

Cancer ecology and evolution

N. Alcalá

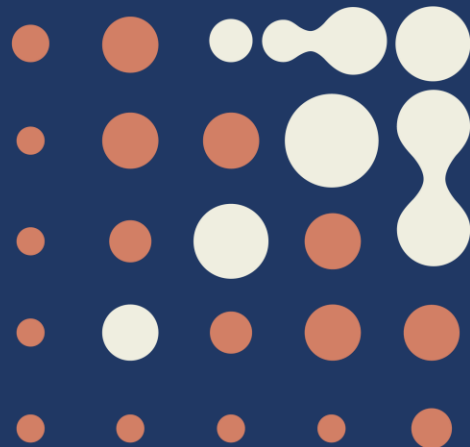
Rare Cancers Genomics Team

October 19th 2022

International Agency
for Research on Cancer



@nlalcala



Plan

1. Introduction: **a theory of cancer**, with ecology and evolution as main conceptual frameworks
2. Reconstructing **tumor evolutionary trajectories**
3. From **microenvironmental pressures to tumor phenotypes**

Tumor ecology & evolution | *Toward a theory of cancer*

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The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†

"One day, we imagine that cancer biology and treatment—at present, a patchwork quilt of cell biology, genetics, histopathology, biochemistry, immunology, and pharmacology—will become **a science with a conceptual structure and logical coherence that rivals that of chemistry or physics.**"

"We foresee **cancer research developing into a logical science**, where the complexities of the disease [...] will become understandable in terms of a **small number of underlying principles.**"

Tumor ecology & evolution | *Cancer evolutionary theory*

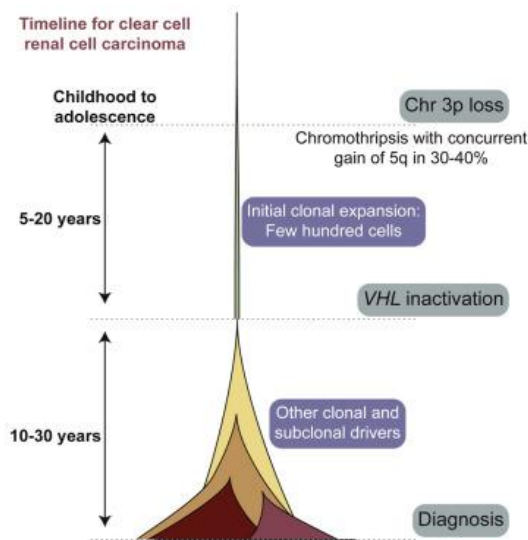
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The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†

"[...] tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells."

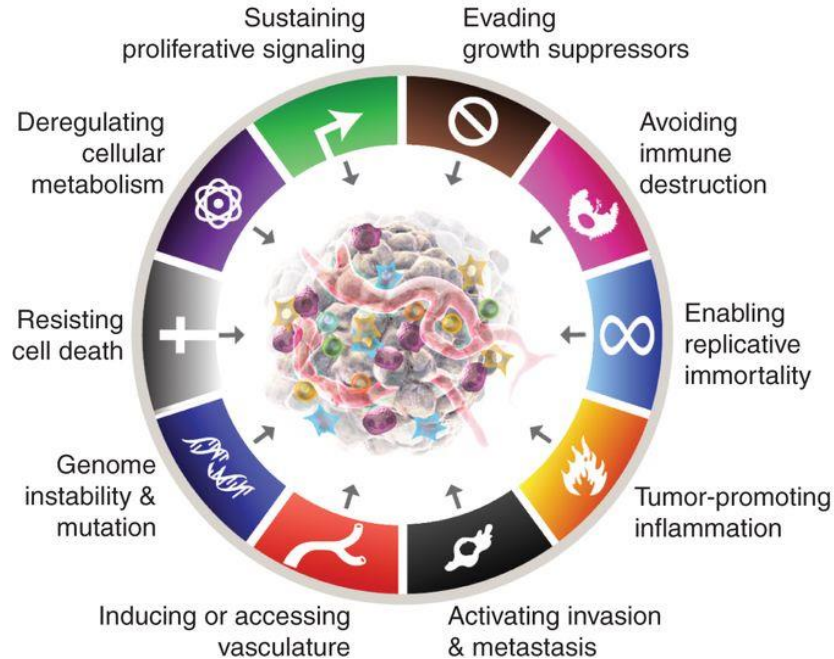


TRACERX project (Mitchell *et al.* 2018).

Tumor ecology & evolution | *Cancer phenotypes*

Enumerating **cancer phenotypes** is central in their endeavor:

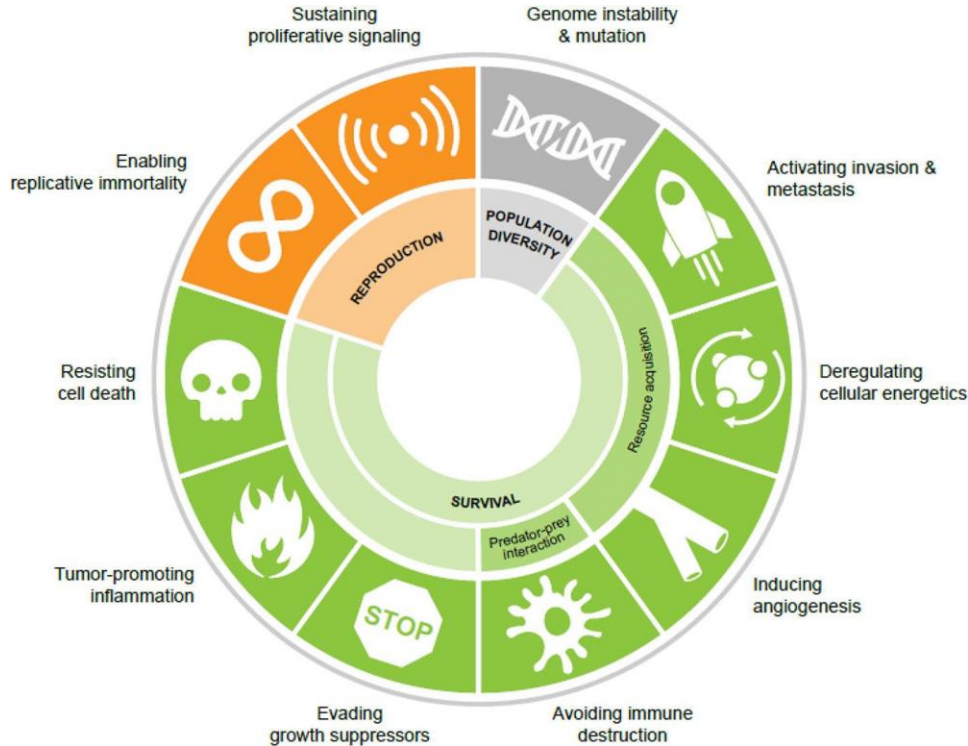
> 10 **hallmarks of cancer**, biological capabilities that enable malignant growth



The hallmarks of cancer (Weinberg and Hanahan 2015).

Tumor ecology & evolution | *Phenotypes and ecology*

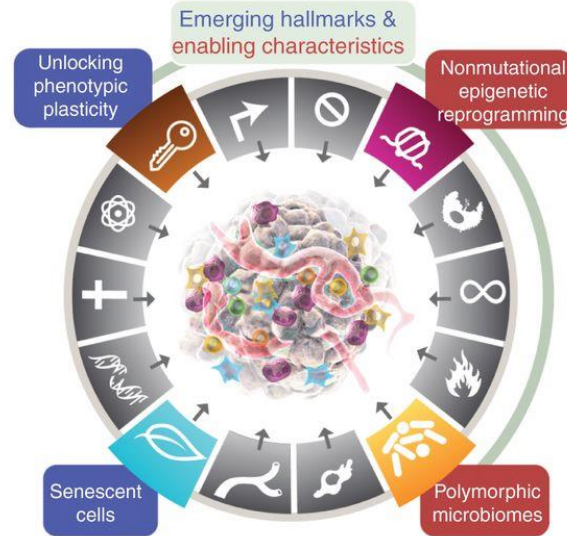
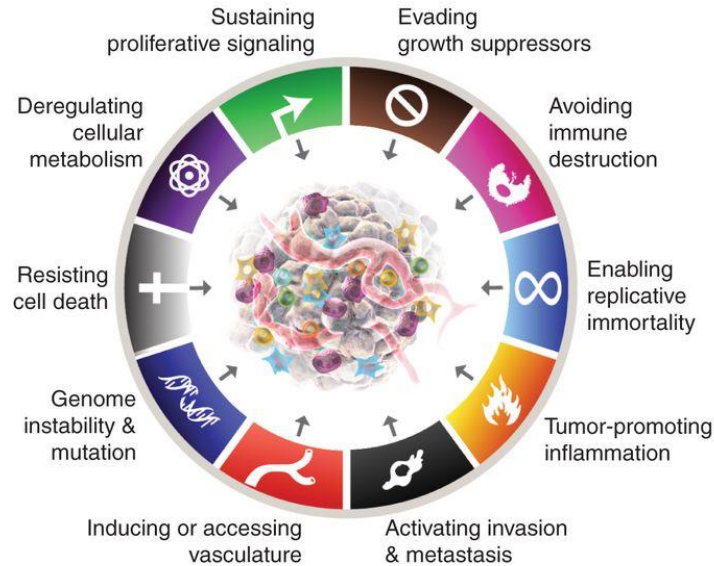
Hallmarks of cancer can be interpreted as **ecological strategies**



Hallmarks of cancer as ecological fitness parameters (Somarelli *Front. Ecol. Evol.* 2021).

