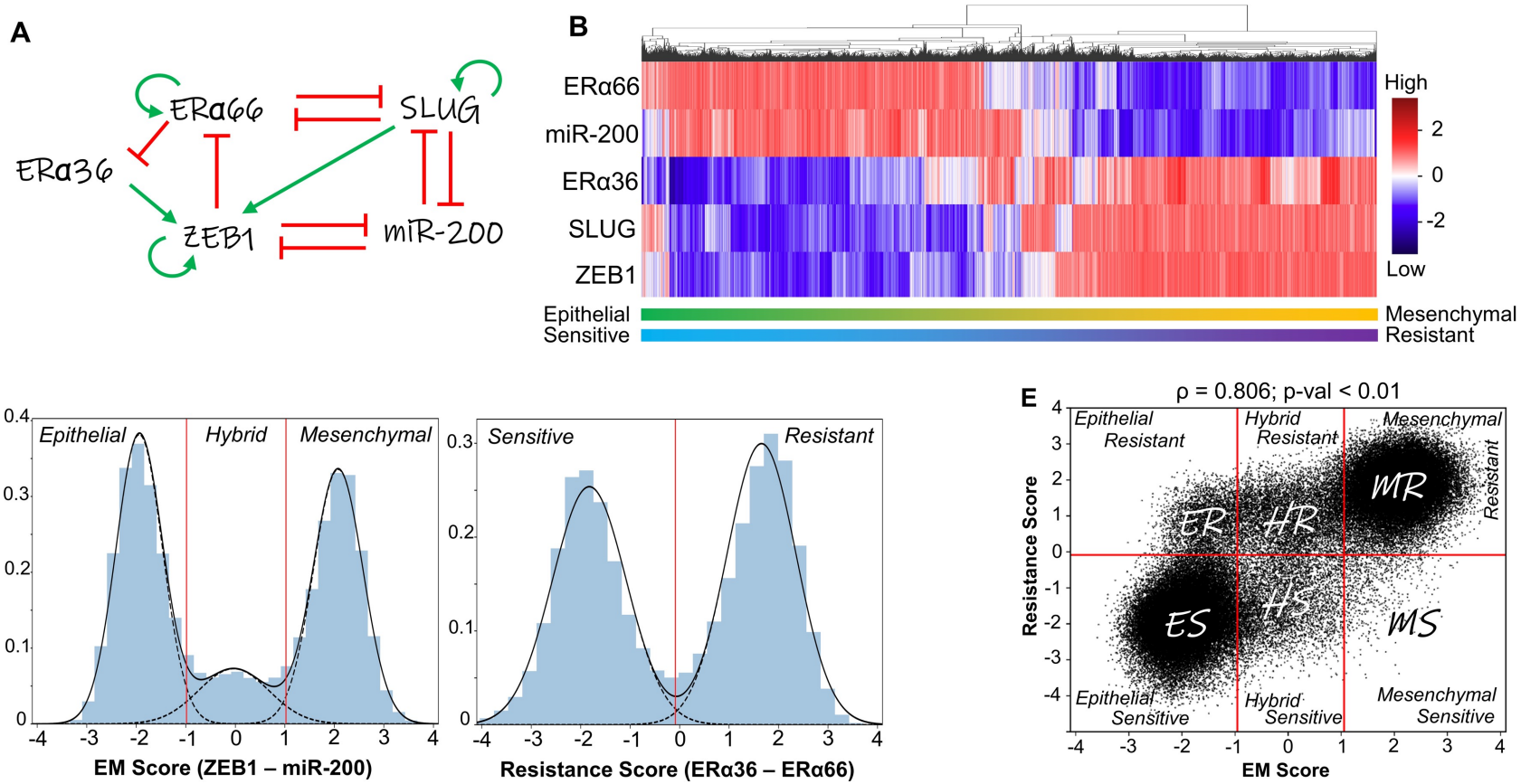
Tamoxifen: 1st targeted therapy; given to ER+ breast cancer patients (75% of BC cases)



- Does EMT drive tamoxifen resistance or *vice versa*?
- Can state-switching enable long-term 'resistance' without genetic changes?

Scheel & Weinberg, Seminars in Cancer Biology 2012

Association between (E, sensitive) and (M, resistant) states

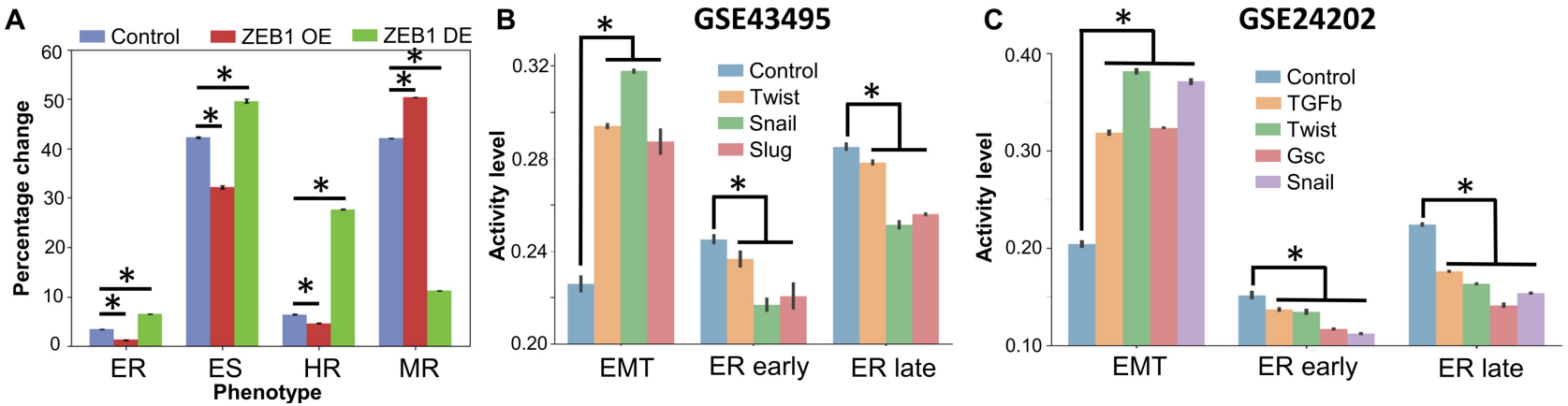


- E state usually Tam-Sensitive; M state usually Tam-Resistant
- Hybrid E/M state can be Tam-Resistant too

