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COMPLEXITY
& BIOSYSTEMS

University of Milan

CLASSIFICATION OF TRIPLE-NEGATIVE BREAST CANCERS THROUGH A BOOLEAN NETWORK MODEL OF THE EPITHELIAL MESENCHYMAL TRANSITION

25 07 2022

Lake Como School

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COMPLEXDATA

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DEPARTMENT OF
ENVIRONMENTAL
SCIENCE AND POLICY



DEPARTMENT OF
PHYSICS
“ALDO PONTREMOLI”

CC&B: CORE PEOPLE

Digital Health
Computational biology
Quantitative Biology
Biophysics



Caterina La Porta

Digital Materials/
Nanomaterials/
Material modelling
Computational biophysics



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Applied mathematics



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Alessandra Micheletti



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Host: Jim Sethna



EYTAN DOMANY





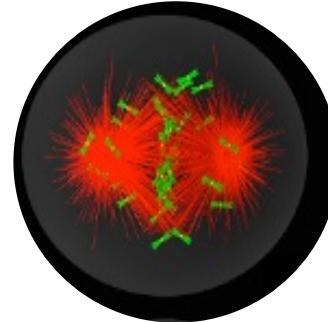
Data science, digital health and sustainable cities



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Biosensors for an agriculture 4.0
(Grade)
Fungi and pathologies



Digital health: Precision Medicine and
Cancer
Migration
Etc....



Digital Health:
Neurodegenerative diseases

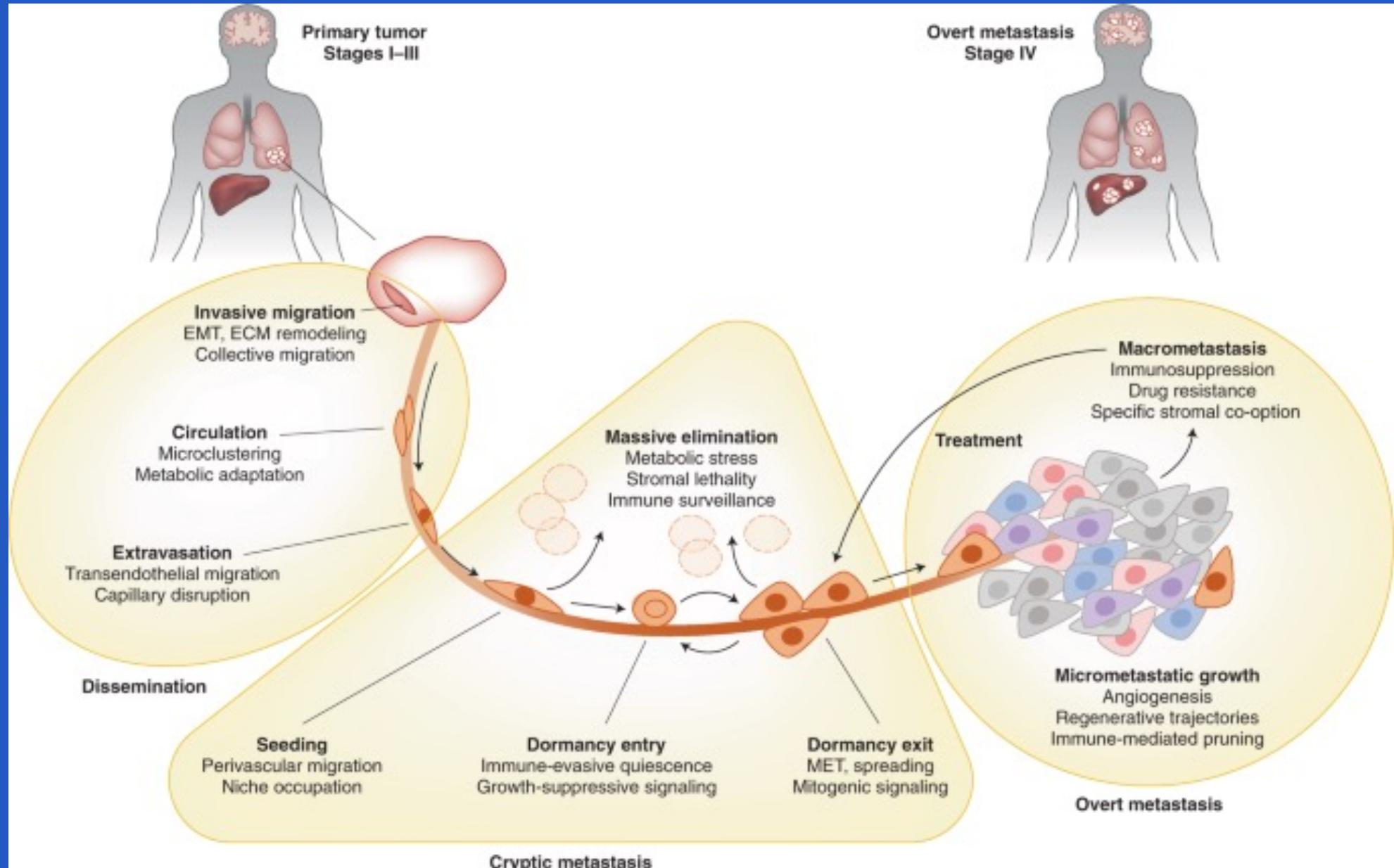
IT IS ESTIMATED THAT METASTASIS IS
RESPONSIBLE FOR ABOUT 90% OF THE
CANCER DEATHS DUE
TO SOLID TUMORS

WHY?

1. SPREAD OF THE CELLS IN UNACCESSIBLE SITES
(flow and geometry)
2. AGGRESSIVENESS OF METASTATIC TUMOR CELLS
(seed and soil)

WHY?

1. SPREAD OF THE CELLS IN UNACCESSIBLE SITES (flow and geometry)

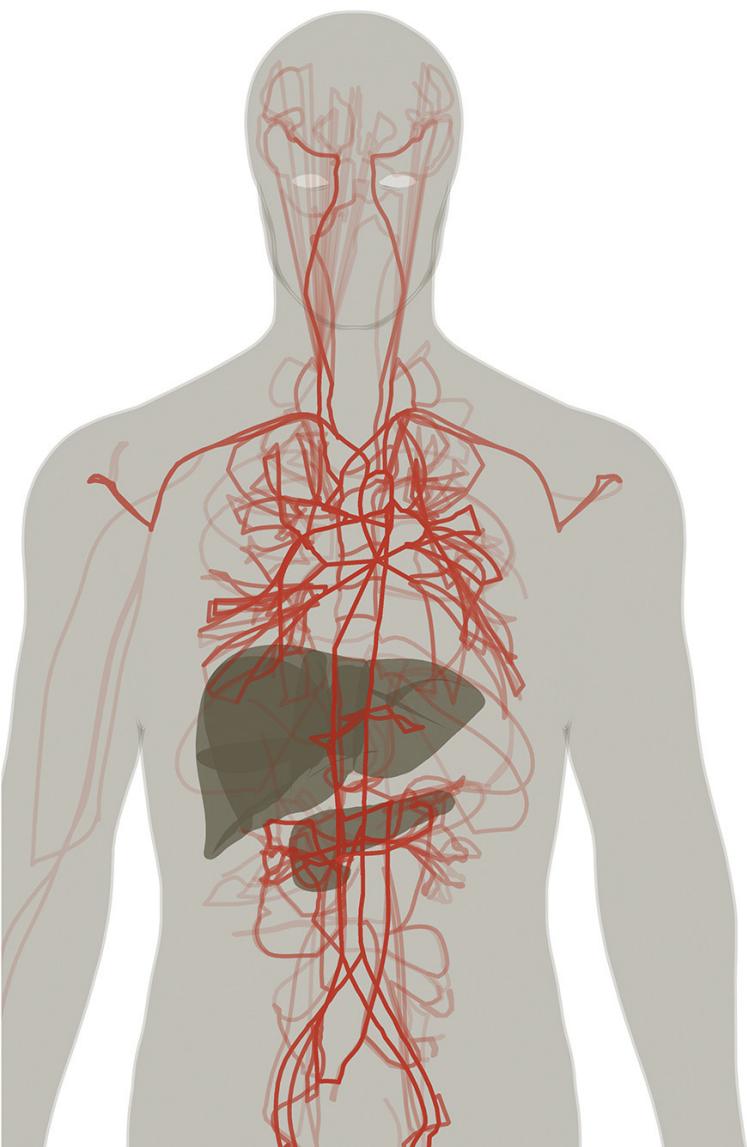


Picture form :Nature Medicine 27, 34–44 (2021)