Tumor ecology & evolution | *Phenotypes and ecology*

Emerging hallmarks give more and more importance to **interactions with microenvironment**



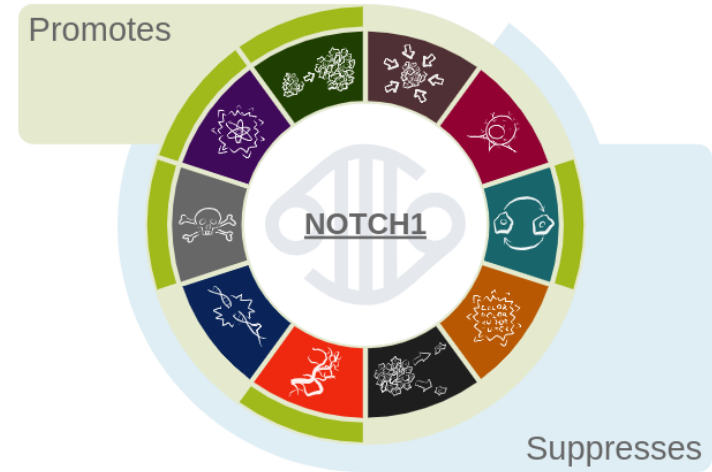
Hallmarks of cancer (Hanahan *Canc Discov*2022).

Tumor ecology & evolution | *From genotypes to phenotypes*

Cancer phenotypes result from a **breach of anticancer mechanisms** because of genetic or epigenetic **alterations in cancer genes**

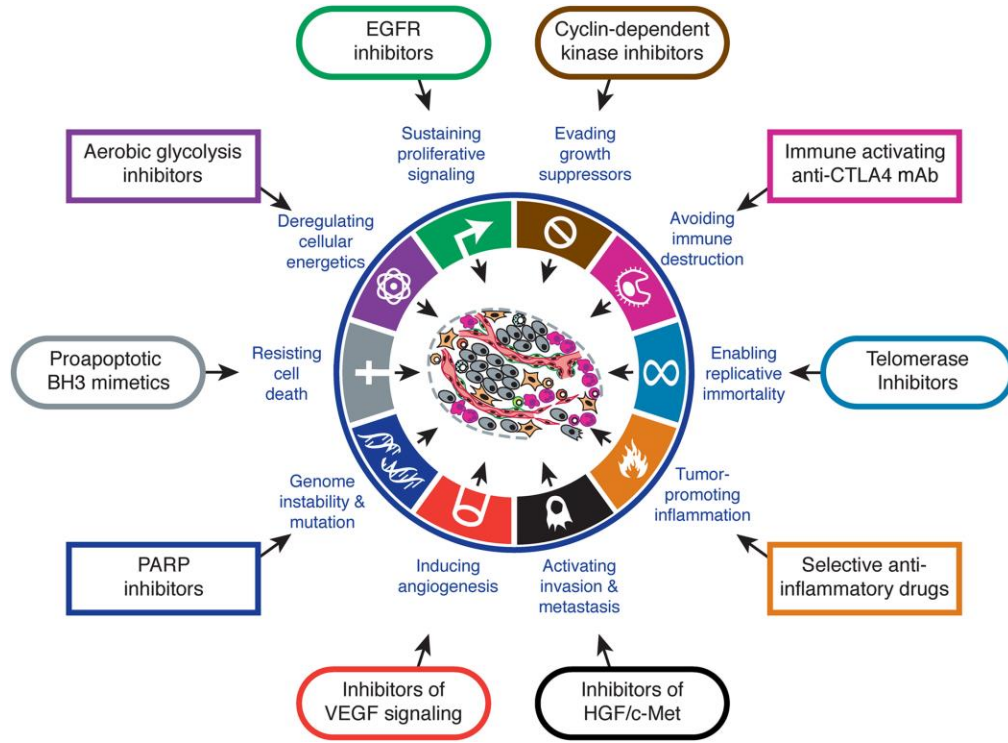
Two types of "cancer genes":

- **Oncogenes**, proto-genes that can be switched on by genetic or epigenetic alteration
- **Tumor suppressor genes**, "house keeping" genes whose inactivation promote cancer



NOTCH1 Hallmarks profile (COSMIC database).

Tumor ecology & evolution | *Hallmarks and treatment*



Therapeutic targeting of the hallmarks of cancer (Weinberg and Hanahan *Cell* 2015).

Reconstructing tumor evolutionary trajectories

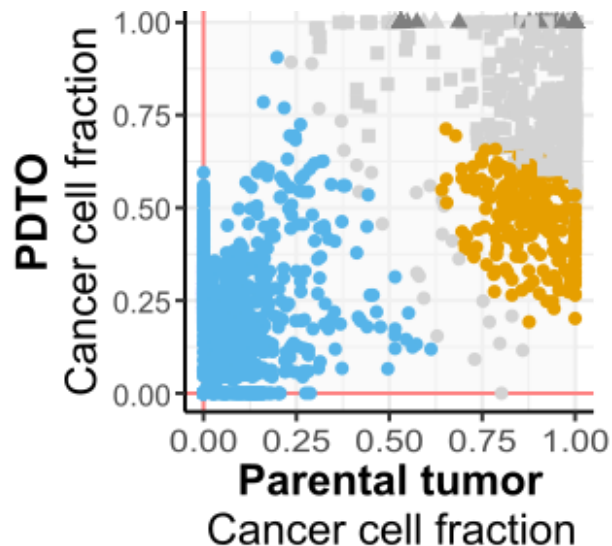
Intra-tumor diversity | *Evolutionary trajectory inference*

Theoretical frameworks are based on

- **molecular phylogenetics**: the study of mutations in species—at macro-evolutionary time-scales
- **population genetics**: the study of mutations in populations—at micro-evolutionary time-scales

Intra-tumor diversity | *Phylogenetic approaches*

1. Cluster mutations based on the **cancer cell fraction** (proportion of cells carrying this mutation, determined in NGS by the allelic fraction, the proportion of reads with the ALT allele)



Clonality

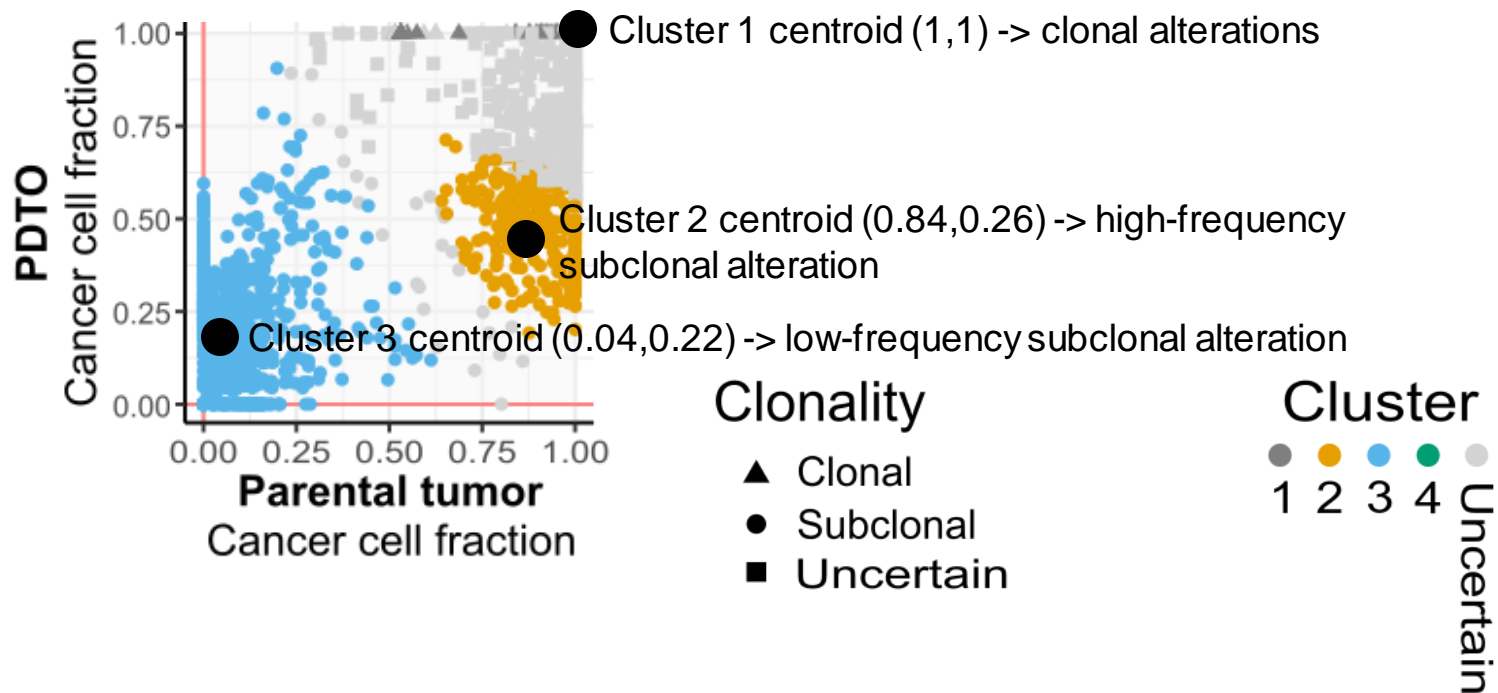
- ▲ Clonal
- Subclonal
- Uncertain

Cluster



Intra-tumor diversity | *Phylogenetic approaches*

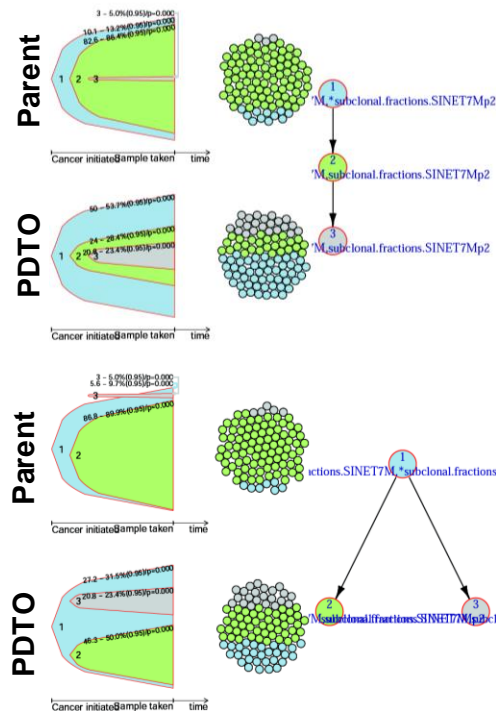
1. Cluster mutations based on the **cancer cell fraction** (proportion of cells carrying this mutation, determined in NGS by the allelic fraction, the proportion of reads with the ALT allele)