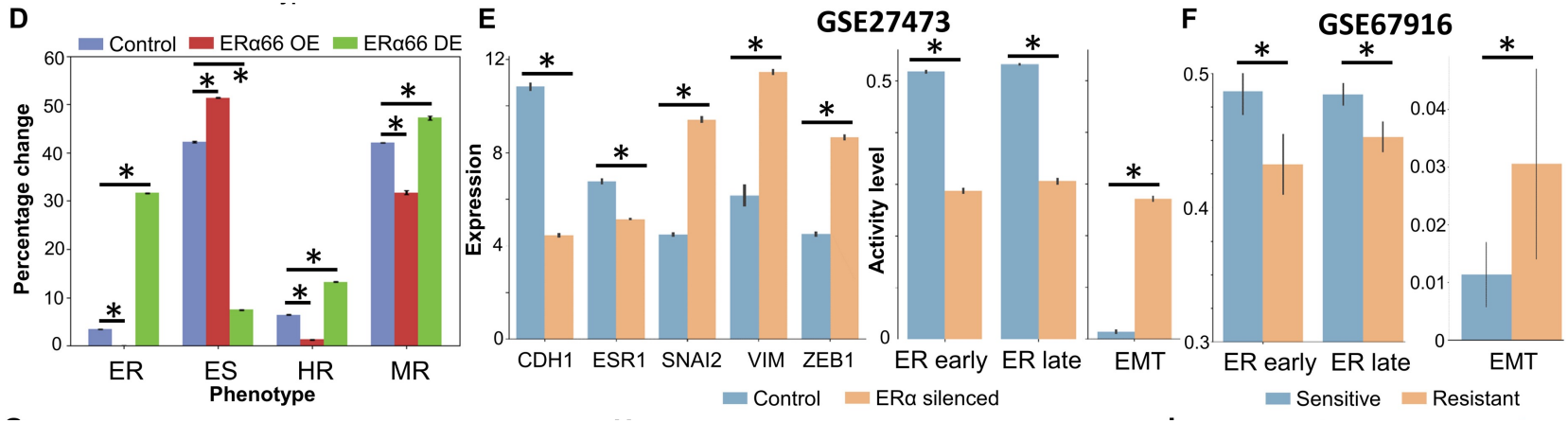
Sarthak Sahoo

Sahoo *et al.* NAR Cancer 2021

EMT & Tam Res can drive each other



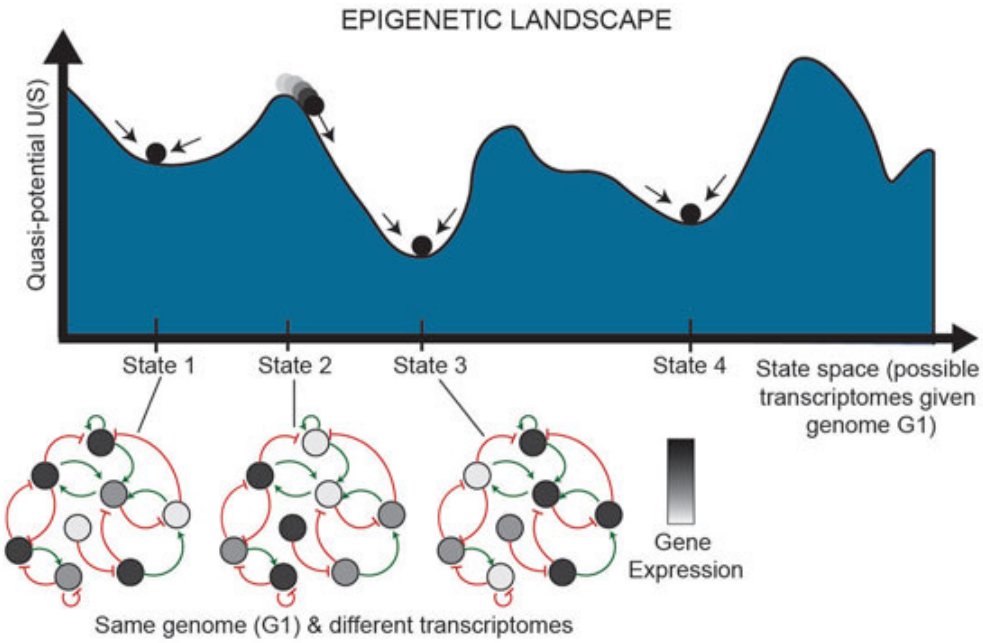
EMT can drive resistance to tamoxifen

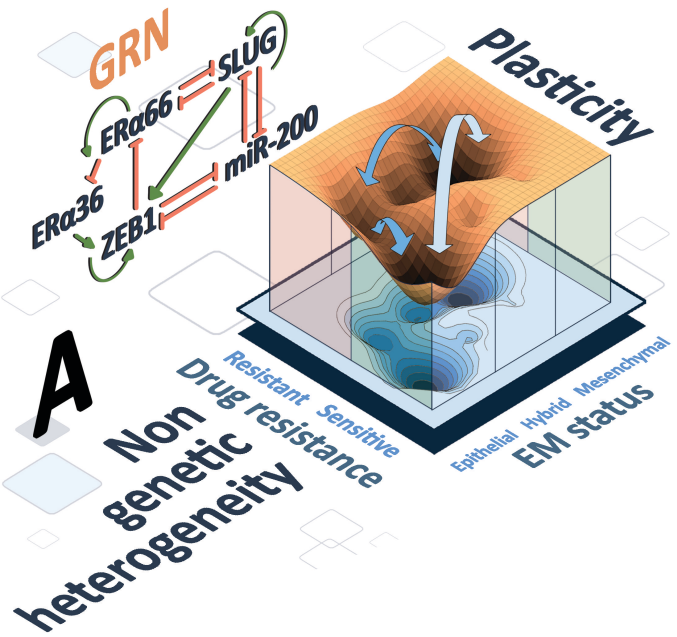


Tamoxifen resistance can drive EMT

Sahoo *et al.* NAR Cancer 2021

Summary (Part 1)

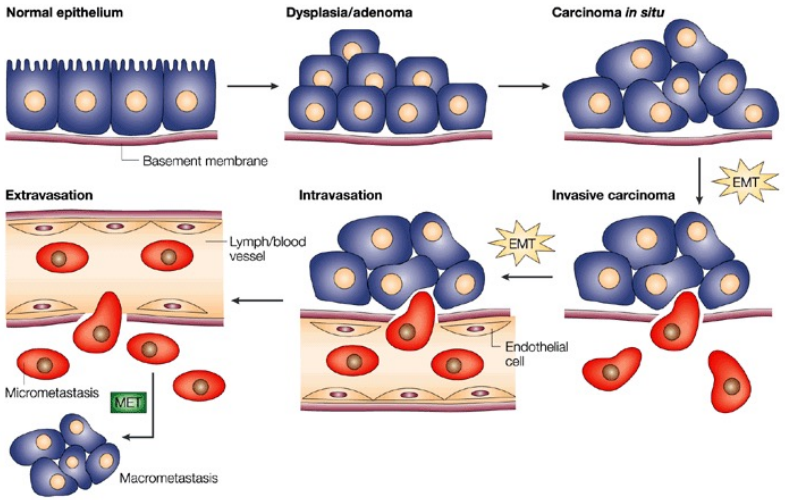




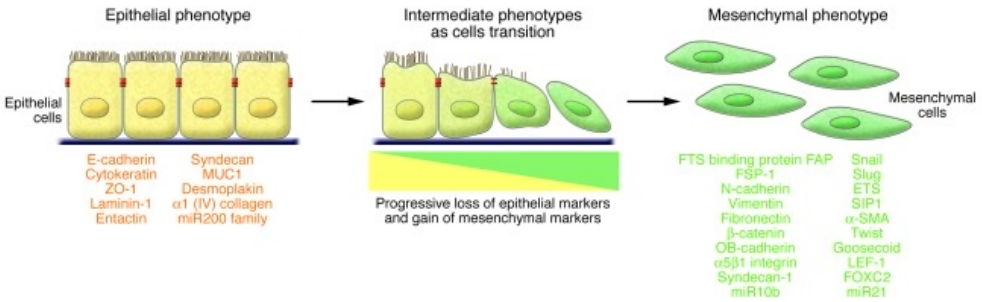
- Regulatory networks underlying melanoma & ER+ breast cancer plasticity are multi-stable in nature.
- Multi-stability allows for spontaneous & (drug-) induced cell-state switching.

What mechanisms control the rate of cell-state switching and can we measure it quantitatively?

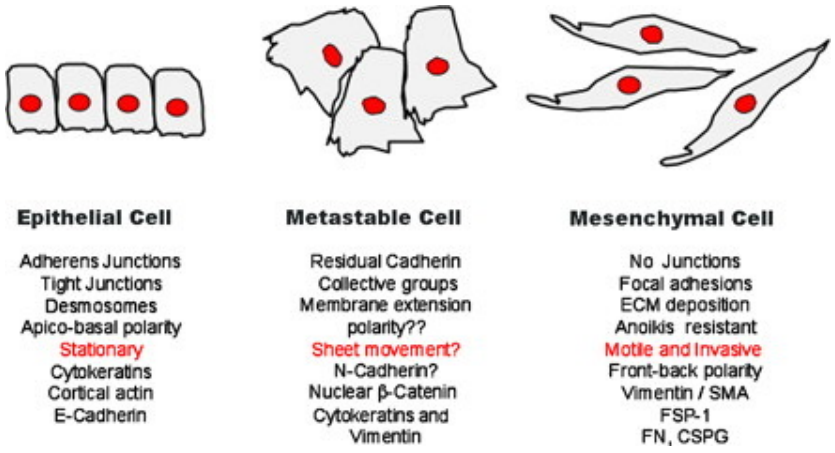
Role of EMT in cancer metastasis (2002 – 2012)