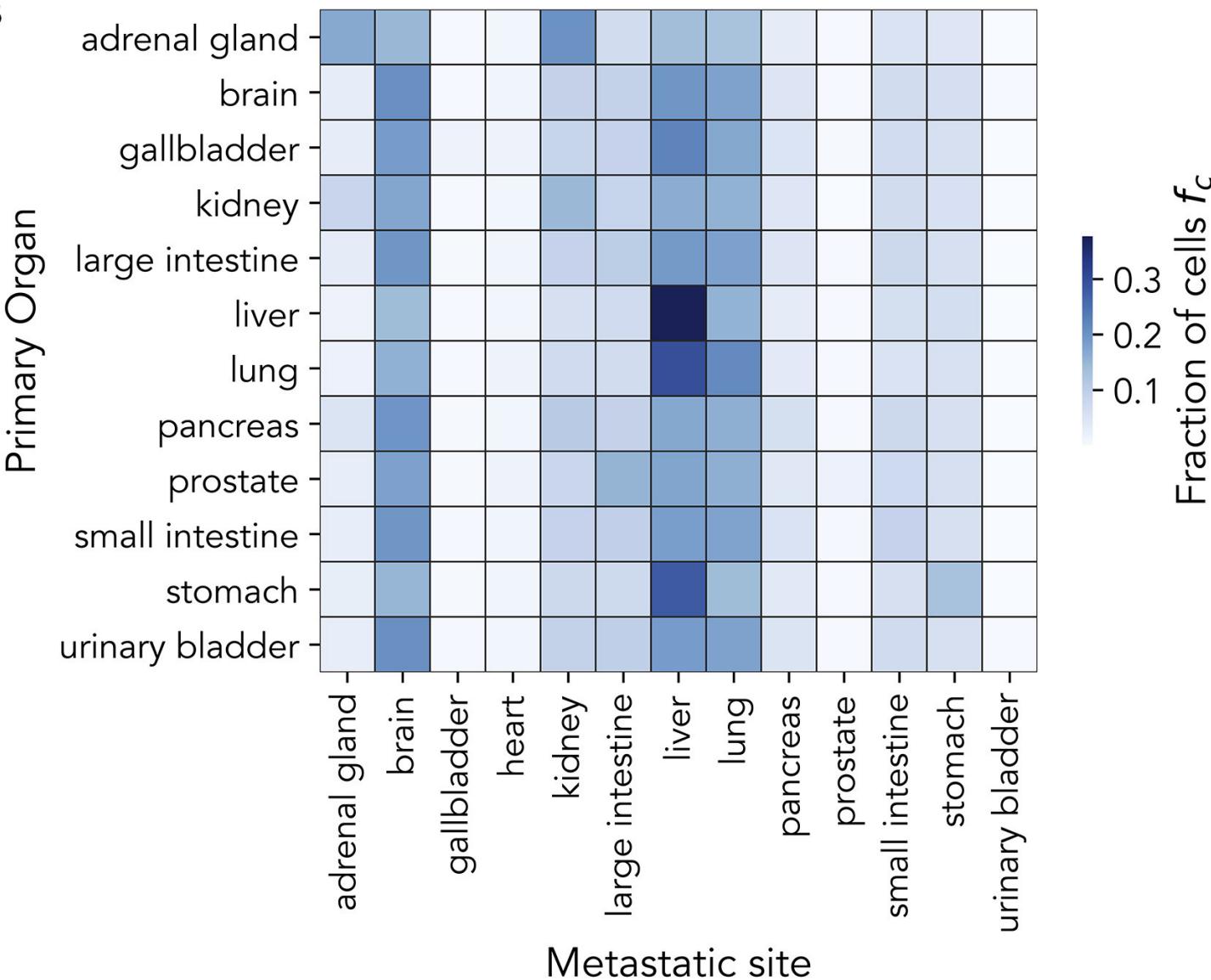
Font-Clos F, Zapperi S, La Porta CA. Blood flow
contributions to cancer metastasis. *Iscience*. 2020 May
22;23(5):101073.

LOCATION OF METASTASIS: MODEL PREDICTIONS

A

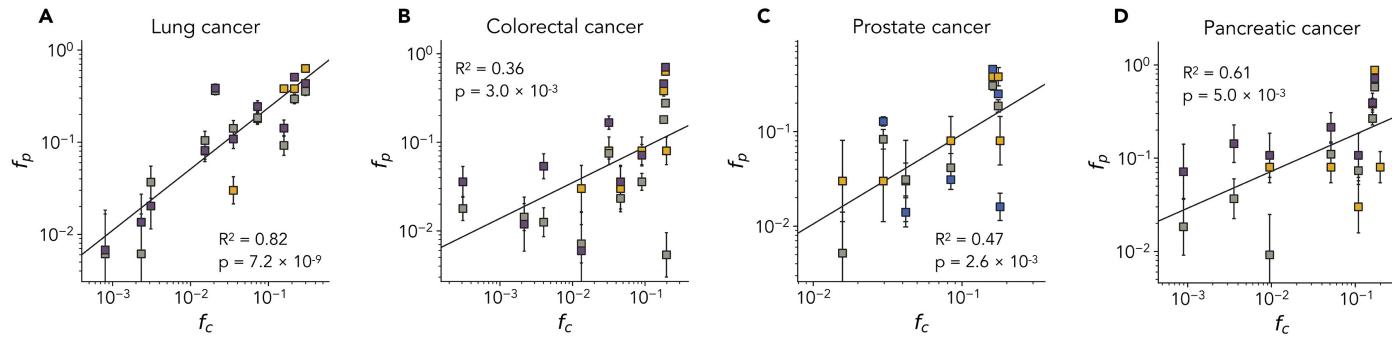


B

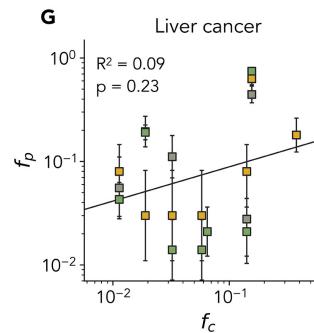
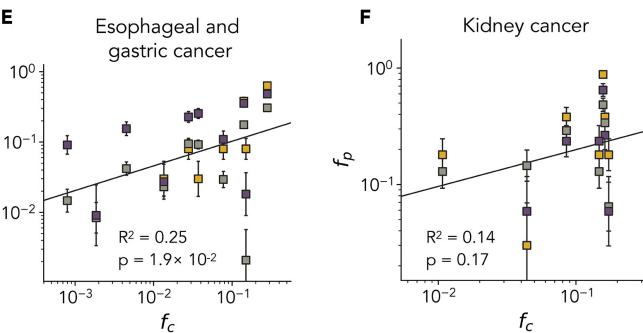


Font-Clos F, Zapperi S, La Porta CA. Blood flow contributions to cancer metastasis. *Iscience*. 2020 May 22;23(5):101073.

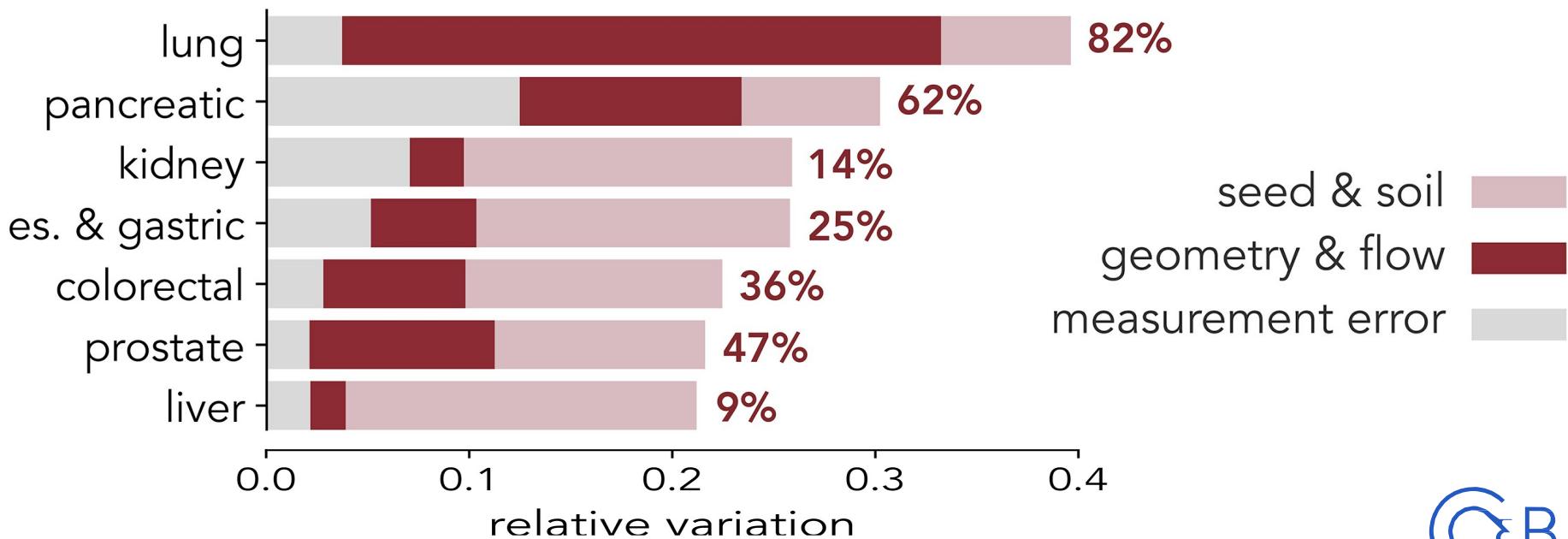
COMPARISON WITH DATA FROM AUTOPSIES



Abrams, 1950
 Bubendorf, 2000
 Budczies, 2015
 diSibio, 2008
 Schlageter, 2016



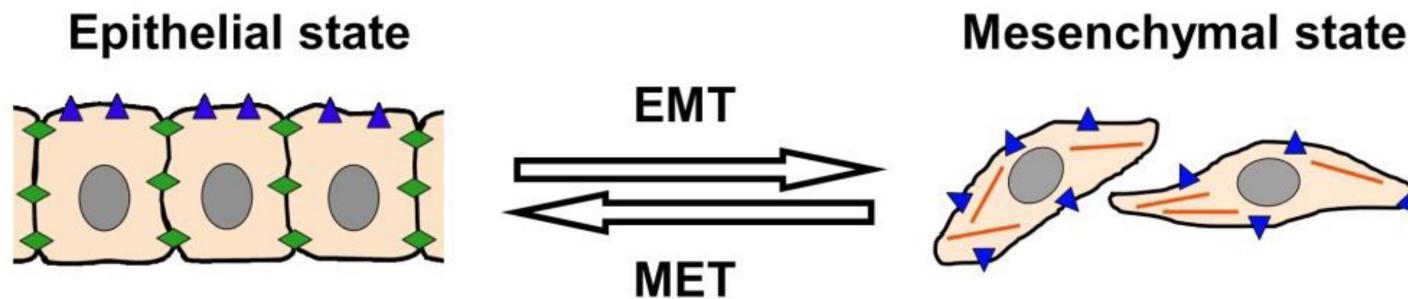
Primary cancer



WHY?