Intra-tumor diversity | *Phylogenetic approaches*

2. Enumerate possible **parsimonious phylogenetic trees** using "pidgeonhole principle": sum of CCF of subclones cannot exceed that of parental clone

- Cluster 1 centroid (1,1) -> clonal alterations
- Cluster 2 centroid (0.84,0.26) -> high-frequency subclonal alteration
- Cluster 3 centroid (0.04,0.22) -> low-frequency subclonal alteration

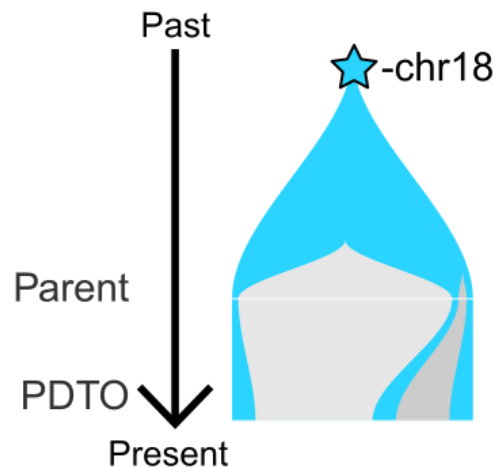
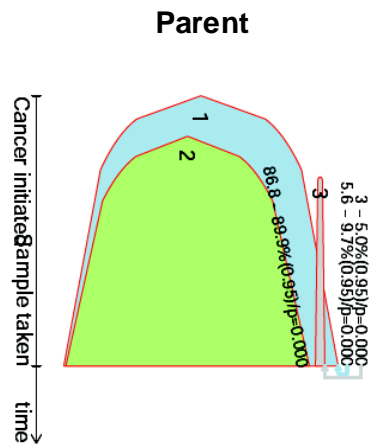
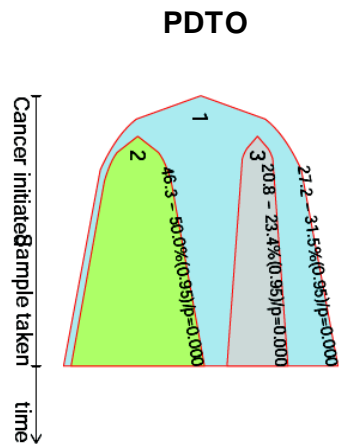


Solution 1: linear evolution

Solution 2: branching evolution

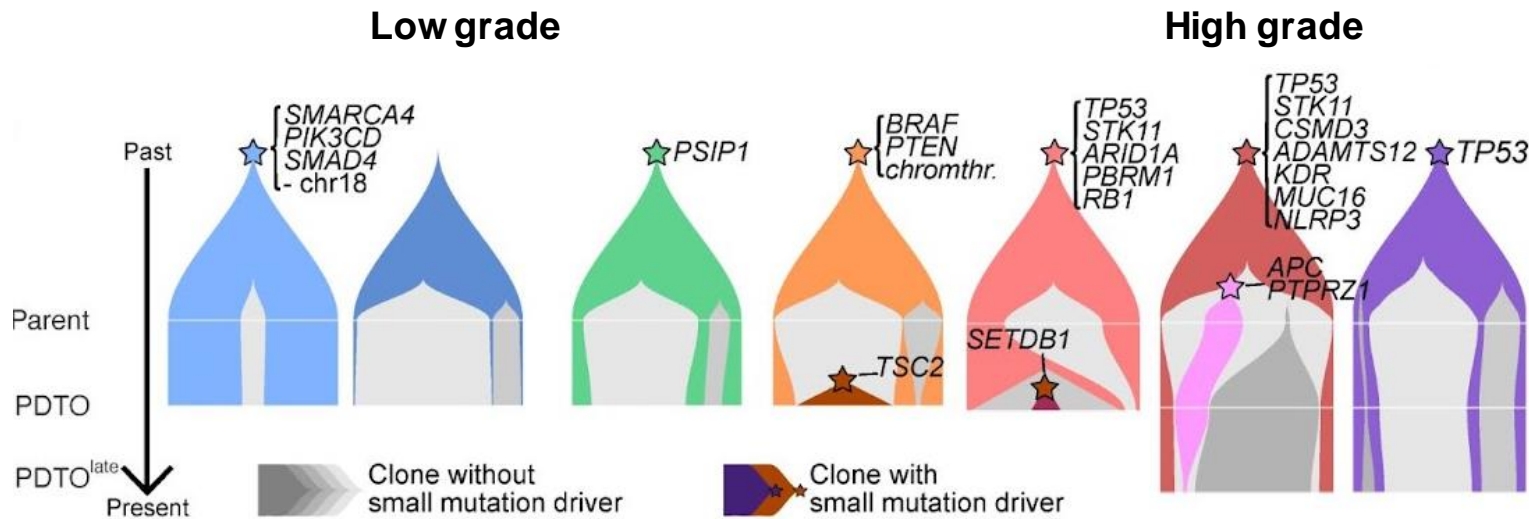
Intra-tumor diversity | *Phylogenetic approaches*

3. Reconcile multiple samples (regions / time-points) to infer spatial or temporal changes in clone frequencies



Intra-tumor diversity | *Phylogenetic approaches*

3. Reconcile multiple samples (regions / time-points) to infer



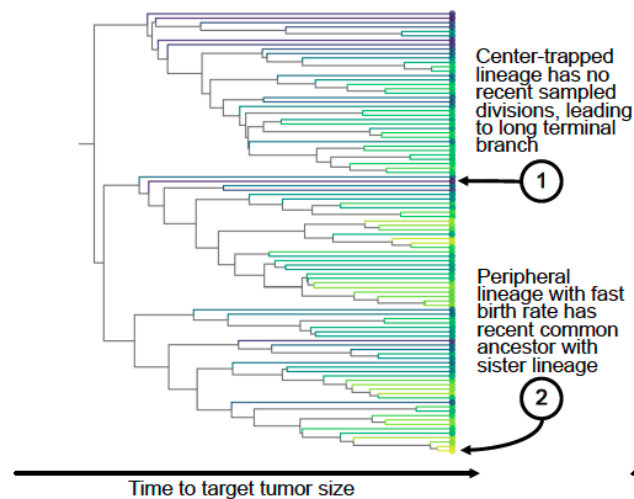
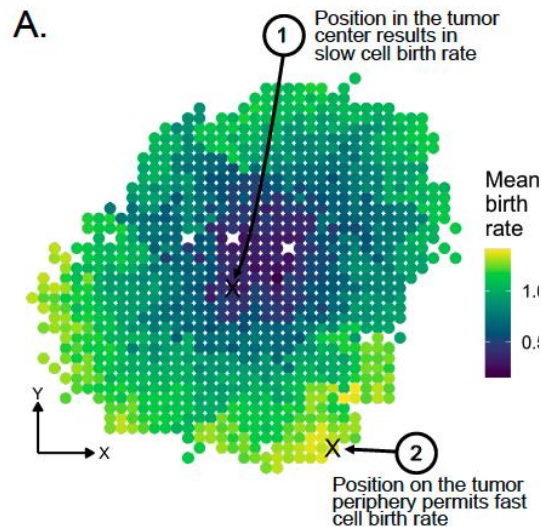
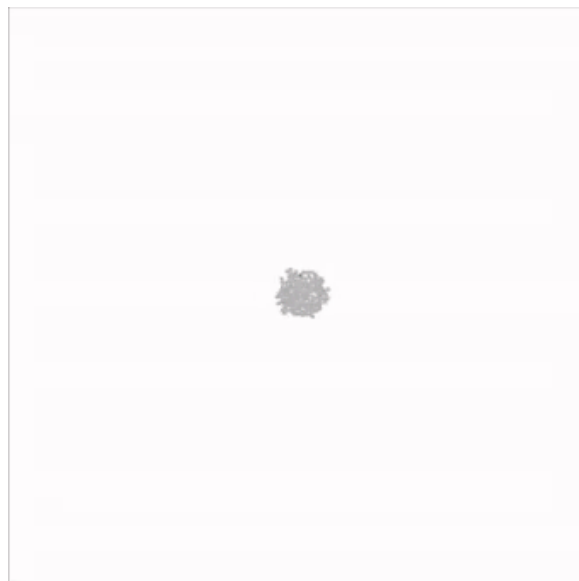
Intra-tumor diversity | *Evolutionary trajectory inference*

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- **population genetics**: the study of mutations in populations—at micro-evolutionary time-scales