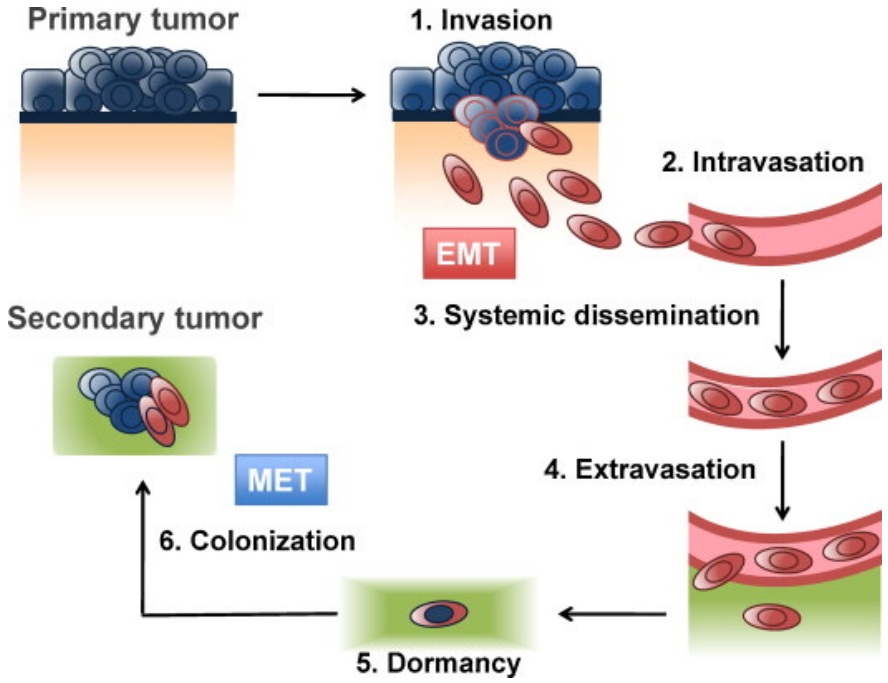
Thiery JP, Nat Rev Cancer 2002



Kalluri & Weinberg, J Clin Invest 2009

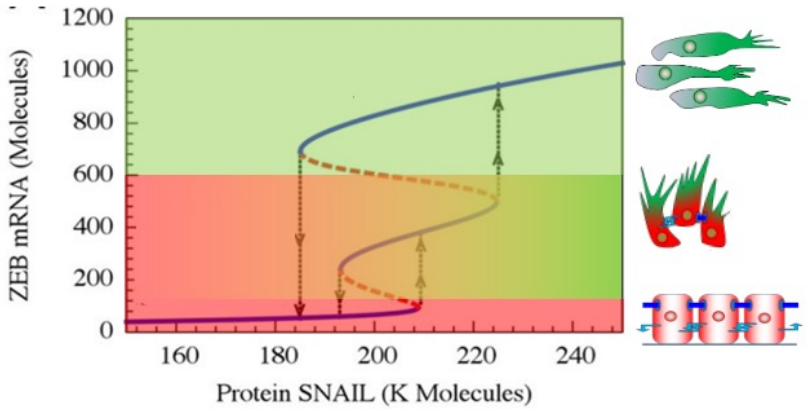


Lee *et al.* J Cell Biol 2006

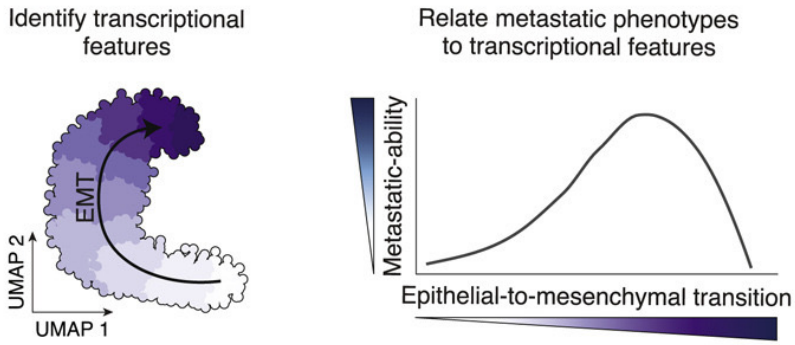


Scheel & Weinberg, Semin Cancer Biol 2012

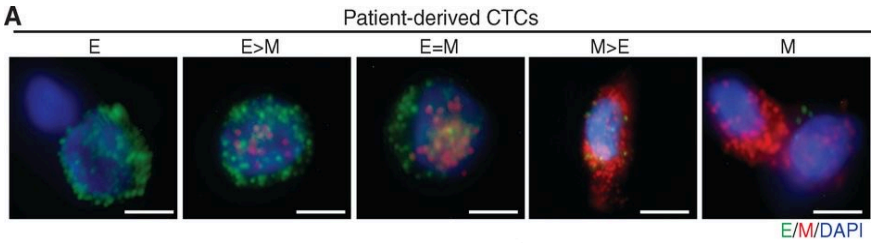
From EMT (2002-2012) to EMP (Epi-Mes Plasticity; 2013-now)



Lu#, Jolly# *et al.* PNAS 2013



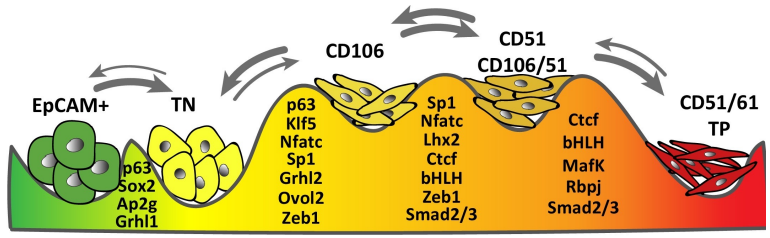
Simeonov *et al.* Cancer Cell 2021



Acquisition of a hybrid E/M state is essential for tumorigenicity of basal breast cancer cells

Cornelia Kröger[a], Alexander Afeyan[a,b], Jasmin Mraz[a,c], Elinor Ng Eaton[a], Ferenc Reinhardt[a], Yevgenia L. Khodor[d], Prathapan Thiru[a], Brian Bierie[a], Xin Ye[a,e], Christopher B. Burge[d], and Robert A. Weinberg[a,f,g,1]

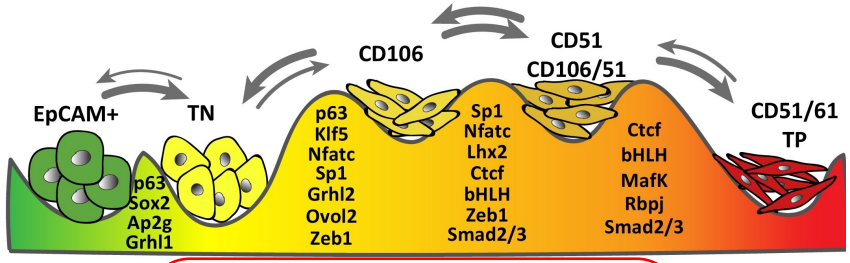
Yu *et al.* Science 2013
Kroger *et al.* PNAS 2019



	Epithelial tumor cells	Early hybrid EMT state	Hybrid EMT state	Late hybrid EMT state	Mesenchymal tumor cells
Proliferation	+++++	++++	+++	++	+
Invasion	+	++	+++	++++	+++++
Plasticity	+	++	+++	++++	++
Stemness	+	+++	+++	+++	+++
Metastasis	+	++++	++++	++	+

Pastushenko & Blanpain, Trends Cell Biol 2019
Pastushenko *et al.* Nature 2018

Hybrid E/M: the ‘fittest’ for metastasis?



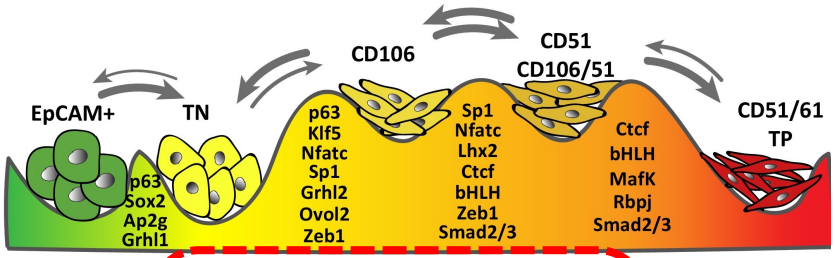
	Epithelial tumor cells	Early hybrid EMT state	Hybrid EMT state	Late hybrid EMT state	Mesenchymal tumor cells
Proliferation	+++++	++++	+++	++	+
Invasion	+	++	+++	++++	+++++
Plasticity	+	++	+++	++++	++
Stemness	+	+++	+++	+++	+++
Metastasis	+	++++	++++	++	+

Pastushenko *et al.* 2019

(*Man vs. Wild* TV series – Bear Grylls)

Why are hybrid E/M cells the ‘fittest’?