2. AGGRESSIVENESS OF METASTATIC TUMOR CELLS (seed & soil)

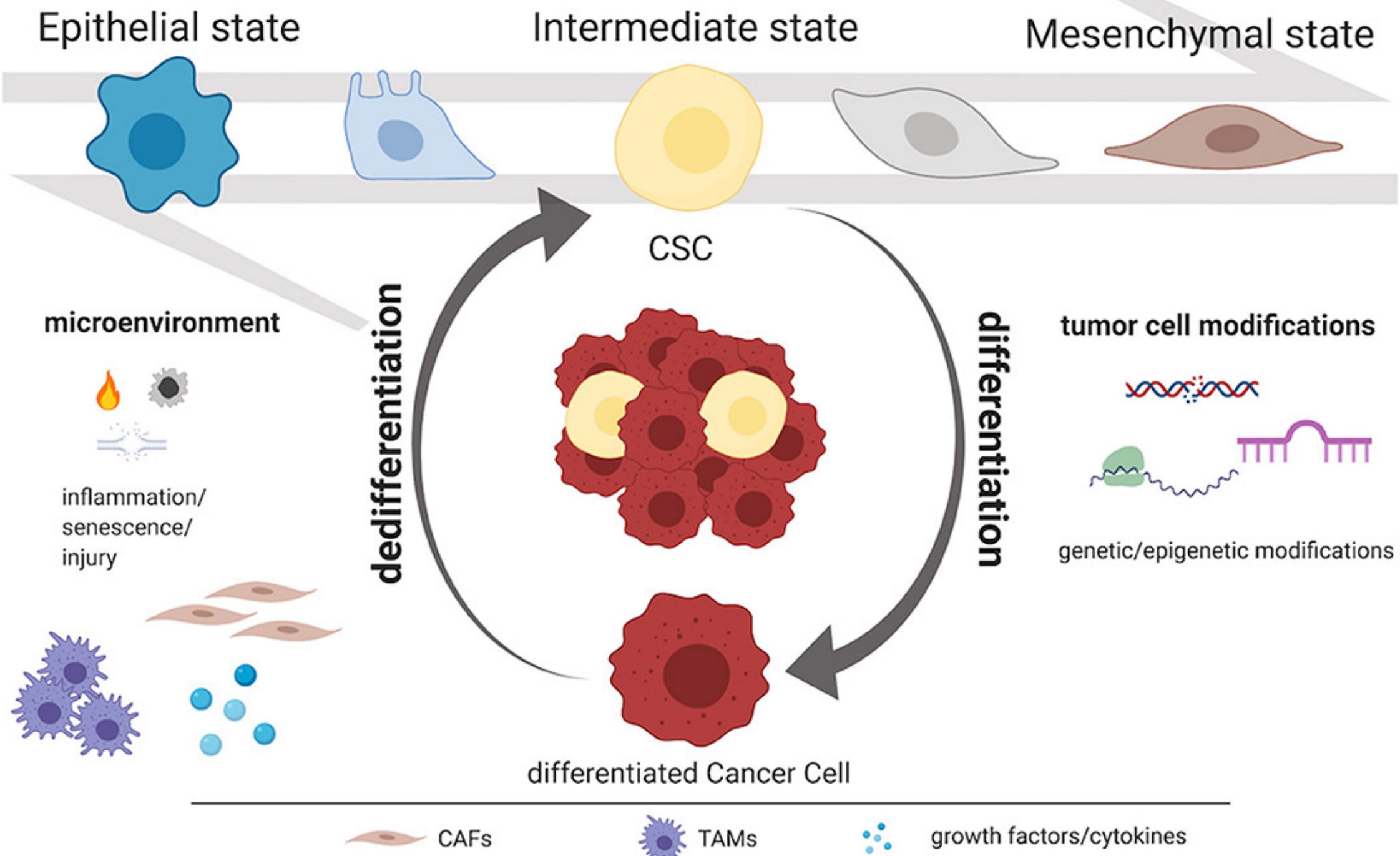
EPITHELIAL MESENCHYMAL TRANSITION (EMT)



- Polygonal/ columnar shape
- Apico-basolateral polarization
- Strong cell-cell adhesion
- Limited migratory potential
- Markers:
E-cadherin, certain cytokeratins,
occludin, claudin
- Spindle-shaped
- Anterior-posterior polarization
- Focal cell-cell contacts
- Strong migratory potential
- Markers:
Vimentin, N-cadherin, fibronectin

Phenotypic switching: EMT phenotype/stem genes

Cancer cell plasticity



PHENOTYPIC SWITCHING

Eur. J. Cancer 2007 CD133/ABCG2

Plos One 2010 CXCR6

Plos Computational Biology, 2012.