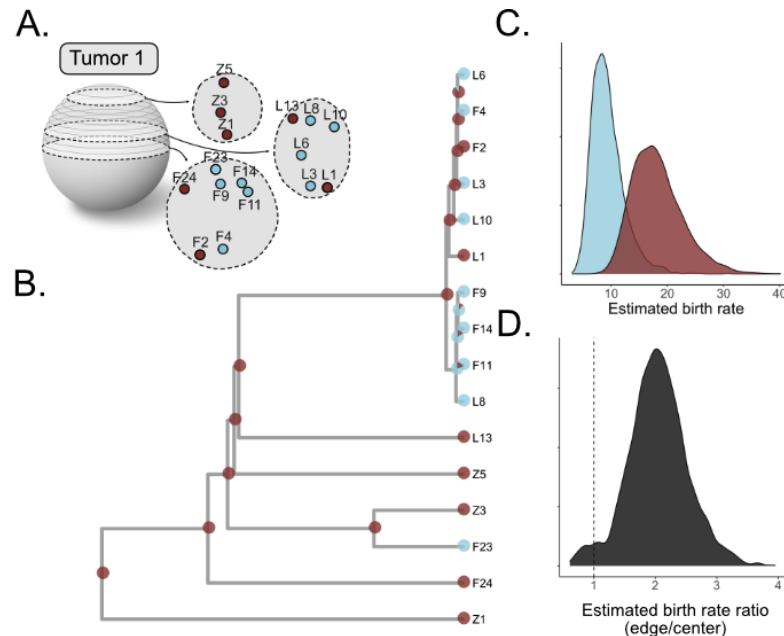
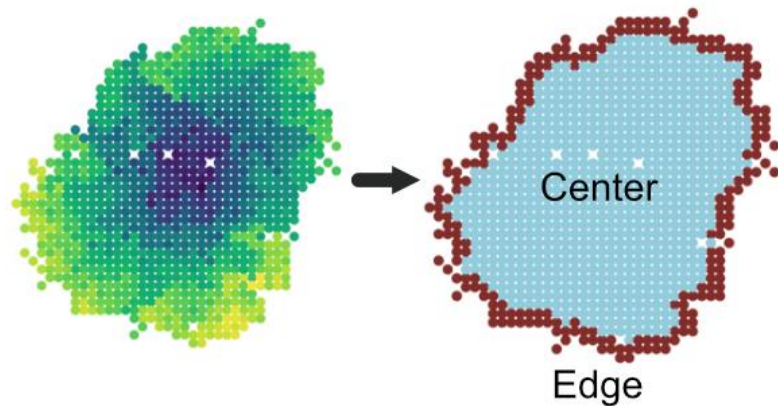
Intra-tumor diversity | *Population-genetic approaches*

1. Model tumor growth
2. Build cell genealogical trees from tumor



Intra-tumor diversity | *Population-genetic approaches*

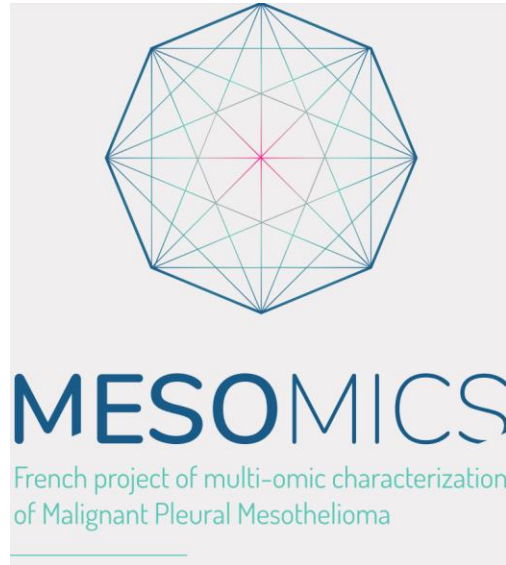
3. Use model predictions (link birth-rate / position) to infer spatial position of cells from genealogies and growth advantage of edge cells



Application to hepatocellular multi-regional sequencing

From micro-environment to tumor phenotype

Example of malignant pleural mesothelioma phenotypes



From environment to phenotype | *Heterogeneity*

Tumors contain a mixture of cells

> we sequence simultaneously different tumor cell populations, immune "predator" cells, neighbouring tissue, ...

From environment to phenotype | *Heterogeneity*

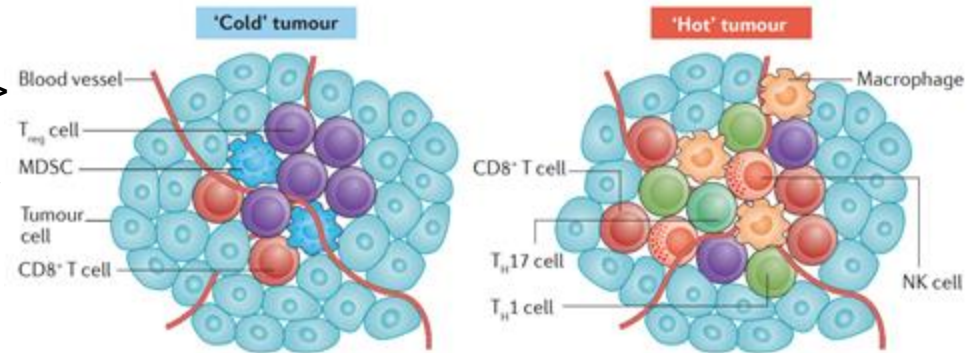
Tumors contain a mixture of cells

> we sequence simultaneously different tumor cell populations, immune "predator" cells, neighbouring tissue, ...

> **multi-omic sequencing** provides an opportunity to learn about the tumor genotype, phenotype, and the tumor micro-environment:

>> genomic data -> tumor genotype, what is "hard-wired" in the tumor

>> transcriptomic data/epigenomic data -> which cells are present in the micro-environment, what pathways are tumor cells activating (phenotypes), how do they interact with the environment

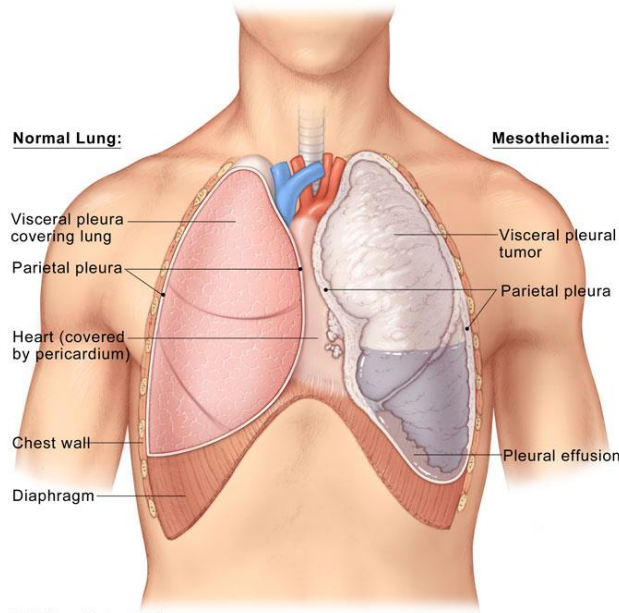


Tumors differ in their level of infiltration. Source: Nagarsheth et al. *Nat Rev Immun* 2017.

From environment to phenotype | *The case of mesothelioma*

Malignant pleural mesothelioma

- Rare and deadly cancer arising in the linings of the lung (pleura)
- Mostly associated with **asbestos exposure**
- Asbestos is banned in many countries but **lag between exposure and disease ~30-40 years** ⇒ incidence still rising

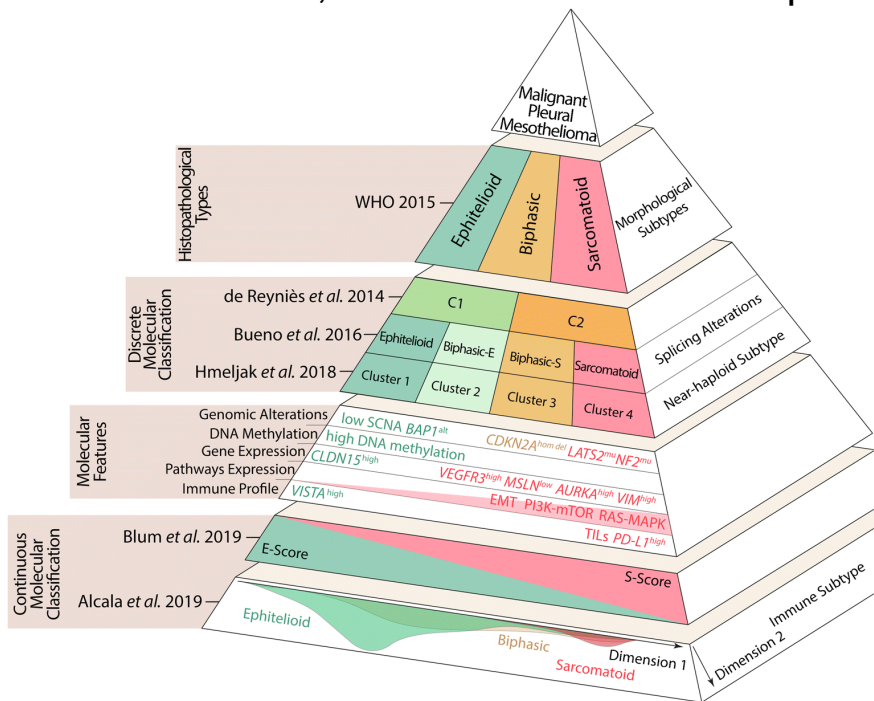


Stanford Medicine Dept of Surgery

From environment to phenotype | *The case of mesothelioma*

Malignant pleural mesothelioma (MPM)

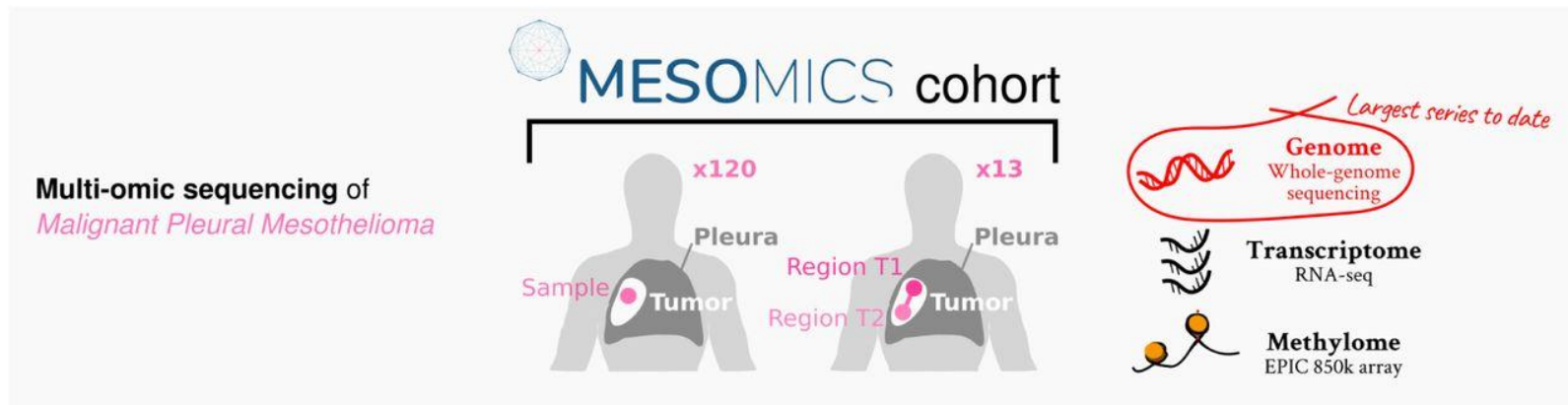
- Current WHO classification considers 3 types; molecular classifications further subdivide them
- Nevertheless, the extent of molecular phenotypes is unknown