Kishore Hari



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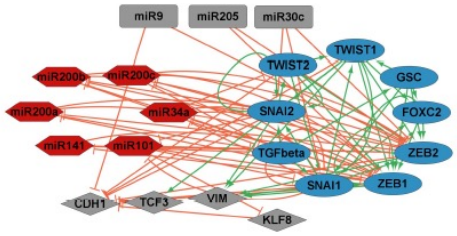
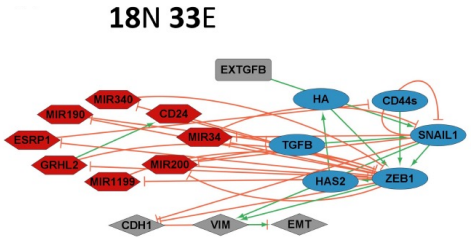
Proliferation	+++++	++++	+++	++	+
Invasion	+	++	+++	++++	+++++
Plasticity	+	++	+++	++++	++
Stemness	+	+++	+++	+++	+++
Metastasis	+	++++	++++	++	+

$$s_i(t+1) = \begin{cases} +1, \sum_j Adj_{ij} s_j(t) > 0 \\ -1, \sum_j Adj_{ij} s_j(t) < 0 \\ s_i(t), \sum_j Adj_{ij} s_j(t) = 0 \end{cases}$$

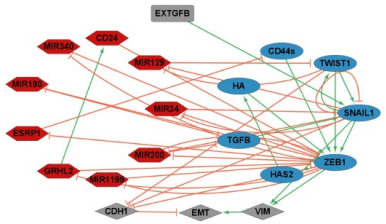
Is the “high plasticity” behavior of hybrid E/M a feature of underlying regulatory networks?



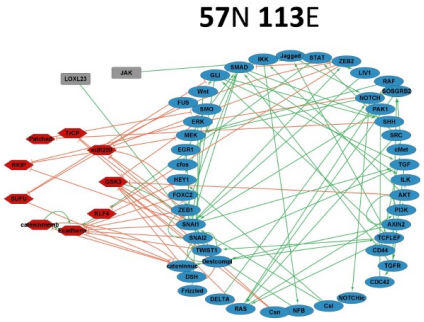
22N 82E



18N 33E



20N 40E

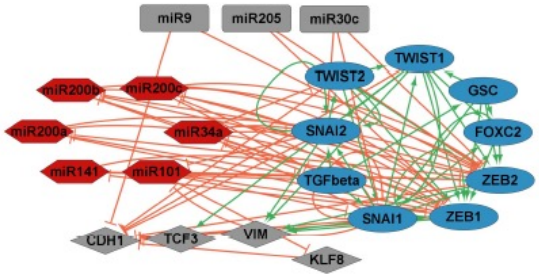


57N 113E

Nodes: Epithelial, Mesenchymal.

Edges: Activation, Inhibition

EMT networks consist of two “teams” of players



22N 82E

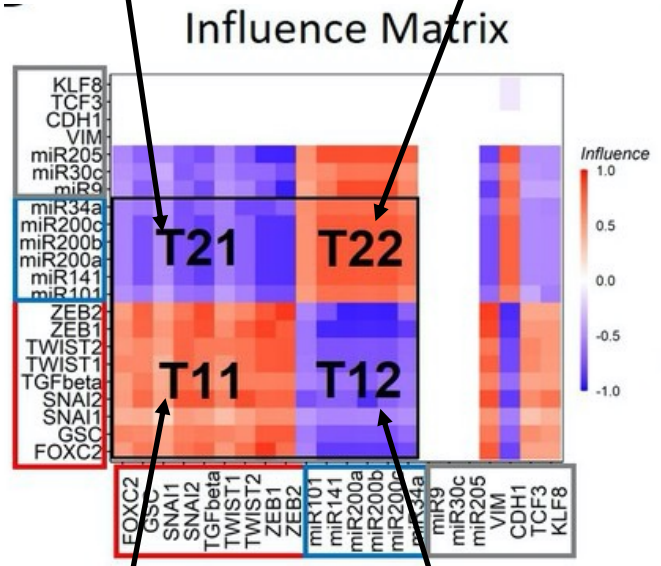
$$Infl = \frac{\sum_{l=1}^{lmax} \frac{Adj^l}{Adj^l_{max}}}{lmax}$$

$$T_{KL} = \frac{\sum_{i \in T_K} \sum_{j \in T_L} Infl_{ij}}{n_{KL}}, K, L \in \{1,2\}$$

$$Ts = \frac{\sum_{K,L \in \{1,2\}} |T_{KL}|}{4}$$

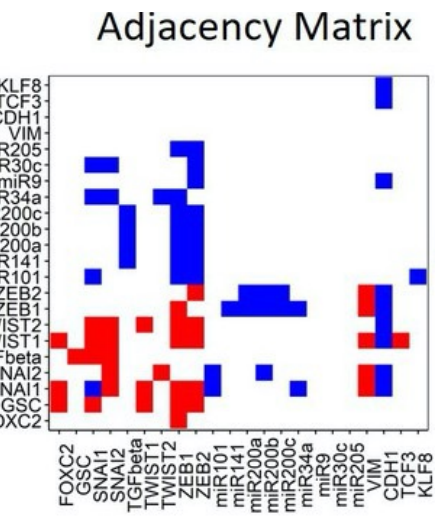
All Epi nodes effectively **inhibit** all Mes nodes.

All Epi nodes effectively **activate** all Epi nodes.



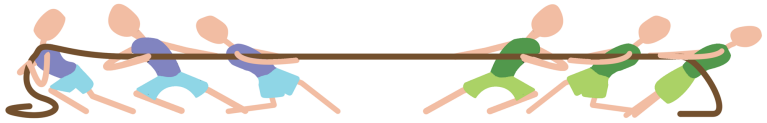
All Mes nodes effectively **activate** all Mes nodes.

All Mes nodes effectively **inhibit** all Epi nodes.

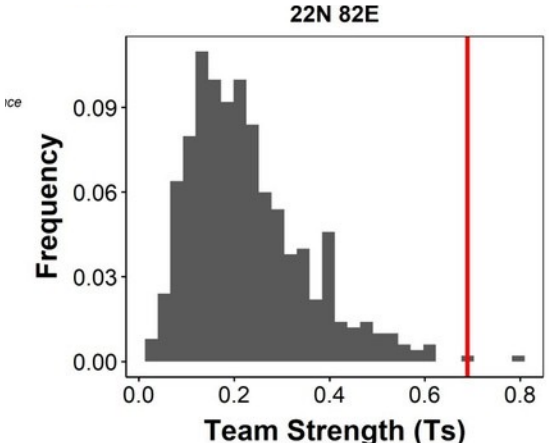


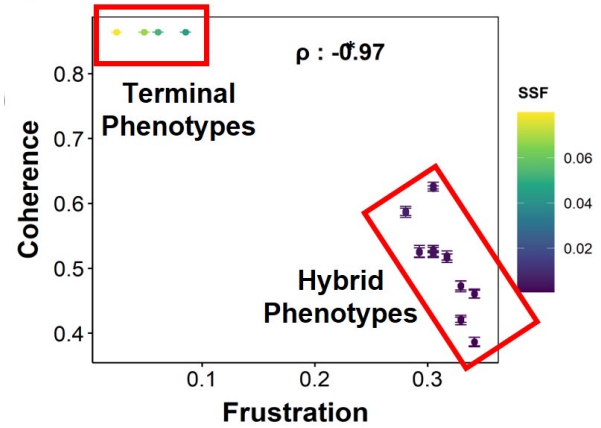
Row => Source; Column => Target

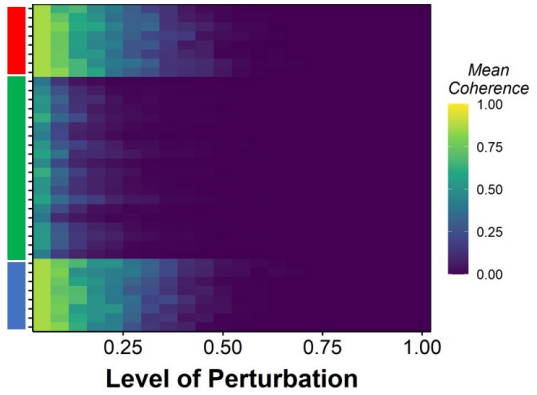
Red (Activation), Blue (Inhibition)