Scientific Reports , 2012

Scientific Reports 2015

Seminars in Cancer Biology 2017

Seminars in Cancer Biology 2018

PNAS 2018

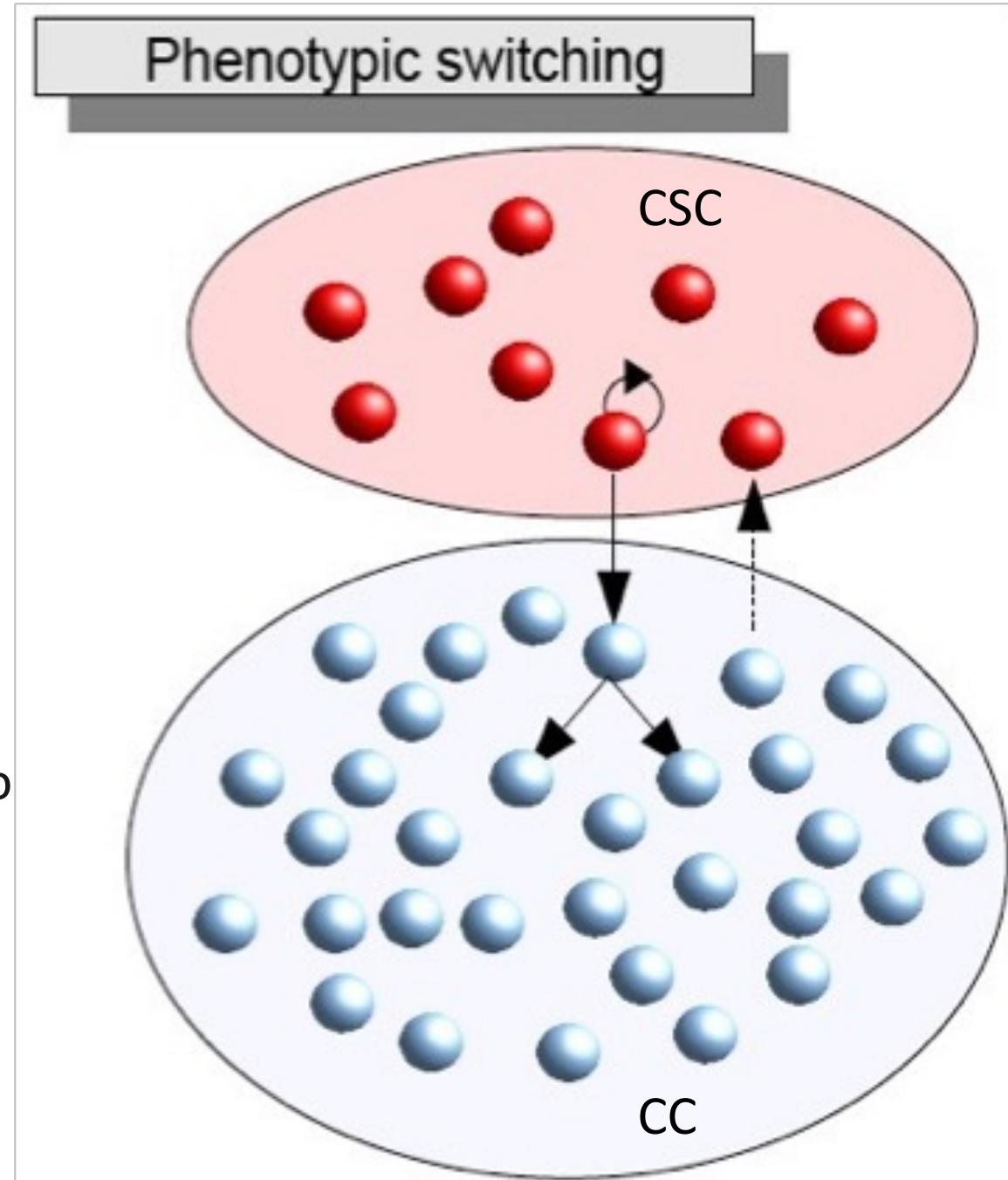
Cancer Microenvironment , 2019

Nature Publisher Journal Systems Bio
and Applications, 2020

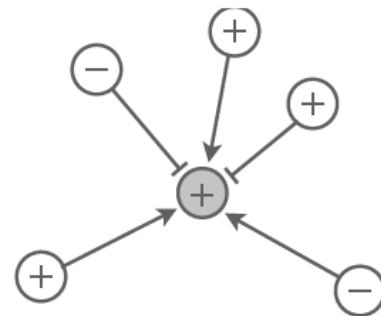
J. Clin. Med. 2020

Cell Systems 2021

Scientific Reports 2022



NETWORK MODEL OF EMT/MET



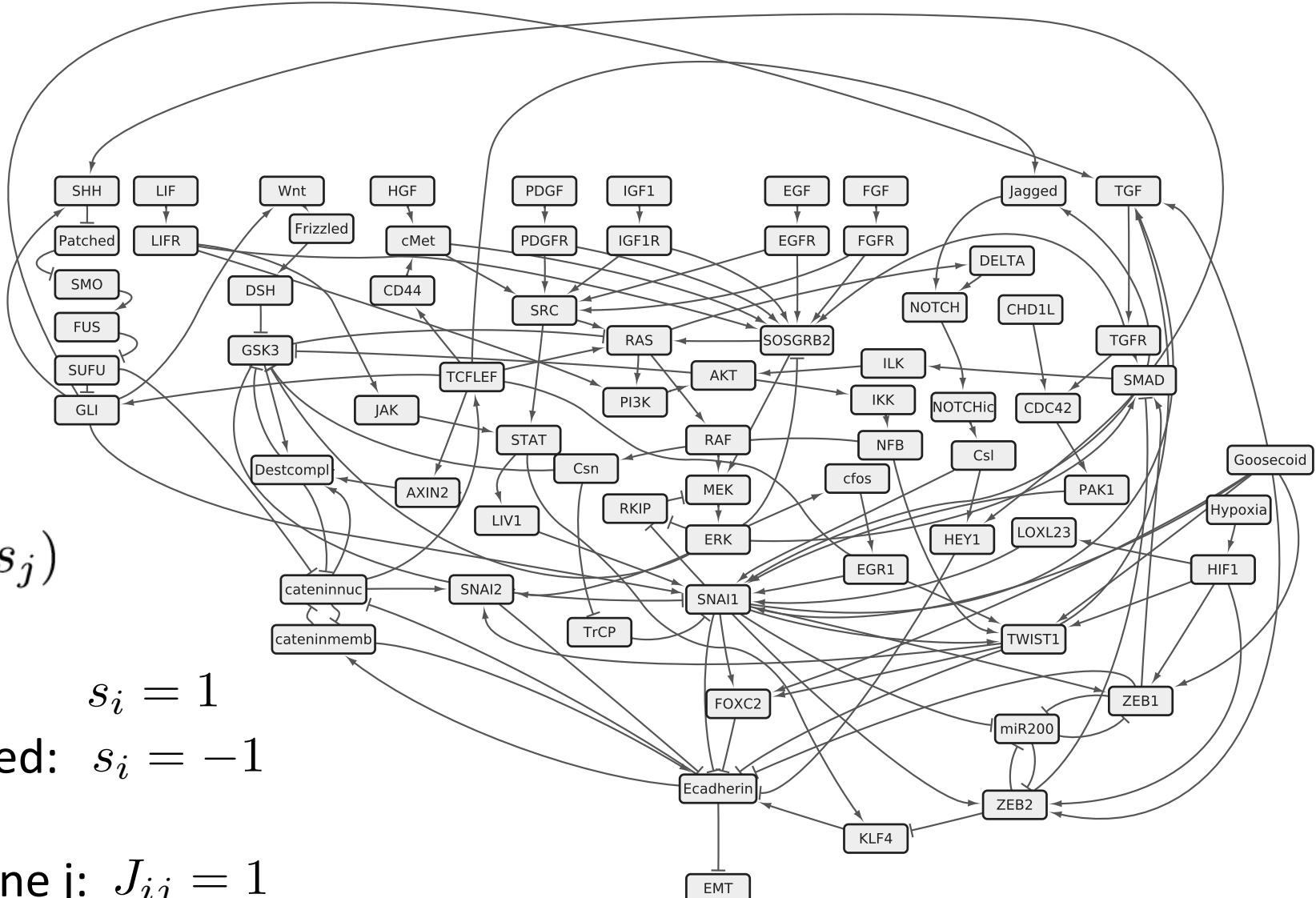
$$s_i = \text{sign}(\sum_j J_{ij} s_j)$$

Gene i expressed: $s_i = 1$

Gene i not expressed: $s_i = -1$

Gene i activates gene j: $J_{ij} = 1$

Gene i inhibits gene j: $J_{ij} = -1$



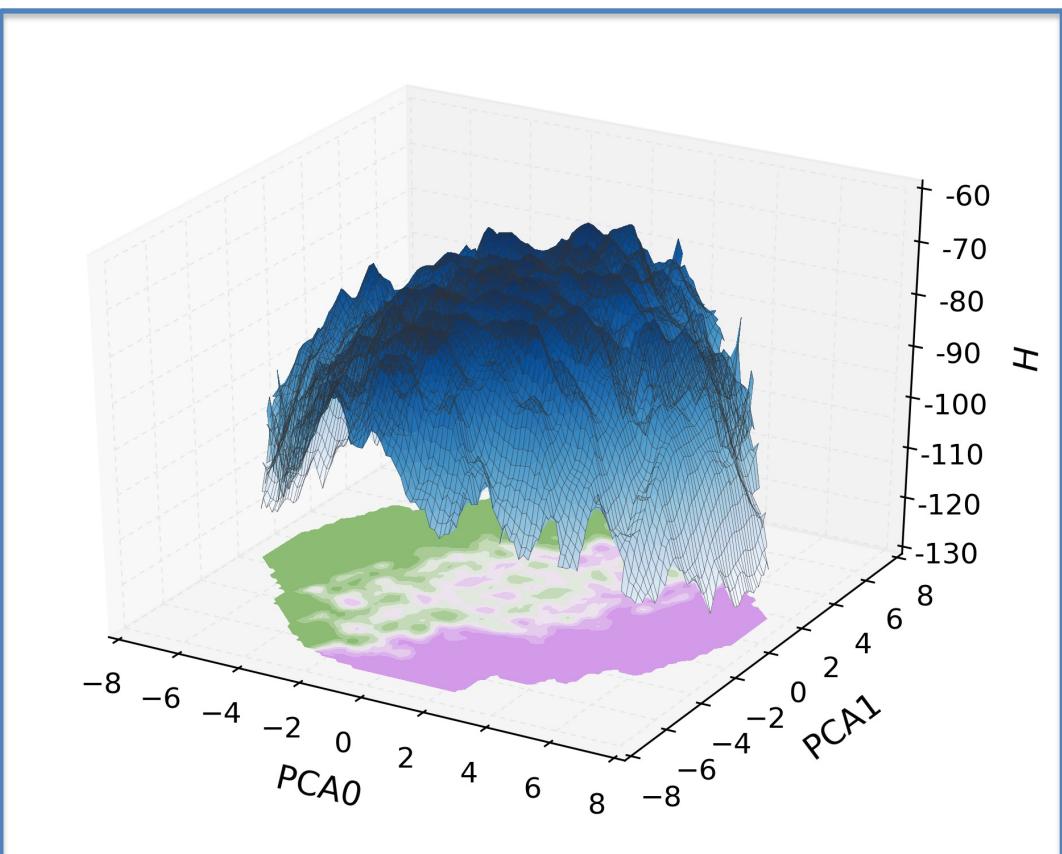
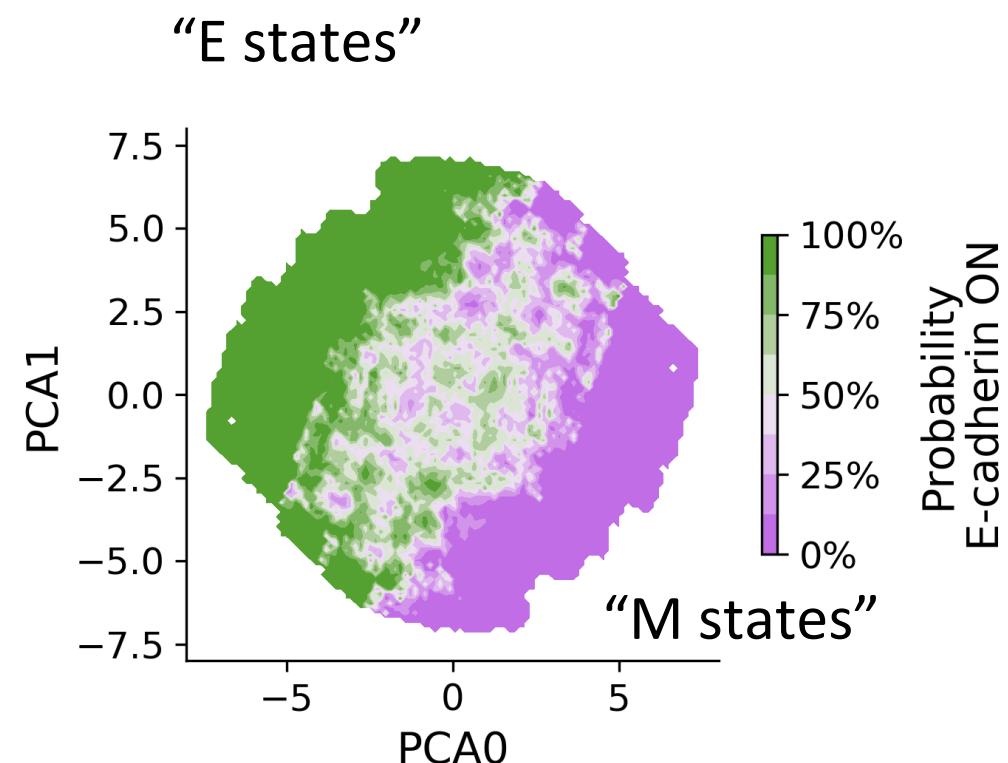
Modified from Steinway et al. 2015