Schematic representation of current MPM classifications (Fernandez-Cesta et al. Virchows Archive 2021)

From environment to phenotype | *The case of mesothelioma*

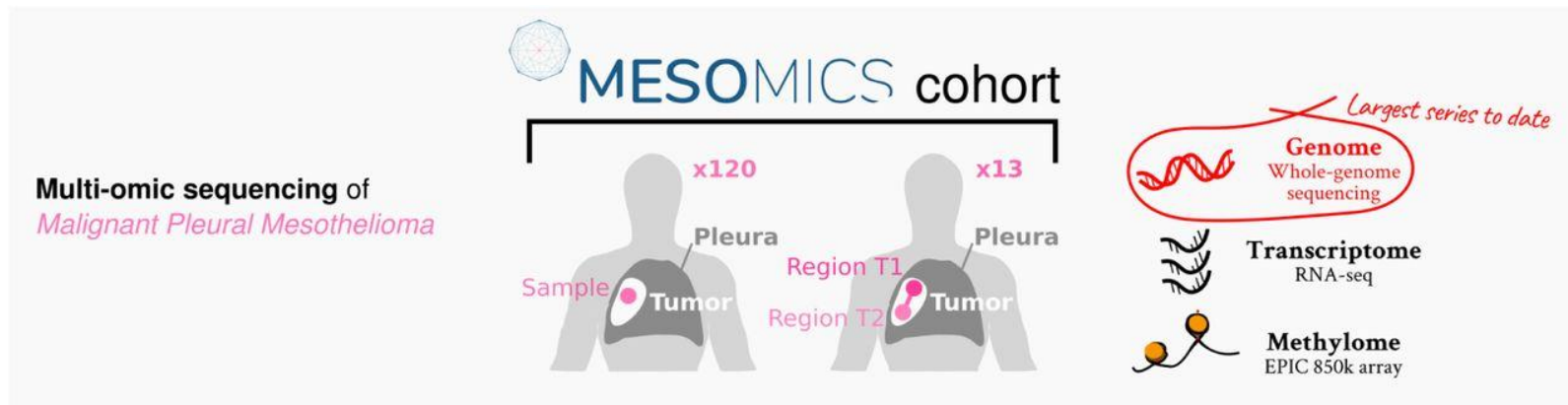
MESOMICS study: further define inter-patient molecular variation



Mangiante*, Alcalá*, Sexton-Oates*, Di Genova*,
et al. (Nature Genetics, In press)

From environment to phenotype | *The case of mesothelioma*

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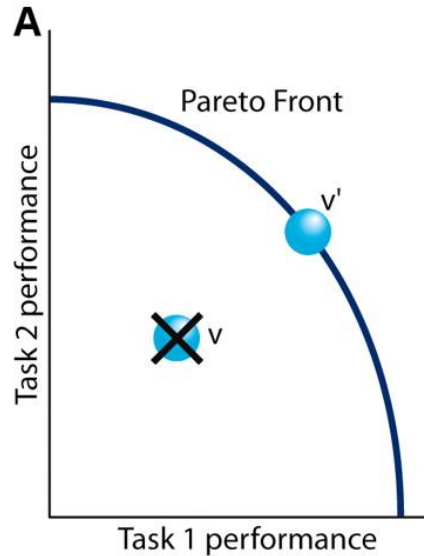
Mangiante*, Alcalá*, Sexton-Oates*, Di Genova*,
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1. Find molecular phenotypes
2. Associate microenvironment and phenotypes
3. Find genomic alterations associated with phenotypes
4. Generate evolutionary hypotheses

From environment to phenotype

Step 1: build a phenotypic map of MPM

Method: Archetypal analysis

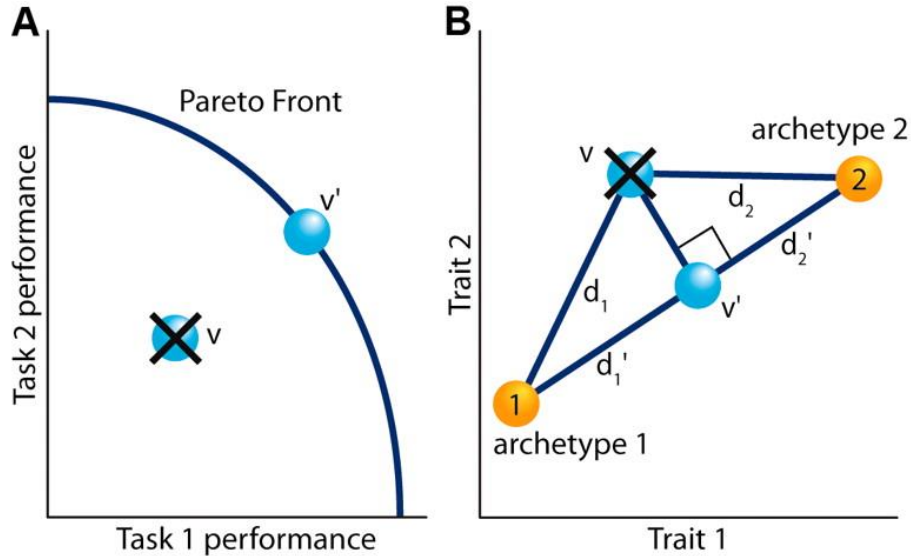


Evolutionary trade-offs and the geometry of phenotypic space (Shoval et al. Science 2012)

From environment to phenotype | *Molecular phenotypes*

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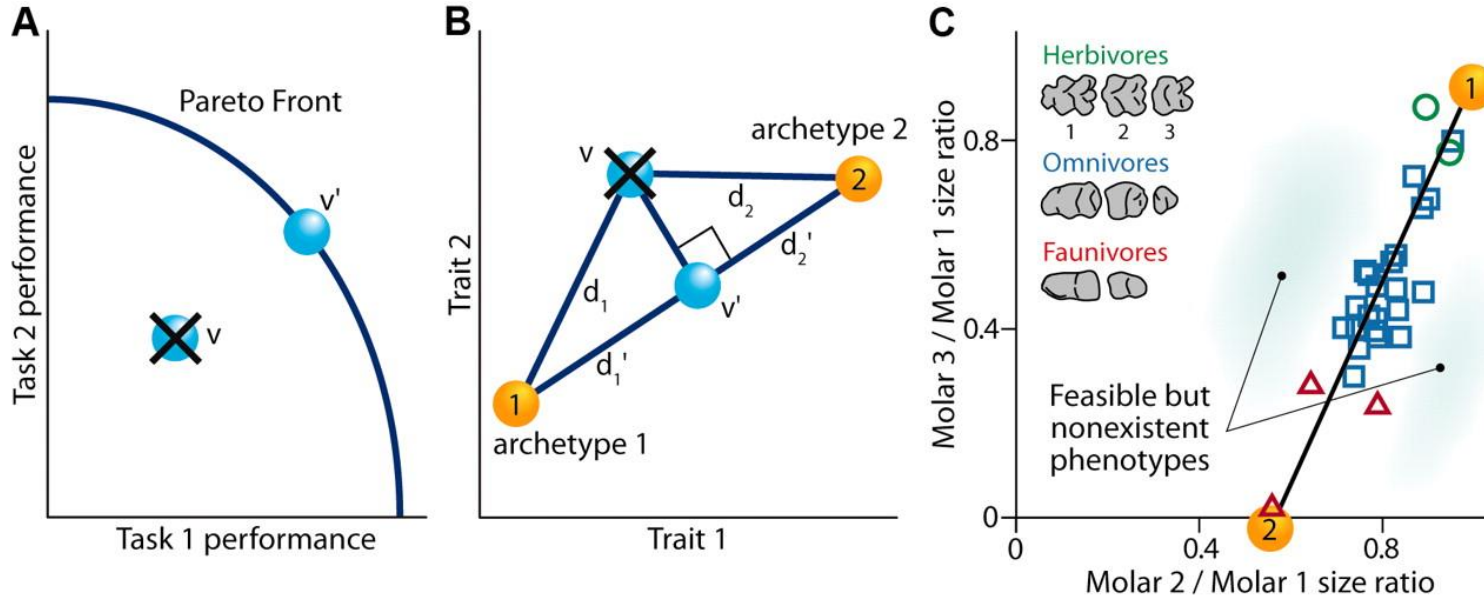


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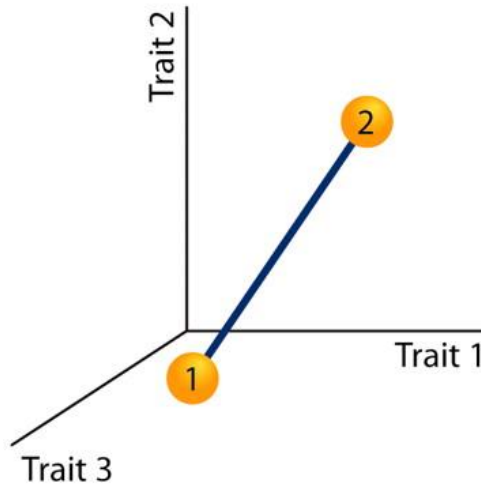
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Tumor ecology & evolution | *A genotype-phenotype map*