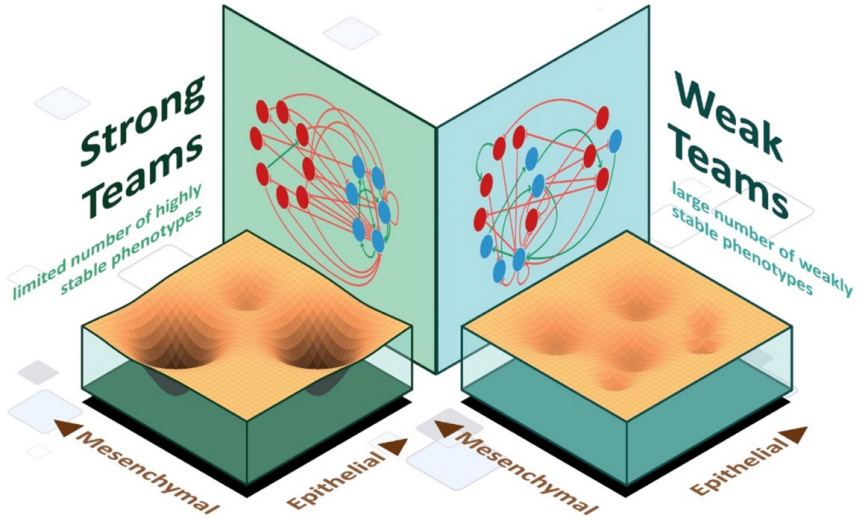


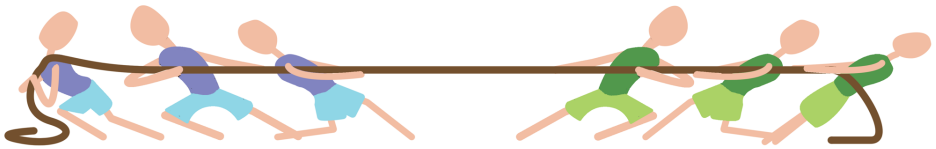
“Teams” offer “resistance” to transition out of E, M











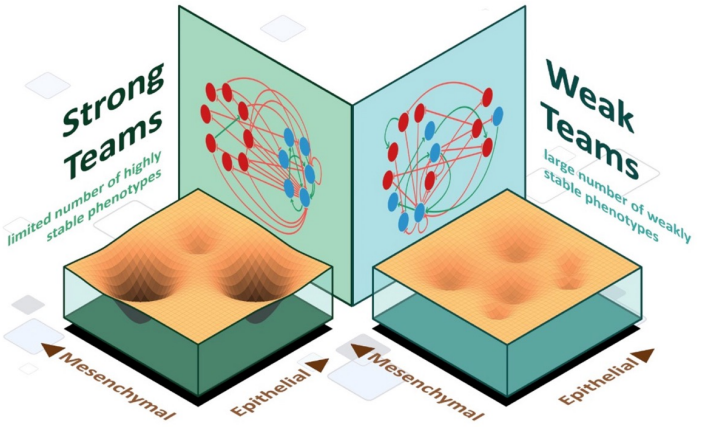
Absence of any “teams” supporting the hybrid E/M phenotypes makes them the ‘fittest’ for metastasis.

Hari *et al.* eLife 2022

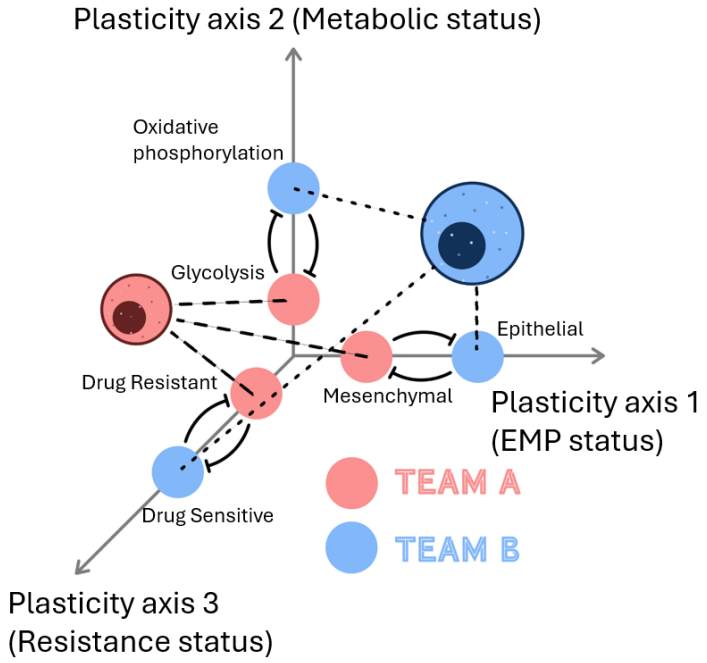
Why do “teams” exist?

To shape the phenotypic plasticity landscape

=> Control the rates of cell-state transitions

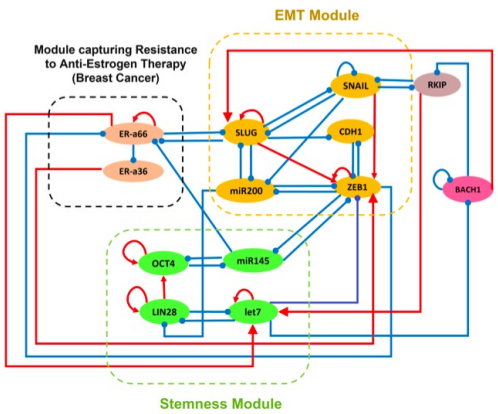


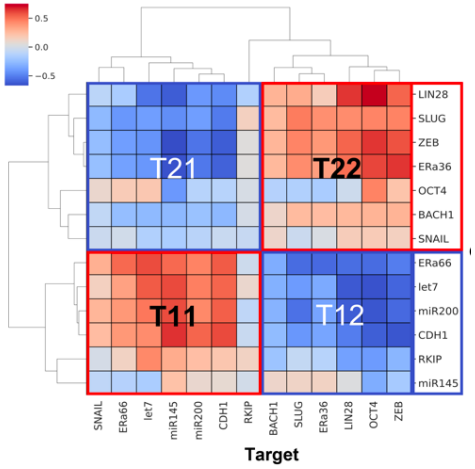
To couple the multiple axes of phenotypic plasticity
=> Increase the ‘fitness’ of metastasizing cells