EXPLORING PHENOTYPES (ATTRACTORS STATES)

- Start from a random state $\{s_i\}$
- Update the rule
- Find fixed point

$$H = - \sum_{i,j} J_{ij} s_i s_j$$

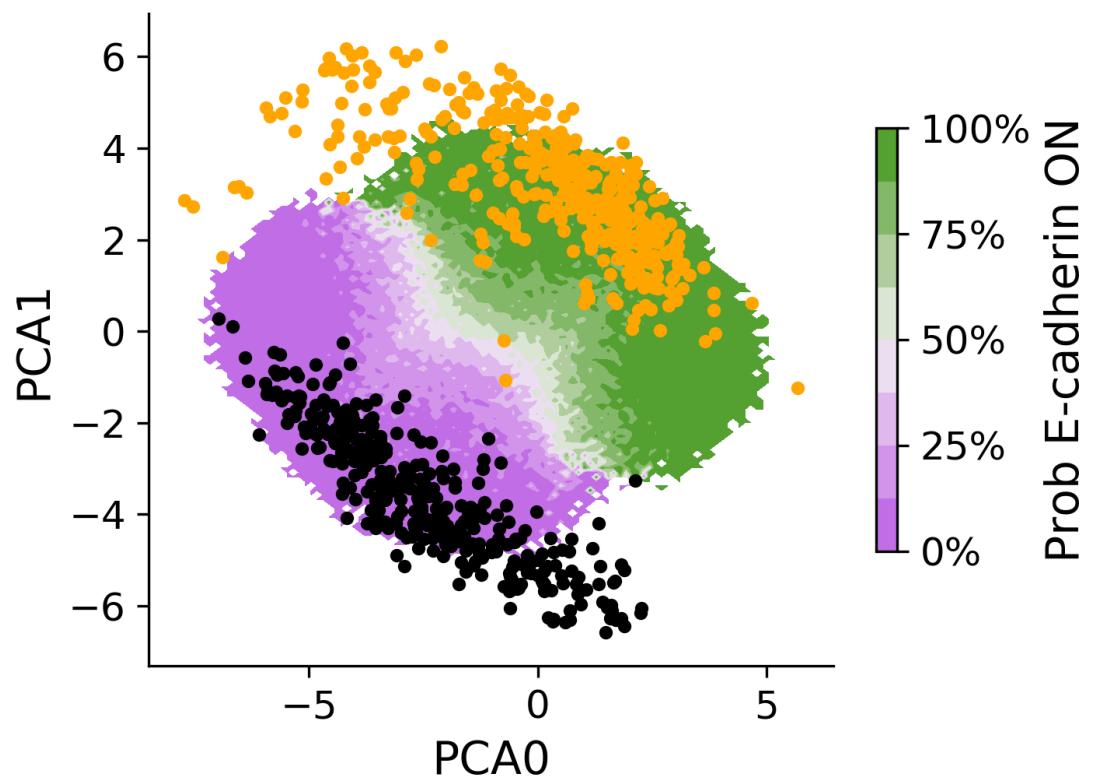
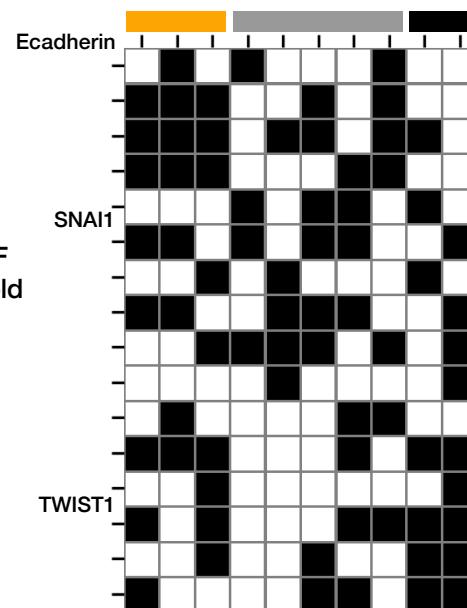
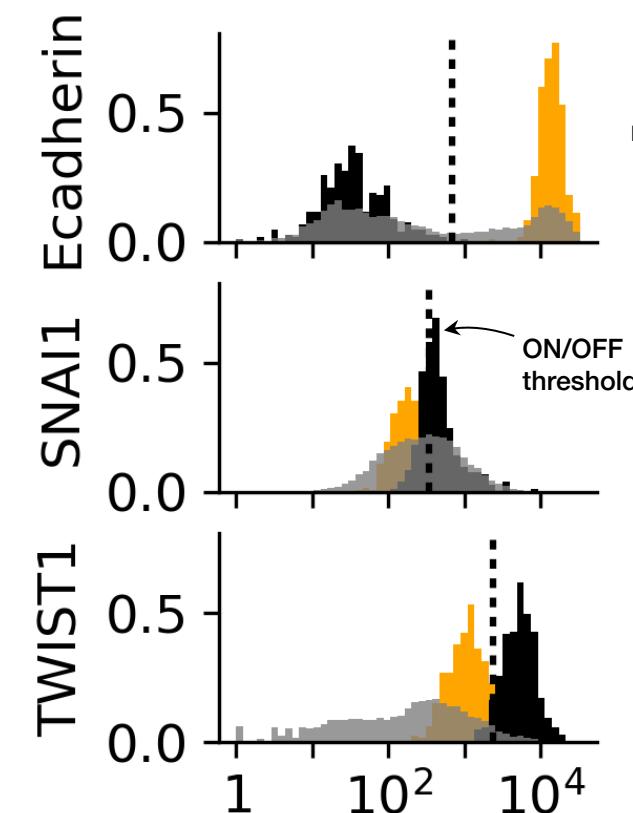
* H is not *exactly* minimized by the dynamics but only approximately $J_{ji} \neq J_{ij}$



MAPPING RNAseq DATA ON THE EMT LANDSCAPE



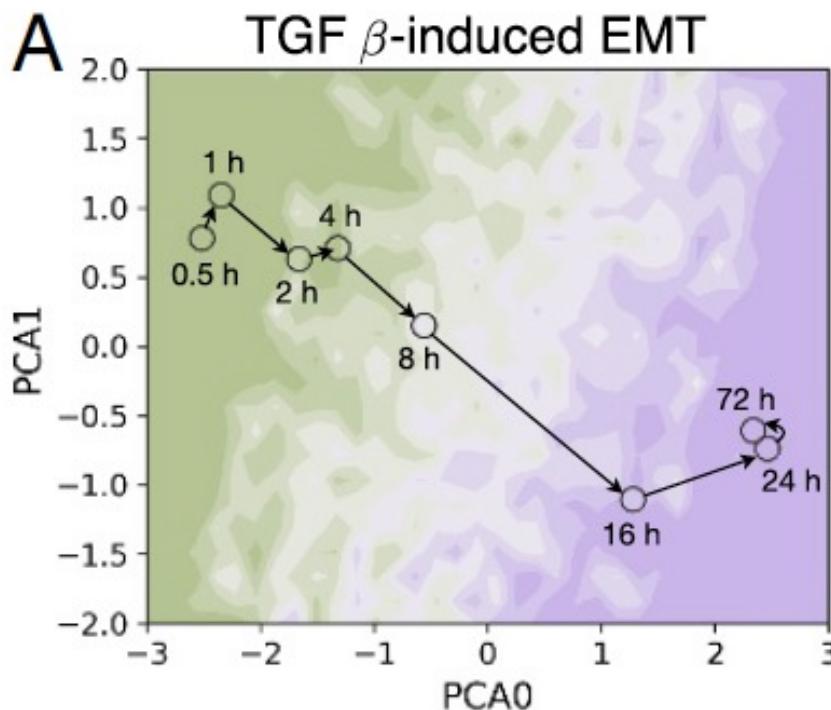
GTEx Data (11k transcriptomes from different tissues)



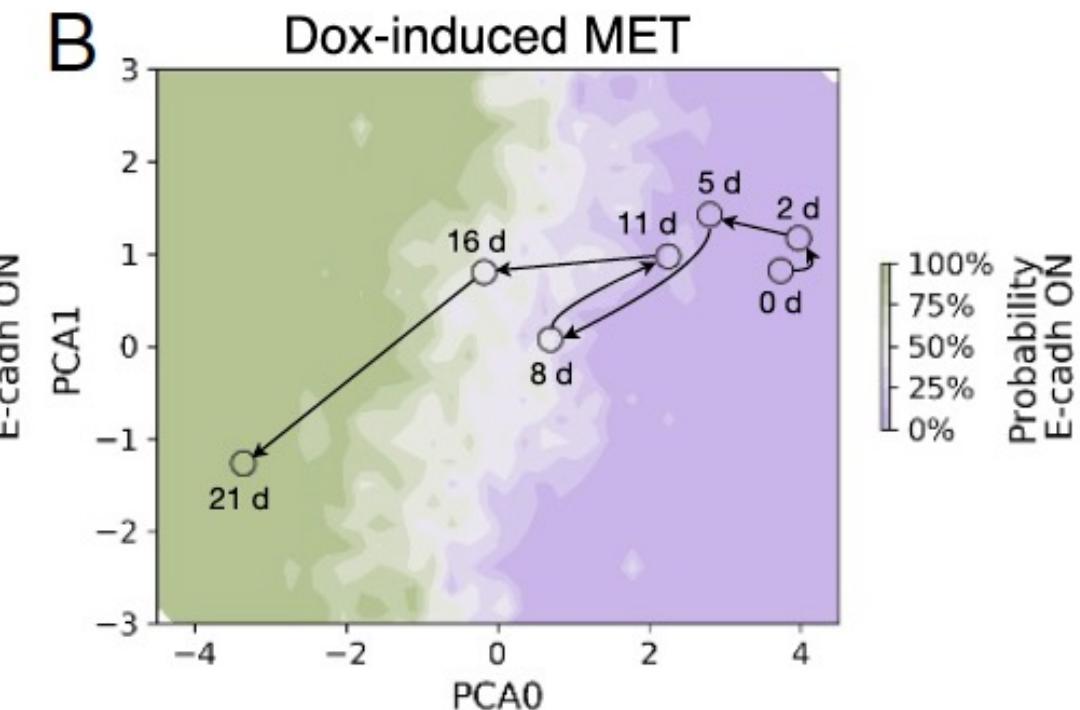
Skin ■
Fibroblasts ■
All tissues ■

MAPPING PHENOTYPIC TRAJECTORIES

Experiments



(Samavarchi-Tehrani et al
Cell Stem Cells 2010)