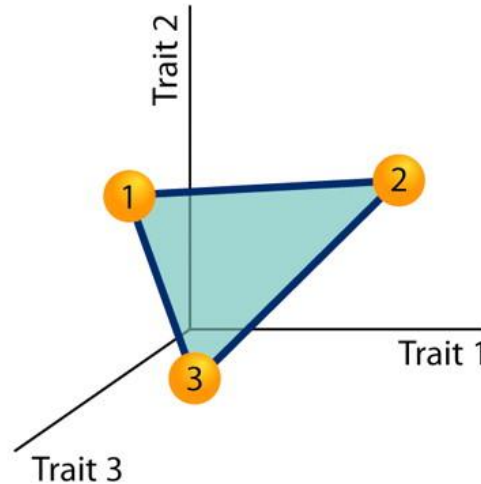
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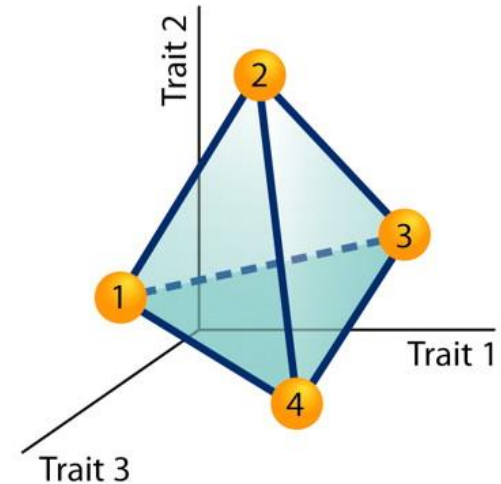
A 2 tasks



B 3 tasks



C 4 tasks

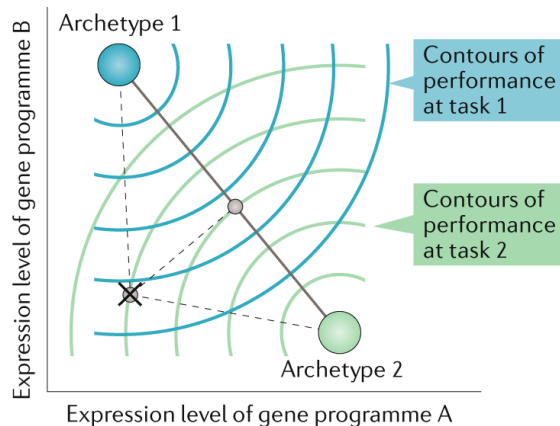


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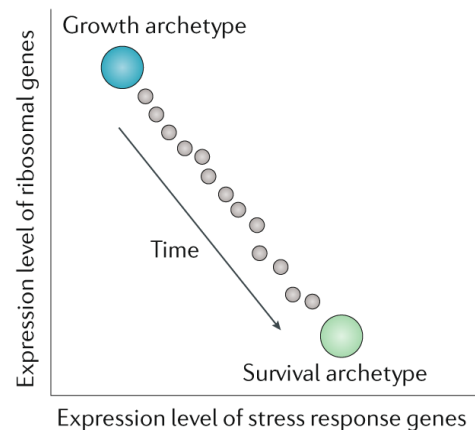
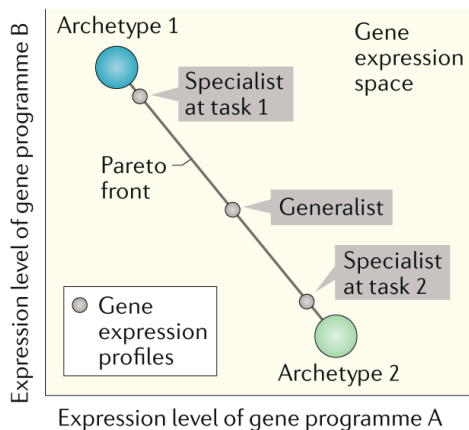
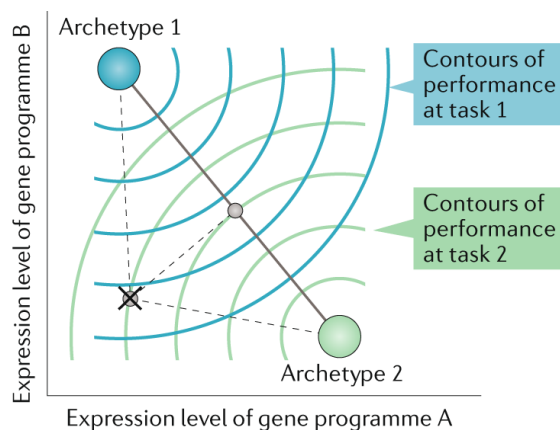


Evolutionary trade-offs in cancer. Expression is considered informative about cell function and thus a proxy for cancer phenotype (Hausser and Alon Nat Rev Cancer 2020)

Tumor ecology & evolution | *A genotype-phenotype map*

Step 1: build a phenotypic map of MPM

Method: Archetypal analysis

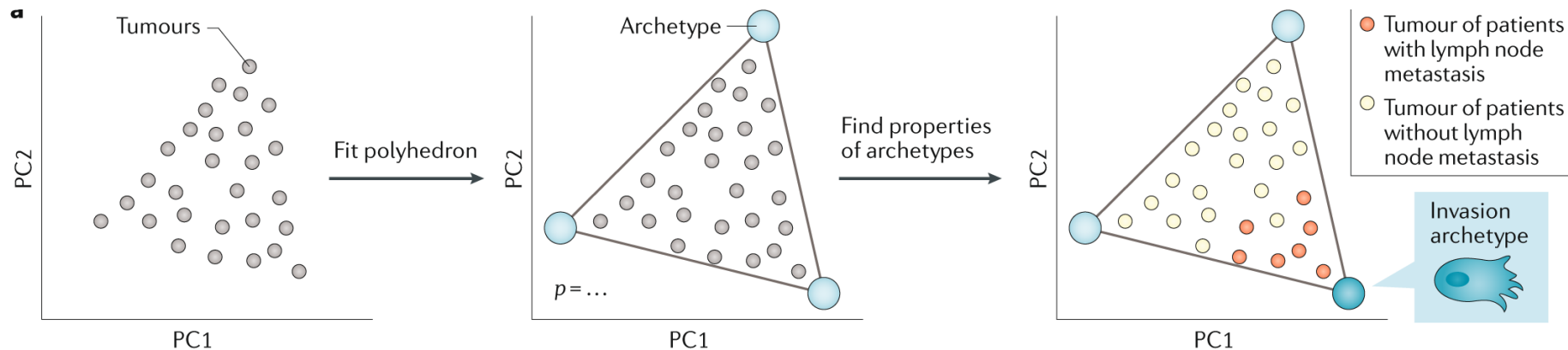


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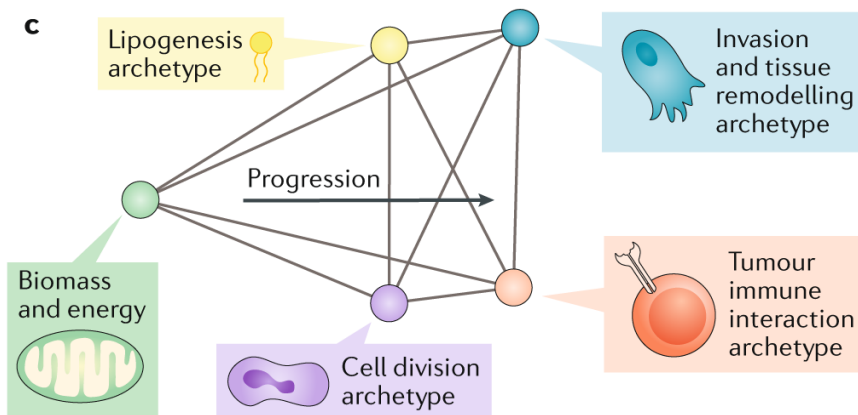
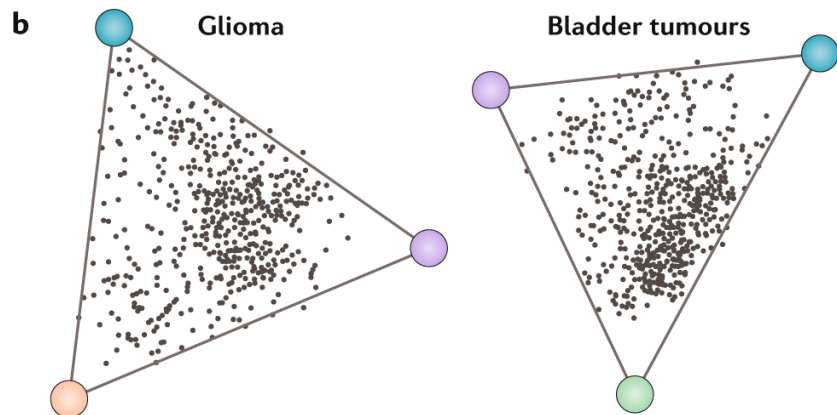


PCA is used as an unsupervised identification of latent expression variables that act as a proxy for cancer phenotypes (Hausser and Alon Nat Rev Cancer 2020)