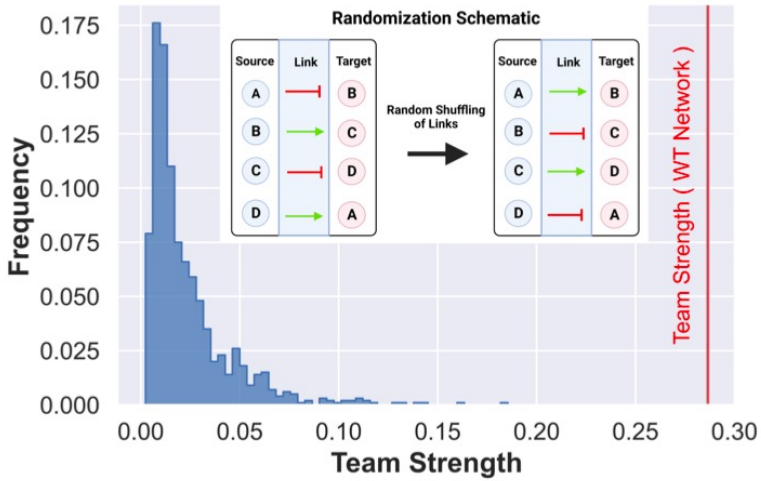


Sahoo *et al.* Curr Opin Cell Biol 2024

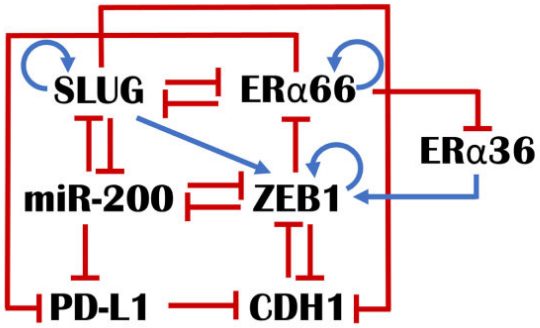
“Teams” enabling coupling between more than 2 axes

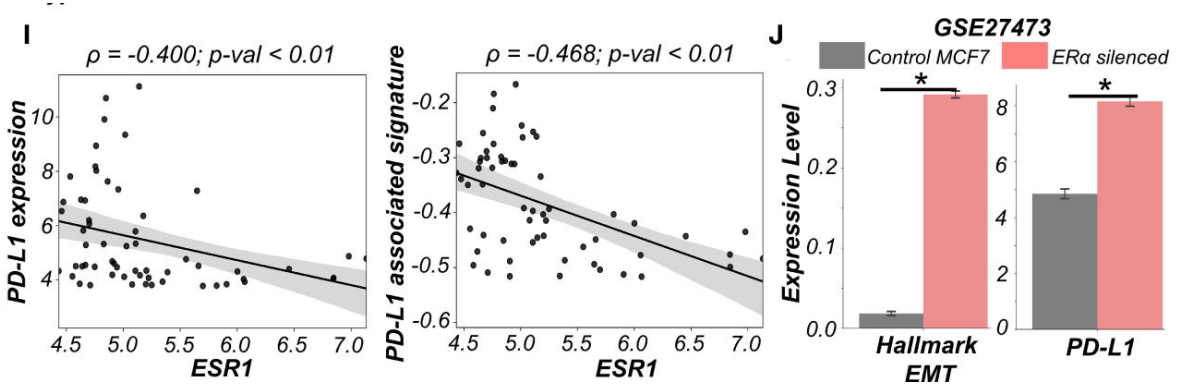






“Teams” connecting EMT, Tam-Res and stemness phenotypes





“Teams” connecting EMT, Tam-Res and PD-L1 (+ve) phenotypes

Sahoo *et al.* Front Immunol 2021; Shyam *et al.* J R Soc Interface 2023

Data deluge era: Mapping different trajectories of EMP

- Multiple trajectories during EMT induction; varying molecular profiles/ functions
- Different possible trajectory(ies) of MET compared to EMT
- Different rates/extents of MET depending on intrinsic EMT state

PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY

Reconstruction of single-cell lineage trajectories and identification of diversity in fates during the epithelial-to-mesenchymal transition

Yu-Chen Cheng[a,b,c,d], Yun Zhang[e], Shubham Tripathi[f], B. V. Harshavardhan[g], Mohit Kumar Jolly[h], Geoffrey Schiebinger[i], Herbert Levine[j,k,1], Thomas O. McDonald[a,b,c,d], and Franziska Michor[a,b,c,d,l,m,1]

communications biology

ARTICLE

Check for updates

https://doi.org/10.1038/s42003-023-05668-3 OPEN

Transcriptional state dynamics lead to heterogeneity and adaptive tumor evolution in urothelial bladder carcinoma

Antara Biswas[1✉], Sarthak Sahoo[2], Gregory M. Riedlinger[1], Saum Ghodoussipour[1], Mohit K. Jolly[2] & Subhajyoti De[1✉]

"Teams" (meaningful dimension-reduction metric) at transcriptional, epigenetic, metabolic levels can help see "mechanistic patterns" in this high-dimensional data.

From ‘data’ to ‘information’: what ‘trajectory’ do we take?

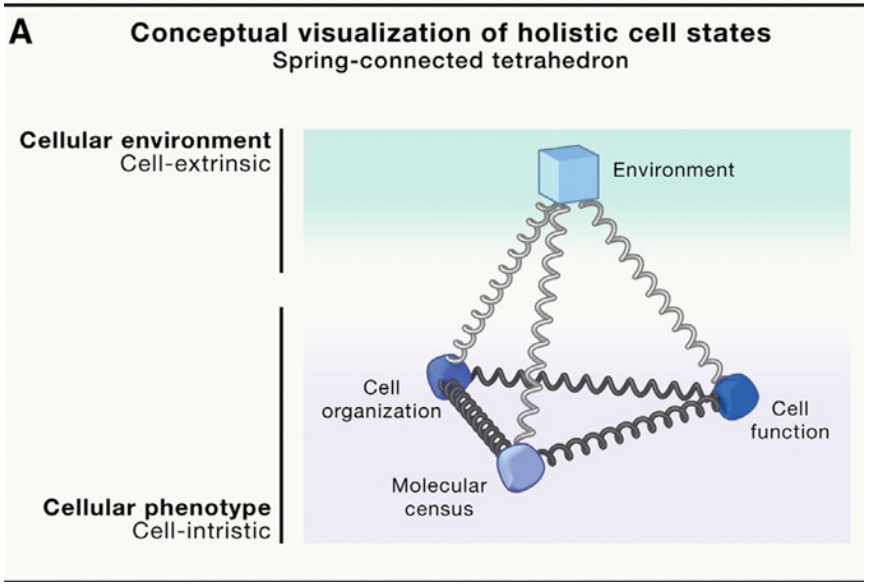
Cell
Leading Edge

Perspective

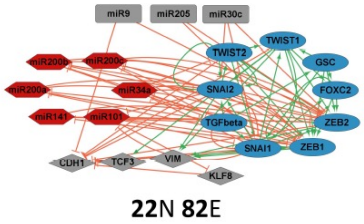
Establishing a conceptual framework for holistic cell states and state transitions

Susanne M. Rafelski[1,*] and Julie A. Theriot[2,*]
[1]Allen Institute for Cell Science, 615 Westlake Avenue N, Seattle, WA 98125, USA
[2]Department of Biology and Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195, USA
*Correspondence: susanner@alleninstitute.org (S.M.R.), jtheriot@uw.edu (J.A.T.)
https://doi.org/10.1016/j.cell.2024.04.035

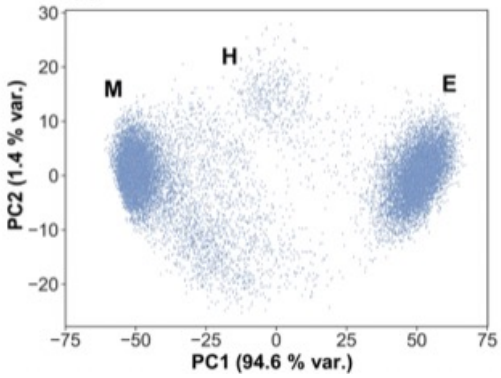
“we must aim to Keplerize the cell, to discover general patterns and concepts that can lead to a better fundamental understanding of how cells work and what it means for a cell to be alive.”

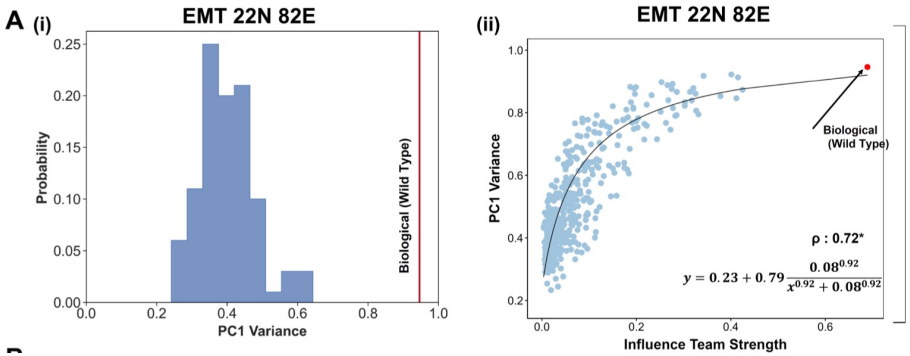


“Teams” – a meaningful dimension-reduction metric?