Somatic cell reprogramming
(Abnaof et al. BCM Syst. Bio. 2014)

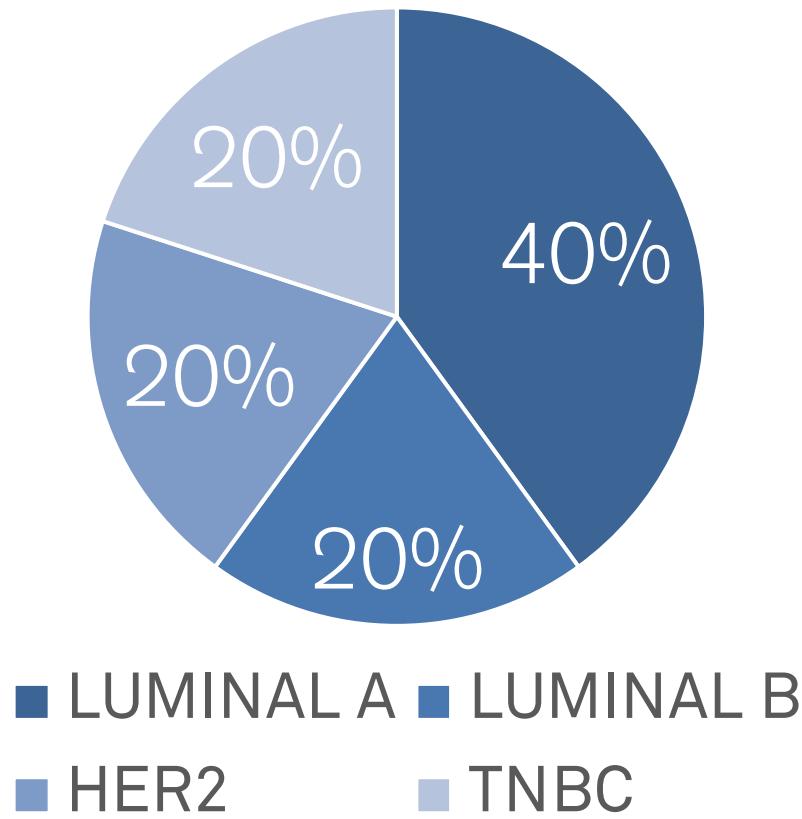
Font-Clos, F., Zapperi, S. & La Porta, C. A. M. Topography of epithelial–mesenchymal plasticity. *Proc. Natl. Acad. Sci. USA* **115**, 5902–5907 (2018).

BREAST CANCER

2.3 MILLION
CASES EACH
YEAR WORLDWIDE

FIRST
CAUSE OF DEATH
FOR WOMEN

BREAST CANCER SUBTYPES

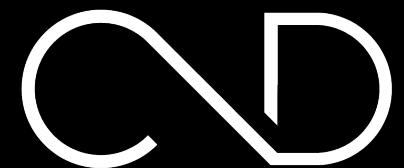


TRIPLE NEGATIVE BREAST CANCER

20% of all breast cancers

No specific drug

30% of patients are
estimated to be
OVERTREATED



COMPLEXDATA

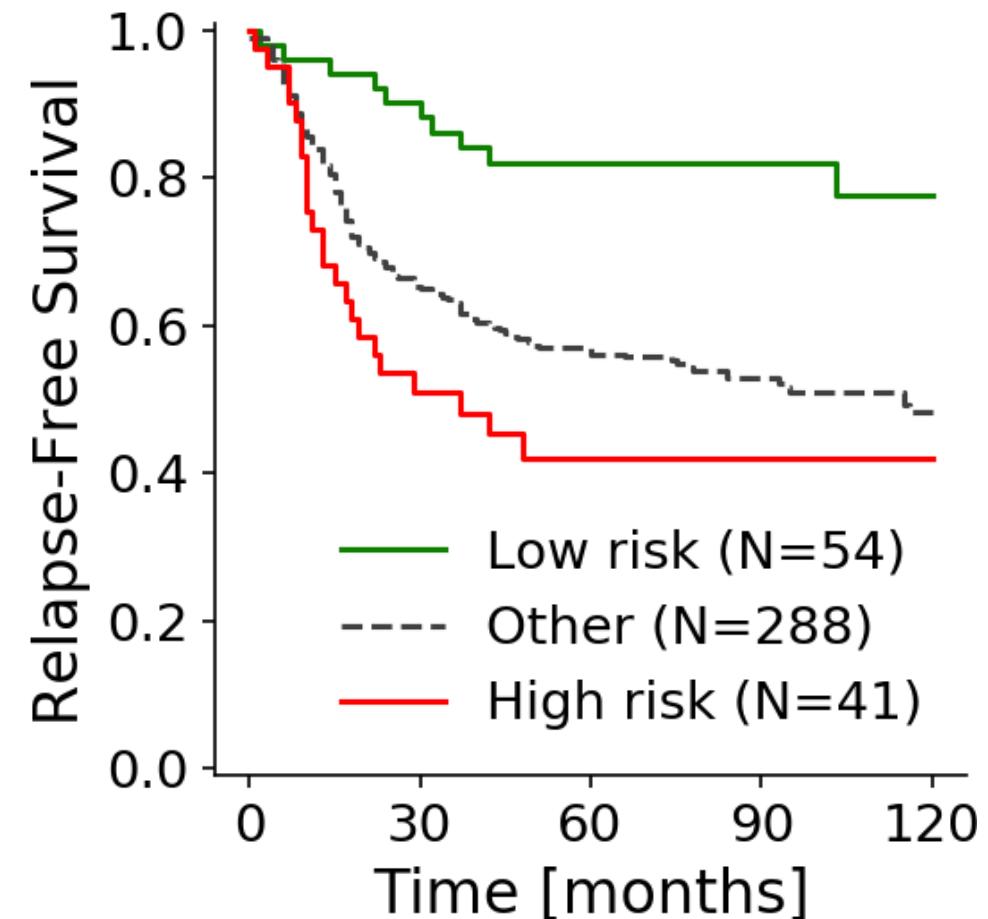
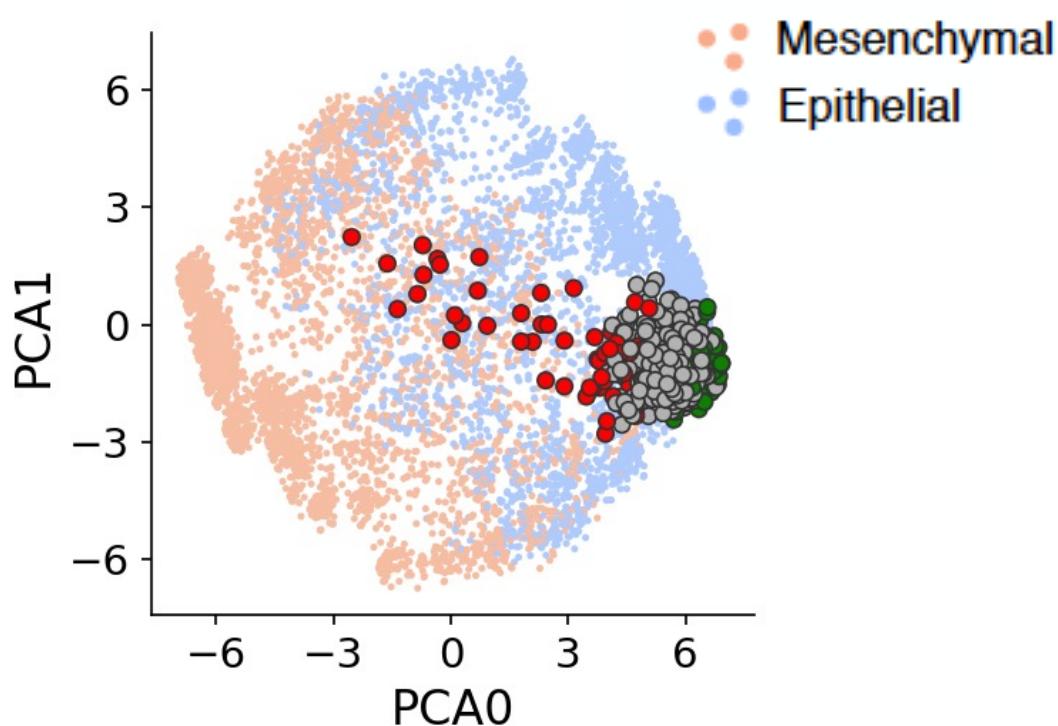
ARIADNE