Tumor ecology & evolution | *A genotype-phenotype map*

Step 1: build a phenotypic map of MPM

Method: Archetypal analysis

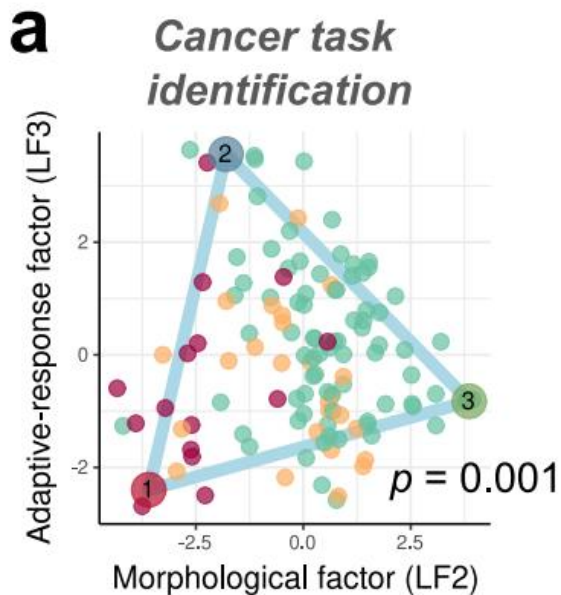


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Tumor ecology & evolution | *A genotype-phenotype map*

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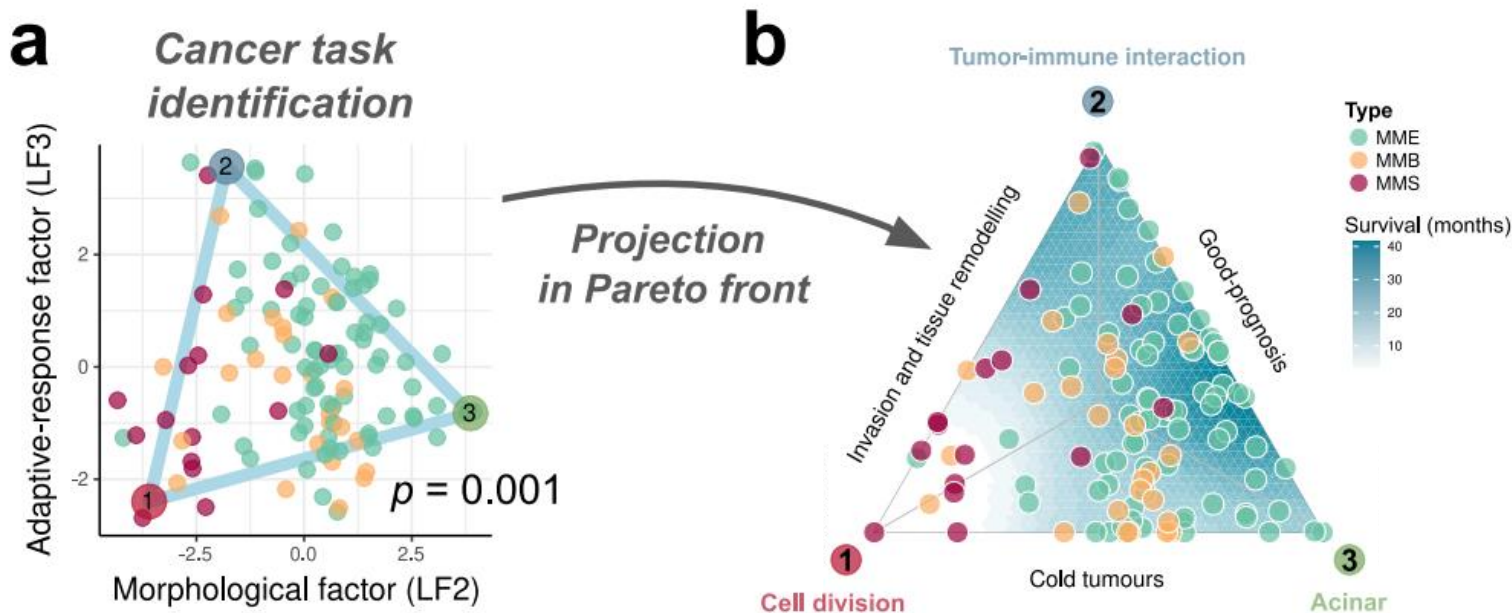


Evolutionary trade-offs in the MESOMICS cohort

Tumor ecology & evolution | *A genotype-phenotype map*

Step 1: build a phenotypic map of MPM

Method: Archetypal analysis

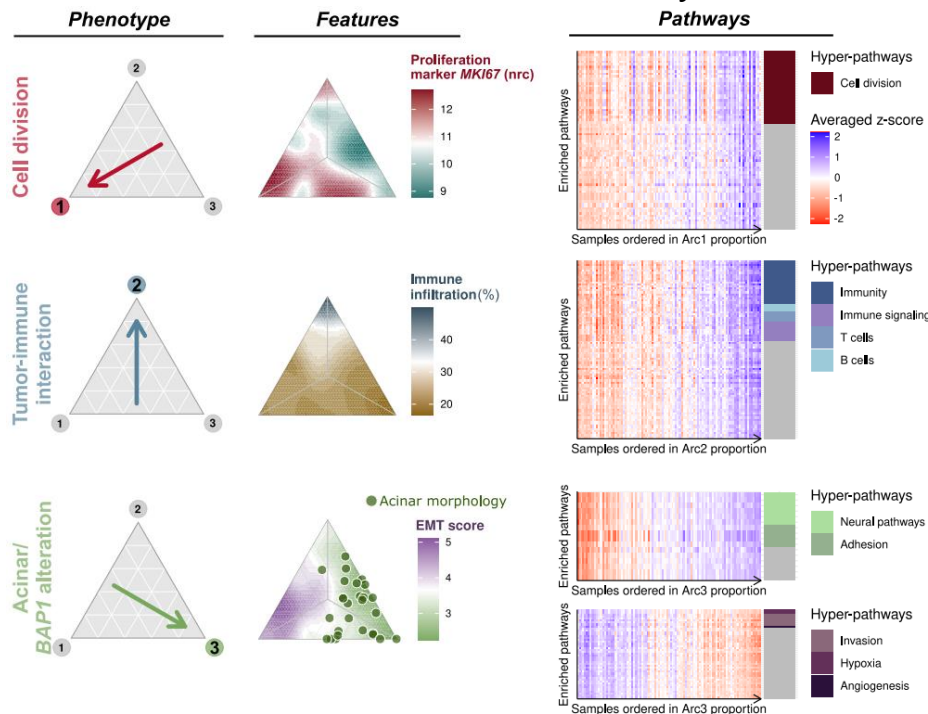


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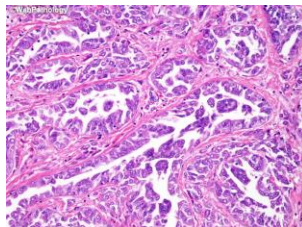
Tumor ecology & evolution | *A genotype-phenotype map*

Step 1: build a phenotypic map of MPM

Method: Gene set enrichment analysis of archetypes, association with cell morphology



Evolutionary trade-offs in the MESOMICS cohort

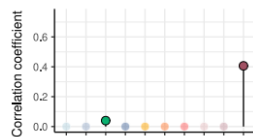
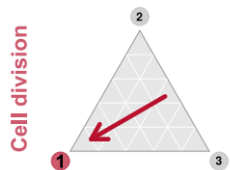


Tumor ecology & evolution | *A genotype-phenotype map*

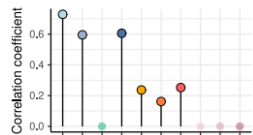
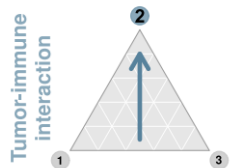
Step 2: infer microenvironmental conditions of each phenotype

Method: Gene set enrichment analysis of archetypes, association with clinical variables

Phenotype **Microenvironment**

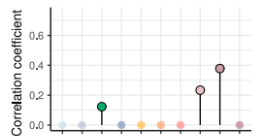
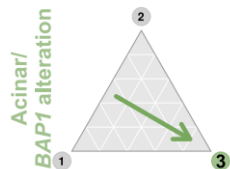


- > Scarce resources (necrosis, hypoxia)
- > Asbestos exposure (chronic inflammation?)



- > Strong immune predation
- > Asbestos exposure (chronic inflammation?)

Microenvironments associated with MPM archetypes

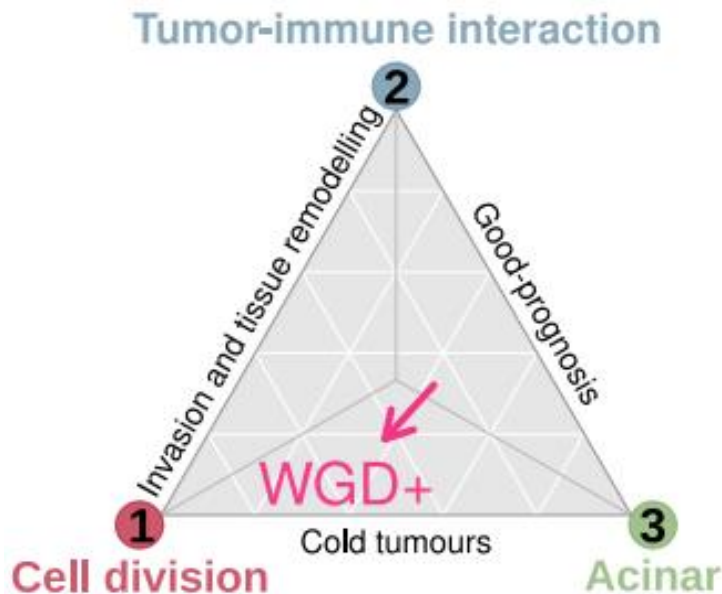


- > Favorable environment

Tumor ecology & evolution | *A genotype-phenotype map*

Step 3: find genomic alterations associated with each phenotype

Method: Compute “effect vectors” linking WT and altered samples in phenotypic space