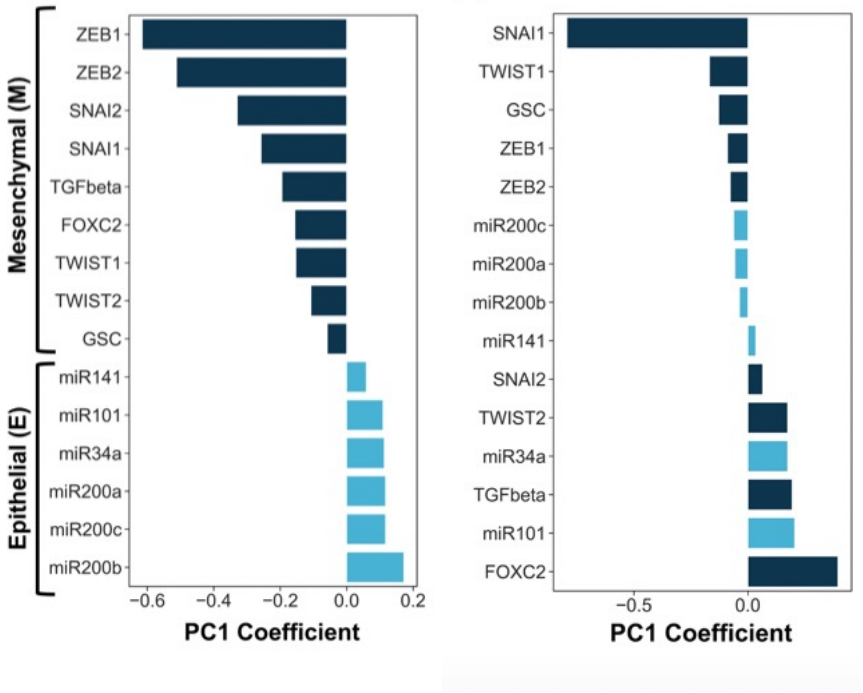
22N 82E





WT network

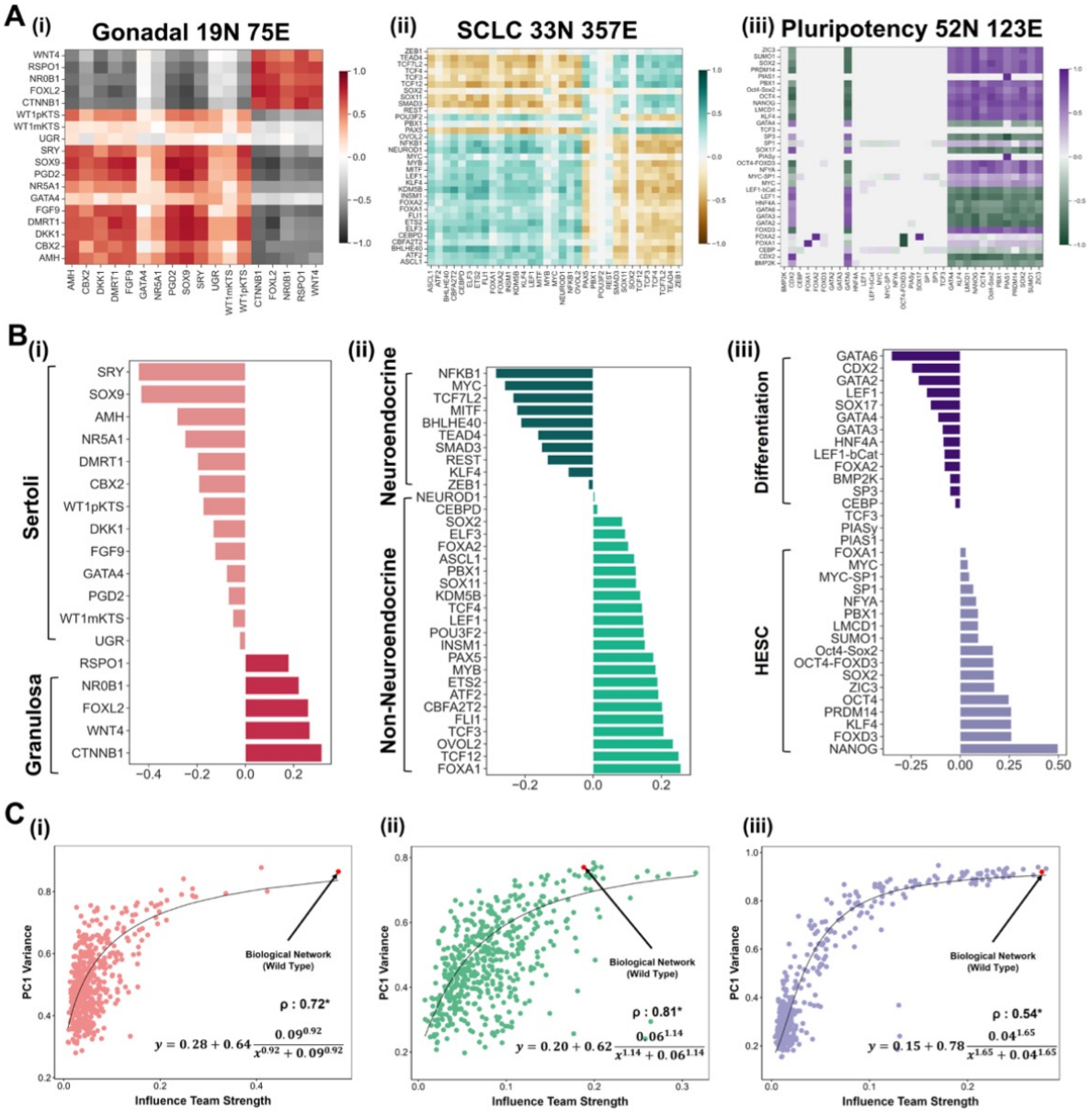
Negative control



- EMT networks or transcriptomic data can be explained mostly by PC1.

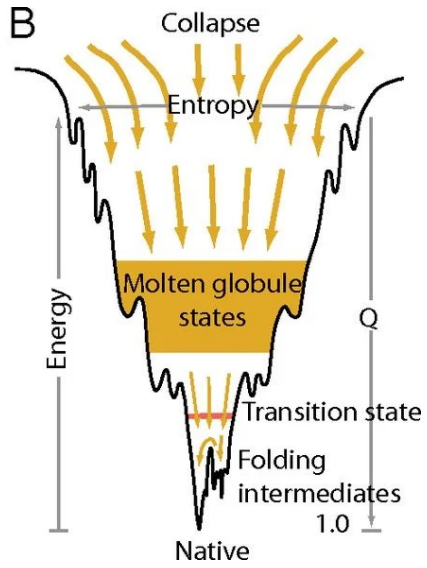
Hari*, Harlapur*, Saxena* *et al.* iScience 2025

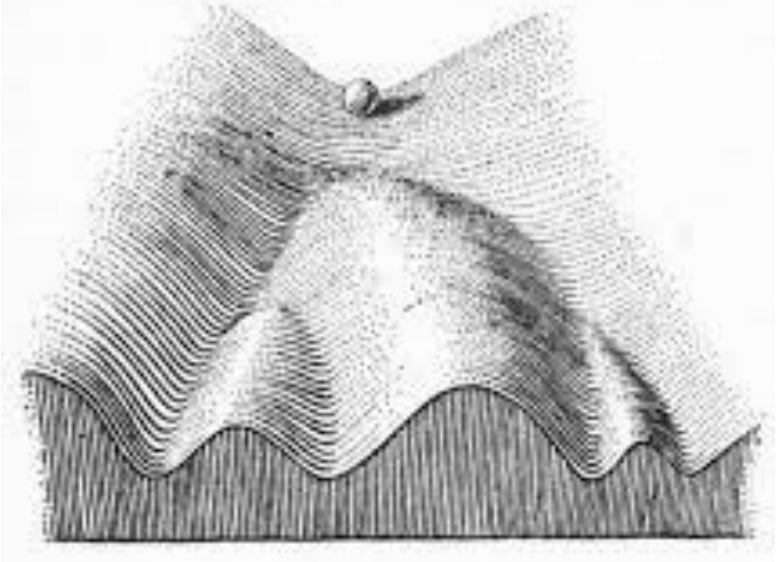
Low-dimensionality of phenotypic space : other examples



Hari*, Harlapur*, Saxena* *et al.* iScience 2025

“Teams” ~ a driving principle of cell-fate canalization?