by ComplexData srl

ARTIFICIAL INTELLIGENCE FOR
BREAST CANCER PREDICTION
AND PERSONALIZED CARE

<http://www.riadneweb.it>

ARIADNE PREDICTS THE RISK OF AGGRESSIVENESS IN TRIPLE NEGATIVE BREAST CANCER

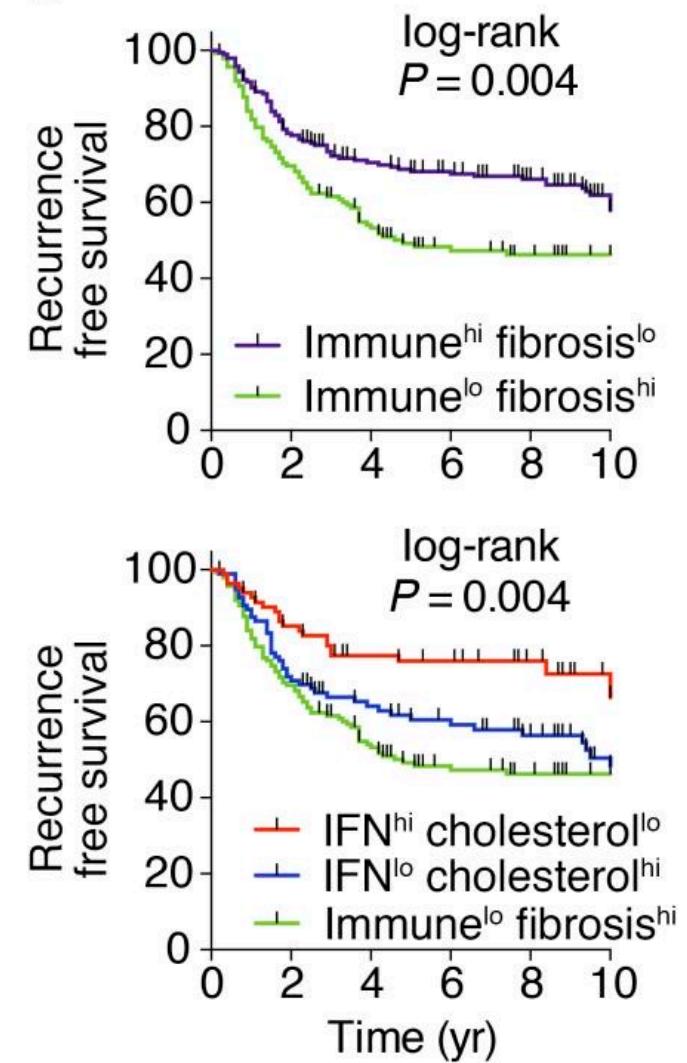
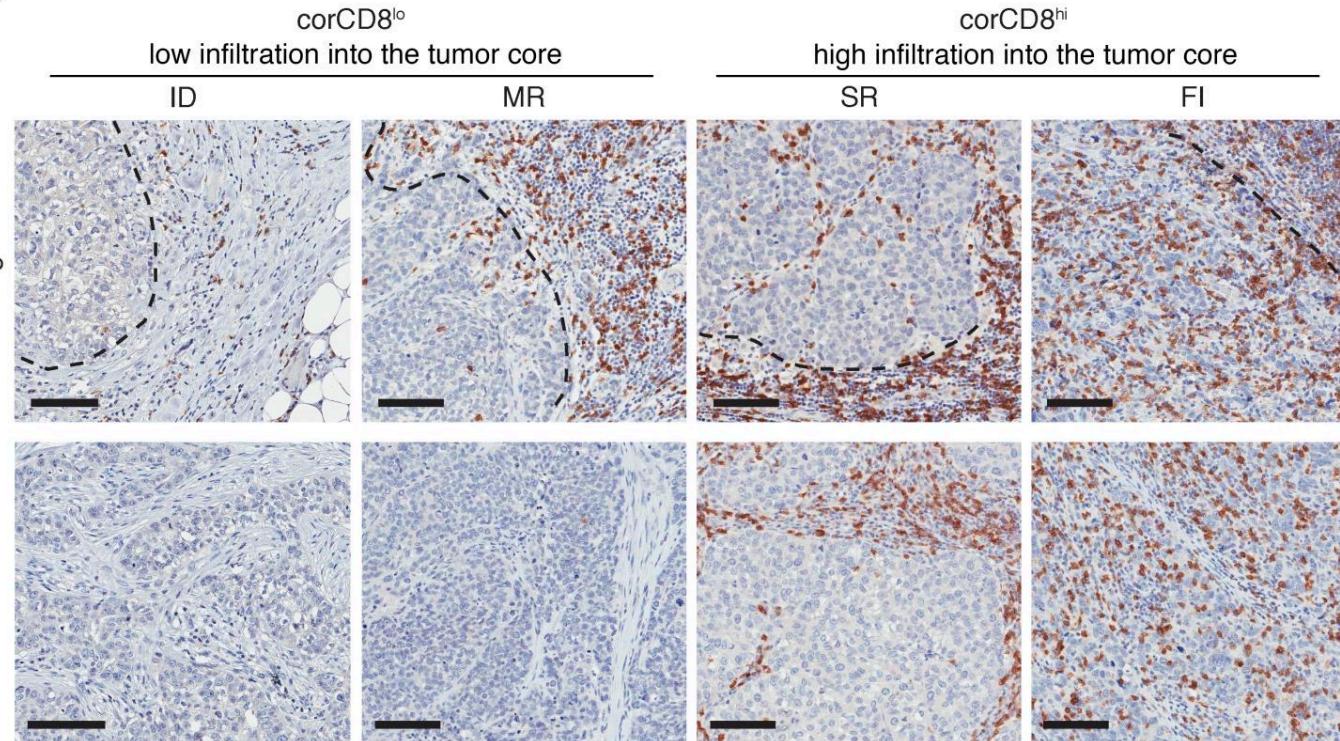


Mont-Clos, F., Zapperi, S. & La Porta, C. A. M. Classification of triple-negative breast cancers through a boolean network model of the epithelial–mesenchymal transition. *Cell Syst.* **12**, 457-462.e4 (2021).

TUMOR IMMUNE MICROENVIRONMENT METASIGNATURE FOR TNBC

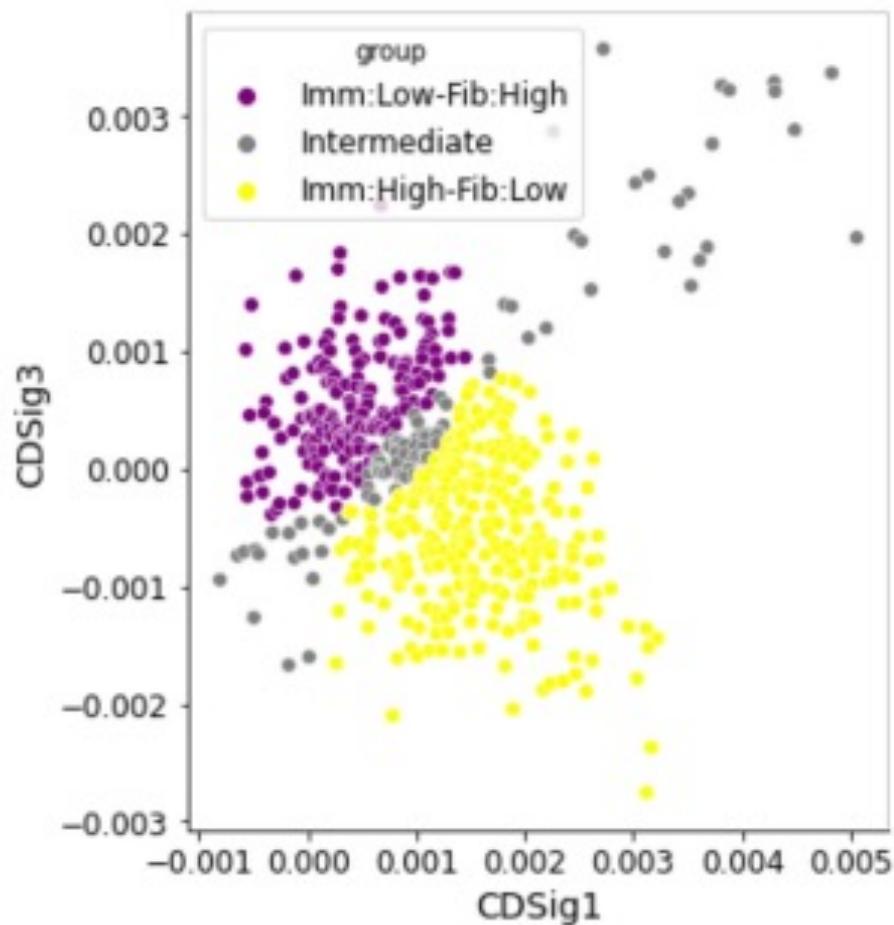
Gruoso, T. et al. Spatially distinct tumor immune microenvironments stratify triple-negative breast cancers. *J. Clin. Investig.* **129**, 1785–1800 (2019).