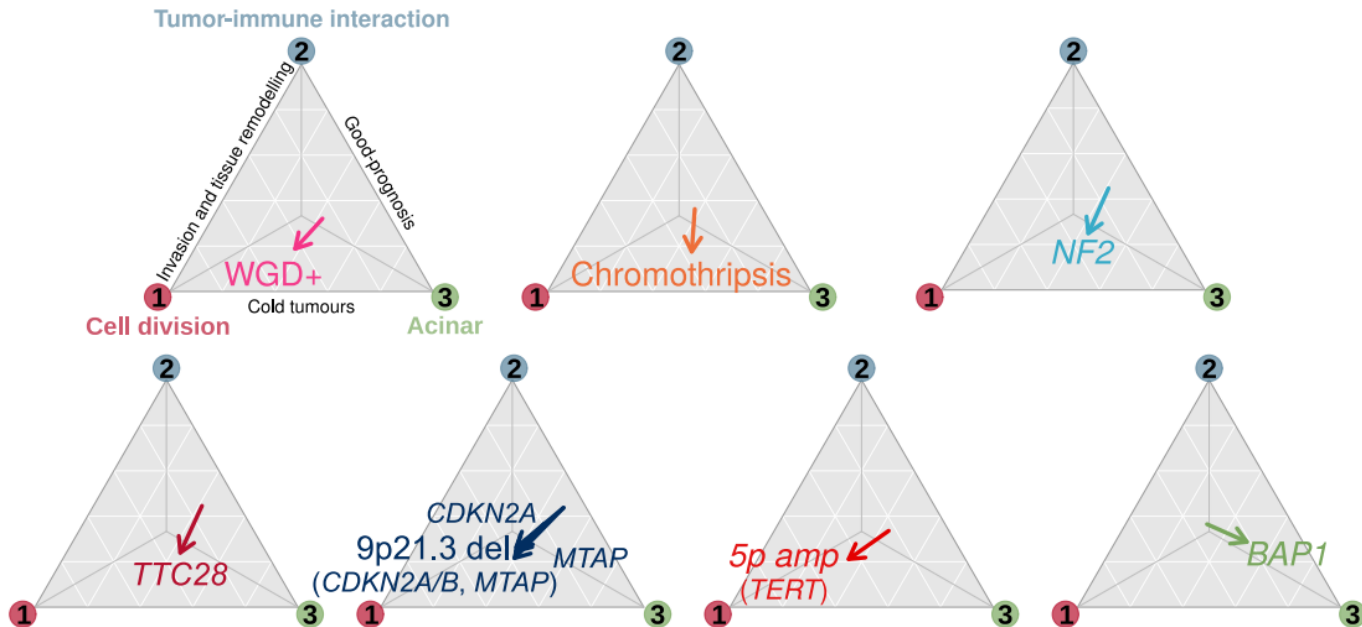


Genomic events tune phenotypic specialization in MPM

Tumor ecology & evolution | *A genotype-phenotype map*

Step 3: find genomic alterations associated with each phenotype

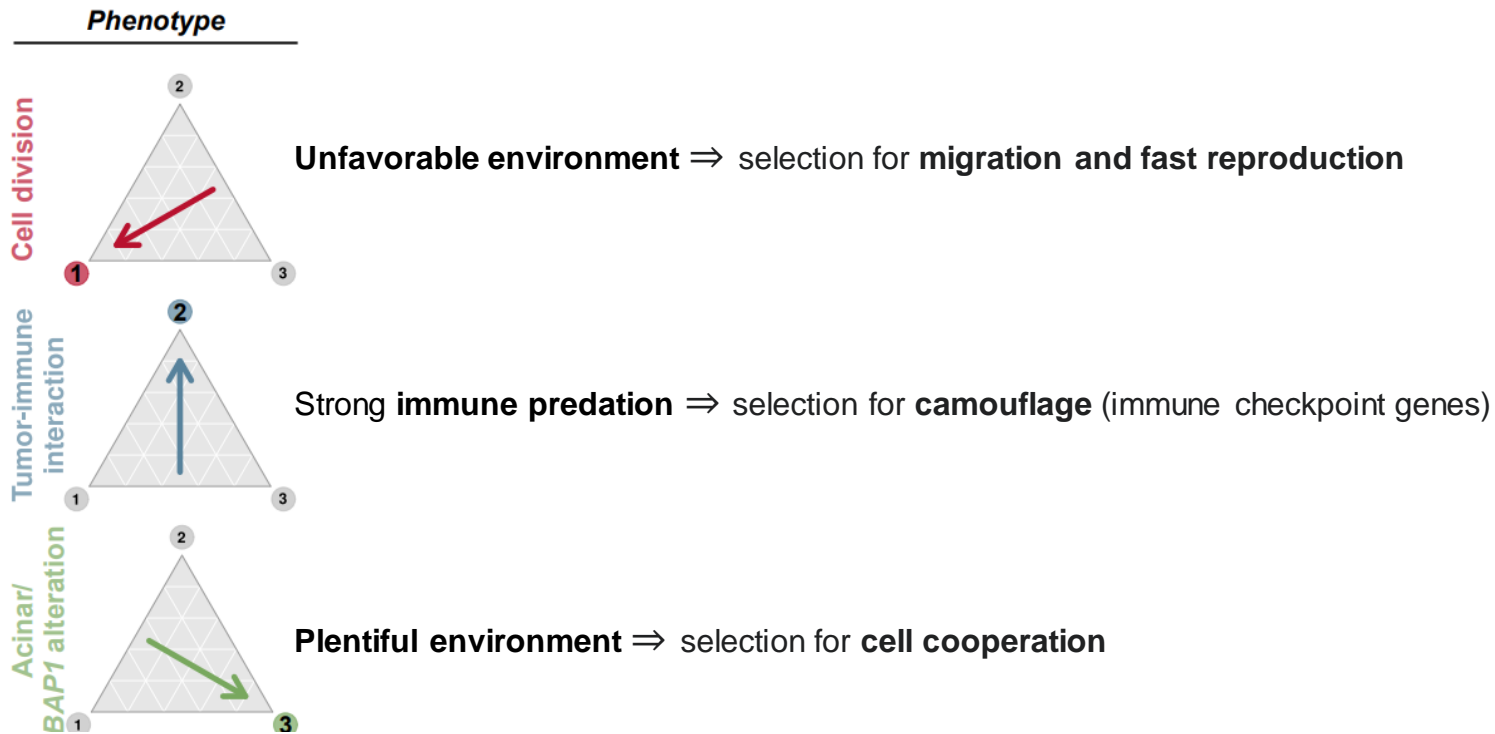
Method: Compute “effect vectors” linking WT and altered samples in phenotypic space



Genomic events tune phenotypic specialization in MPM

Tumor ecology & evolution | *A genotype-phenotype map*

Step 4: evolutionary hypotheses



Tumor ecology & evolution | *Toward a theory of cancer*

- > The **convergence of experimental and theoretical models** can lead to **a theory of cancer as dreamt by Hanahan and Weinberg**
- > This novel theory of cancer will likely **have ecology and evolution at its center**

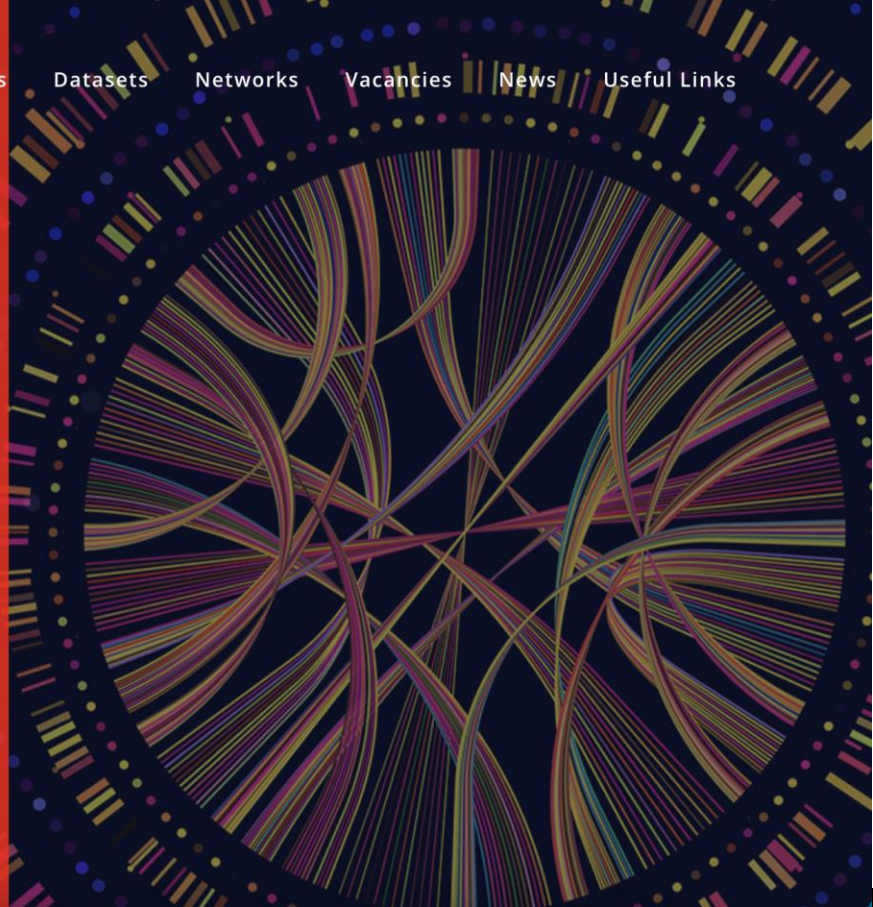
Tumor ecology & evolution | *References*

- > Hanahan and Weinberg. The Hallmarks of cancer, *Cell* 2000
- > R scripts for tumor phylogenetics of lung NEN organoids https://github.com/IARCBioinfo/MS_panNEN_organoids
- > R scripts for Pareto task inference of malignant pleural mesothelioma https://github.com/IARCBioinfo/MESOMICS_data
- > the <https://rarecancersgenomics.com/> initiative

www.rarecancersgenomics.com

Rare Cancers Genomics

Multidisciplinary and multi-omics molecular
characterisation of rare cancers



THANKS