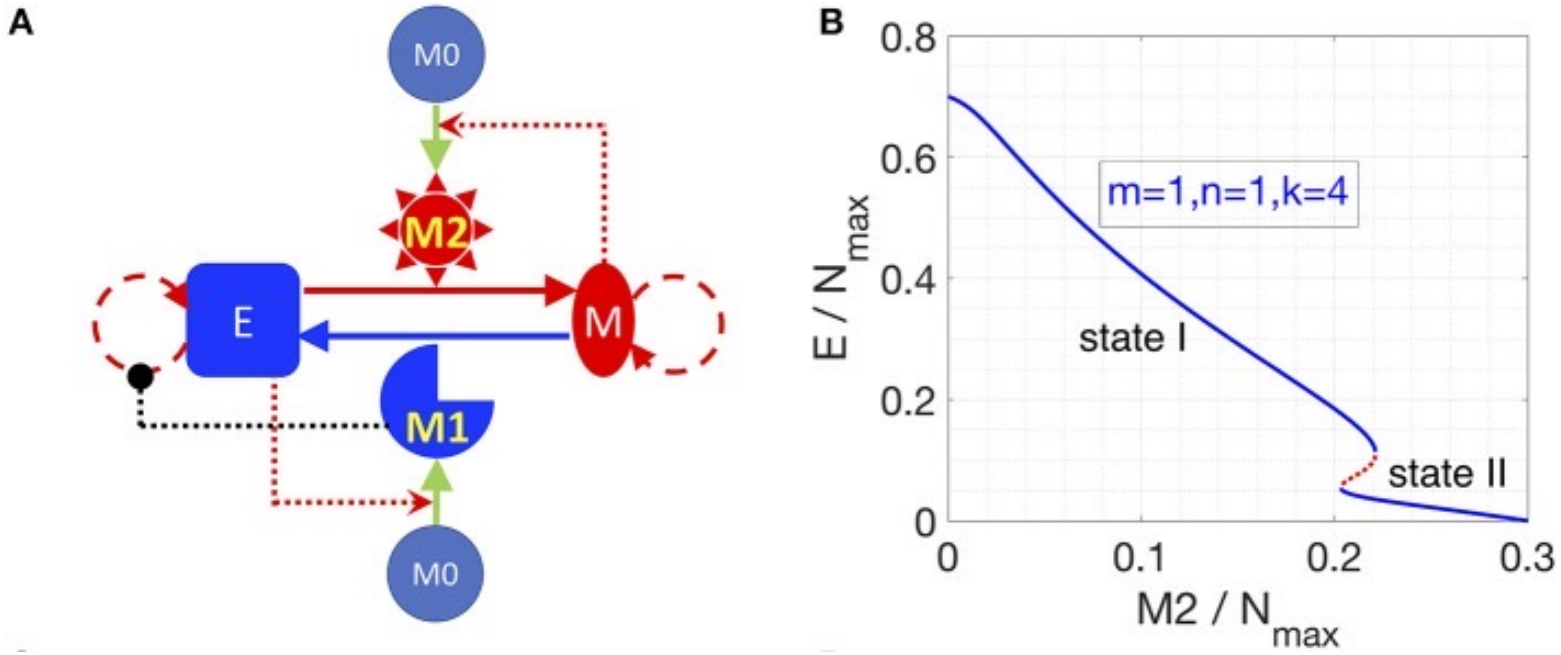




Englander & Mayne, PNAS 2014; Waddington, 1942

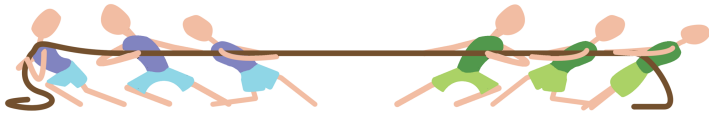
“Teams” can minimize “frustration” in EMT networks,
allowing only a limited number of trajectories and cell-states.

From “teams” of nodes in a cell to “teams” of cells in a tissue



Two states of the cell population model:

1. Epithelial cancer cells, M1 macrophages
2. Mesenchymal cancer cells, M2 macrophages



More recent reports on M1/M2 mixed macrophages - that may stabilize hybrid E/M?

Li*, Jolly* *et al.* Front Oncol 2019

Summary (Part 2): Why do “teams” exist?

- “Teams” can coordinate many axes of plasticity (EMT, TamRes *et al.*) that can facilitate therapy-driven adaptive responses, aggravating outcomes.
- “Teams” can explain why cancer cells that are not killed become stronger.
- Math models can help in identifying better therapeutic strategies (rational combinations of drugs).

Avada Kedavra
(Targeted therapy)

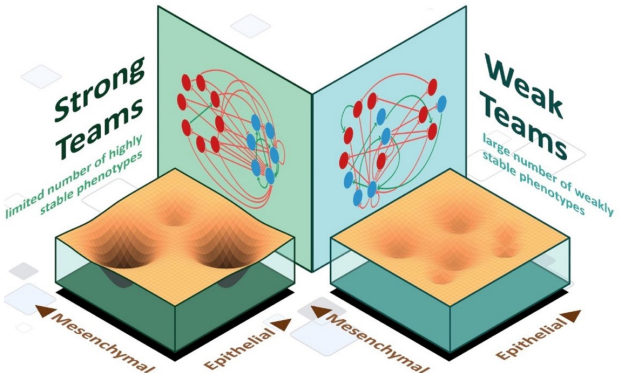
Cells that adapt & survive:
Hail the “Team” Potter!

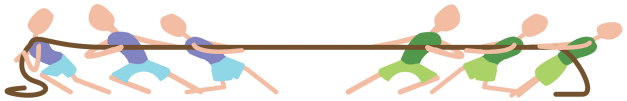
Summary

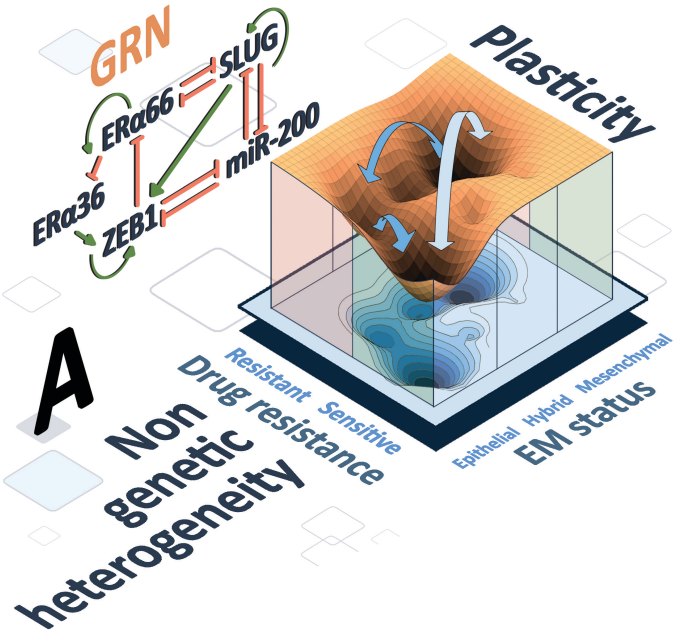
- ‘Design principles’ of regulatory networks driving cell-state switching:

1. Multistable dynamics => Phenotypic plasticity & heterogeneity
2. Existence of “teams” exist in multiple such networks

- Drug-induced cell-state transitions can aggravate tumor progression
- Math models can help identify rational combinatorial strategies







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- Engineers

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- Electrical Engineering
- Bioinformatics
- Physics
- Mathematics
- Cancer Biology

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Open for new collaborations : mkjolly@iisc.ac.in