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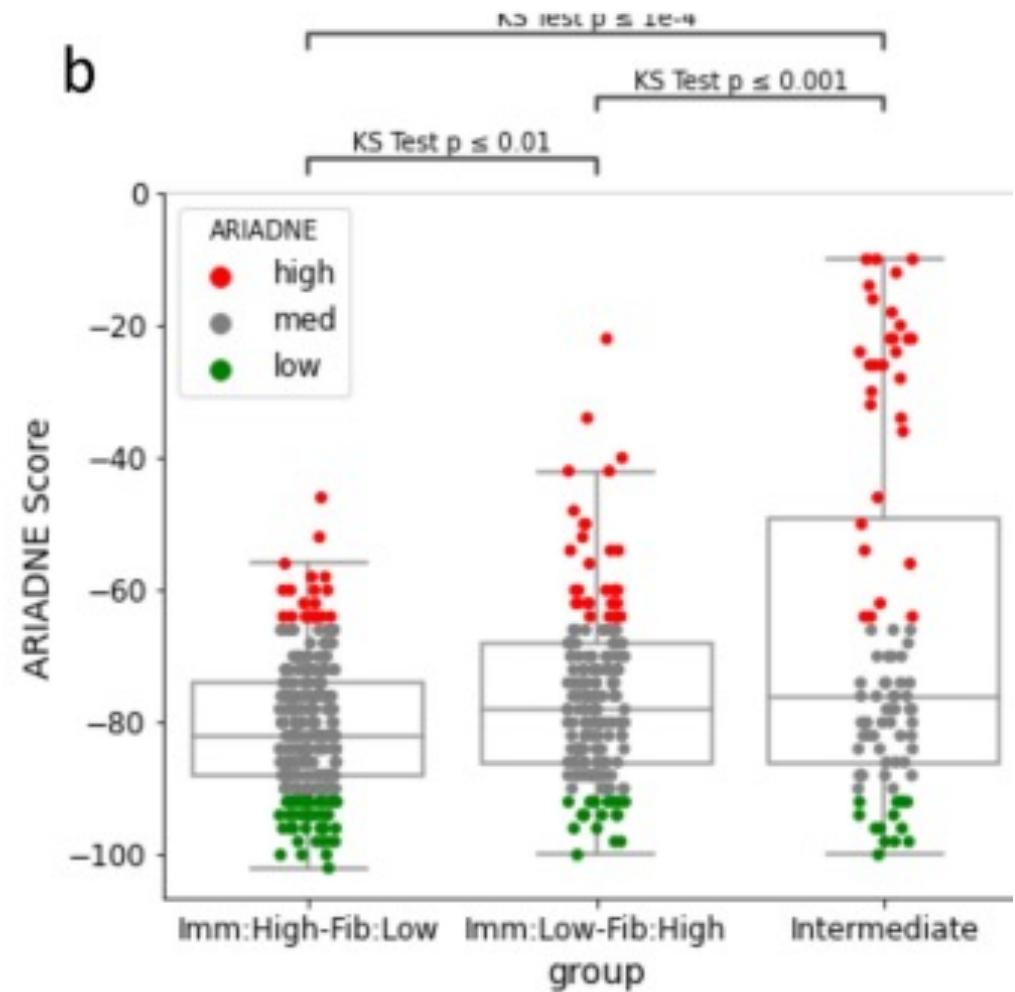


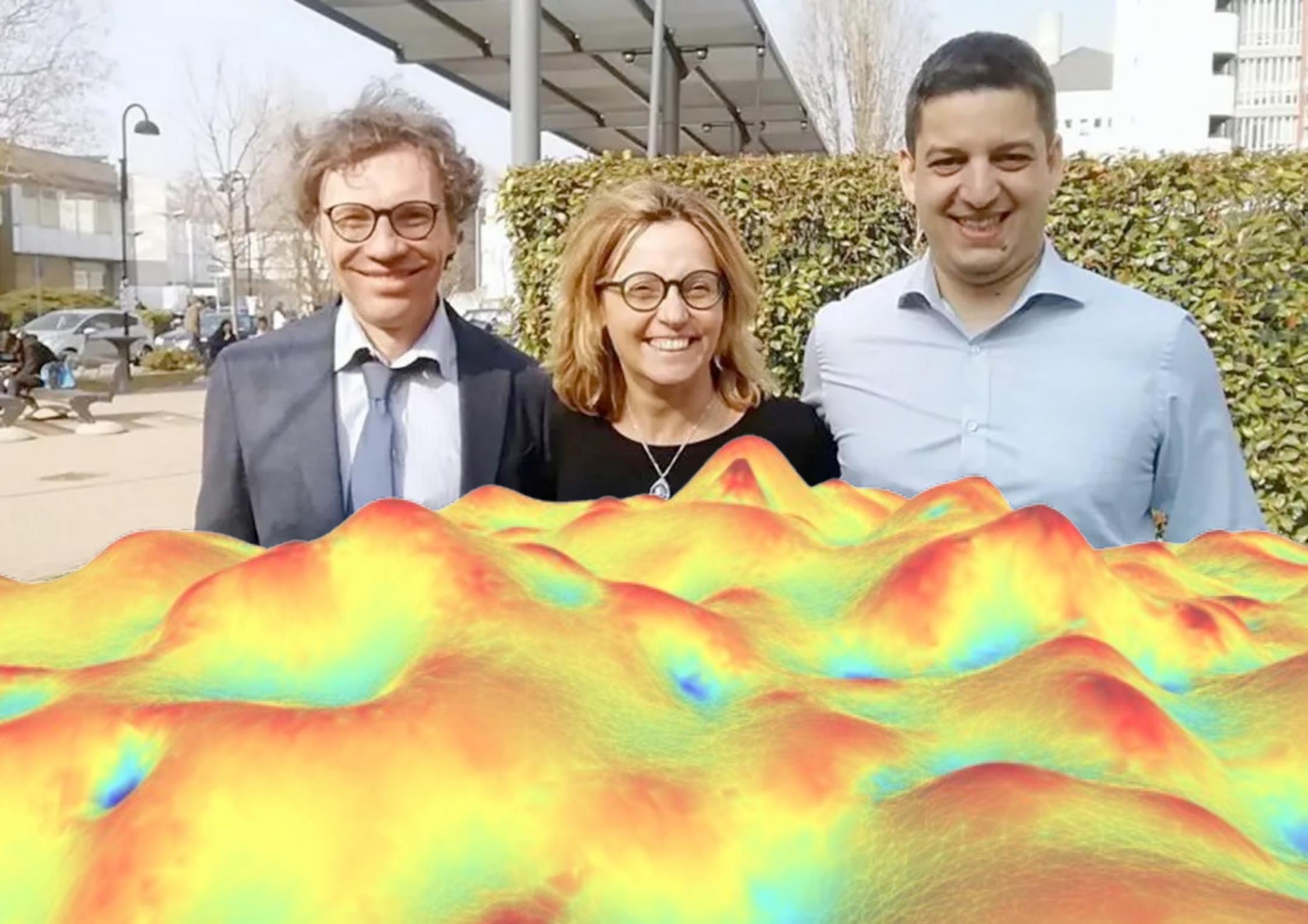
ARIADNE IS DISTINCT FROM THE IMMUNE METASIGNATURE

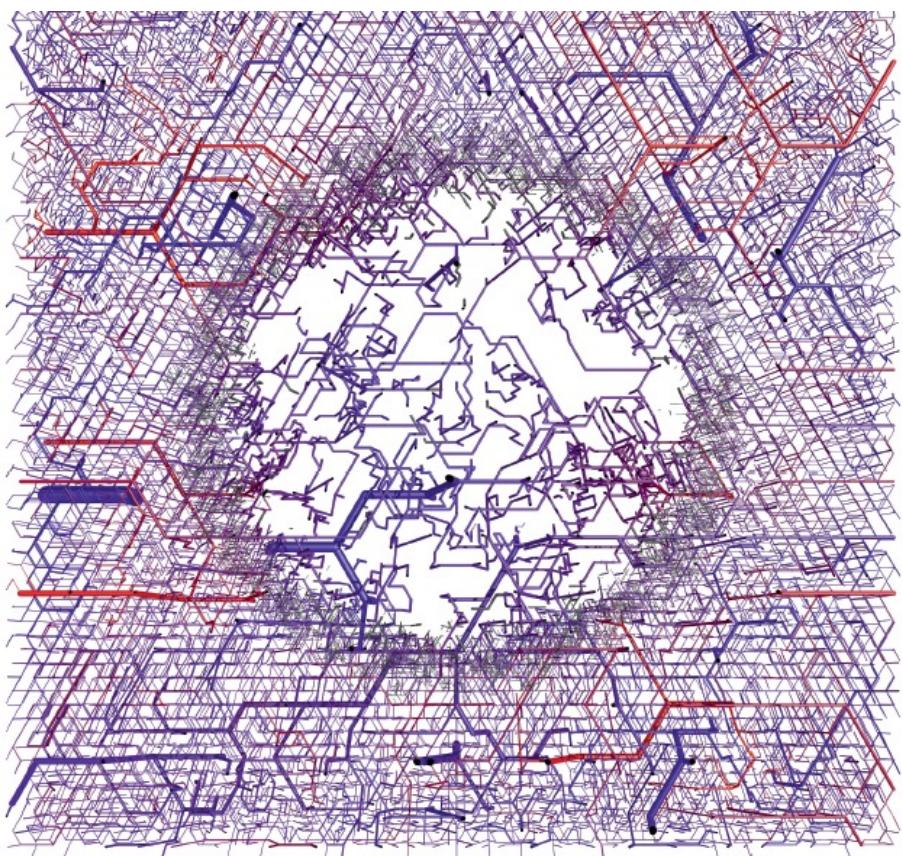
a



b

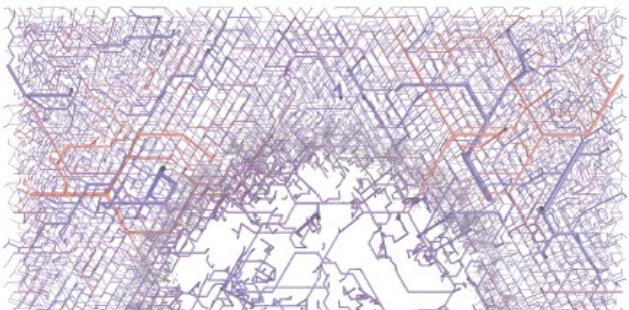






Caterina La Porta and Stefano Zapperi

The Physics of Cancer



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THANK YOU FOR YOUR
ATTENTION!