The hallmarks of cancer BIO-392

What is cancer ?

- Disease of extraordinary complexity at every level:
  - Genetic complexity: Not just one ”cancer gene”
  - Histological/pathological: Multiple stages of progression
  - Prognostic & therapeutic complexity: Many variables
- What can account for such complexity?
  - Is each tumor a different disease?
  - Or can we expect any common underlying principles?

Rationalizing the complexity of cancers

- Observations:
  - *Multiple barriers normally prevent cancerous growth*
  - *<u>Some</u> of these barriers differ between organs*

- Hypothesis: Complexity reflects a spectrum of biological solutions to overcome tissue-specific and common barriers

- Prediction: Even seemingly disparate cancers may share some fundamental capabilities ("Hallmarks")

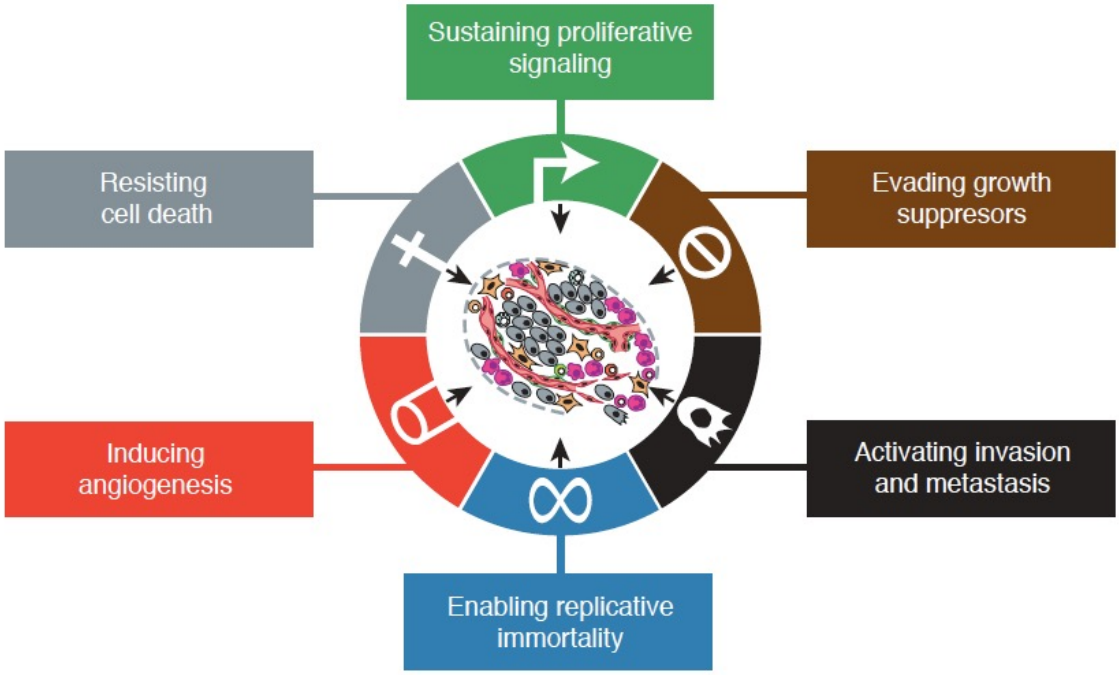
Why is this prediction so important?

Classification of tumors based on hallmarks?

- molecular diagnosis ?
- tumor staging ?
- prognosis ?

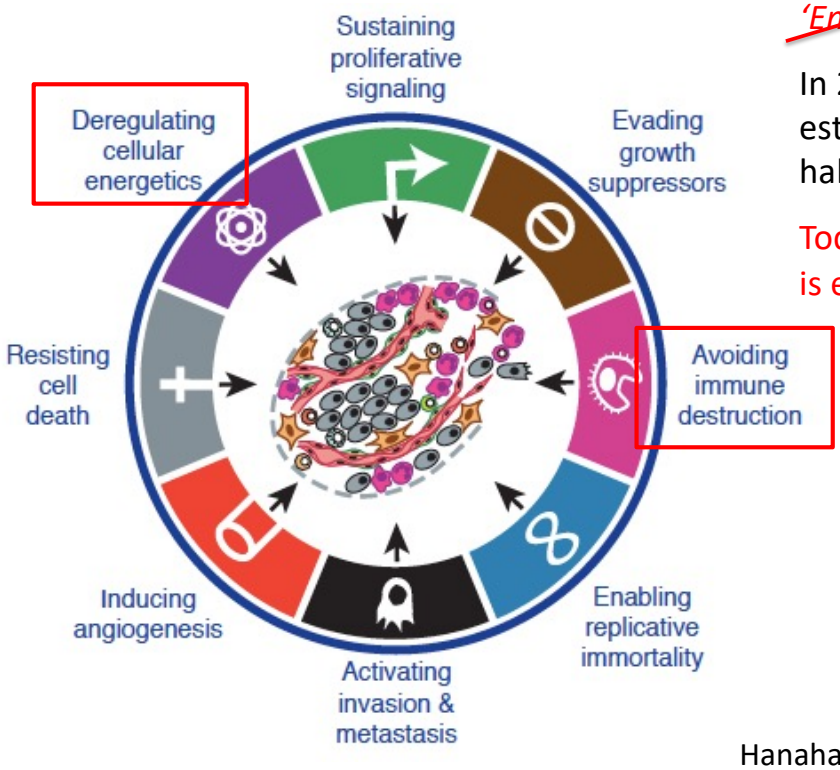
Choice of alternative targeted therapies based on hallmarks?

The Hallmarks of Cancer



proposed by Douglas Hanahan and Robert Weinberg in 2000

Hallmarks of Cancer : the next generation



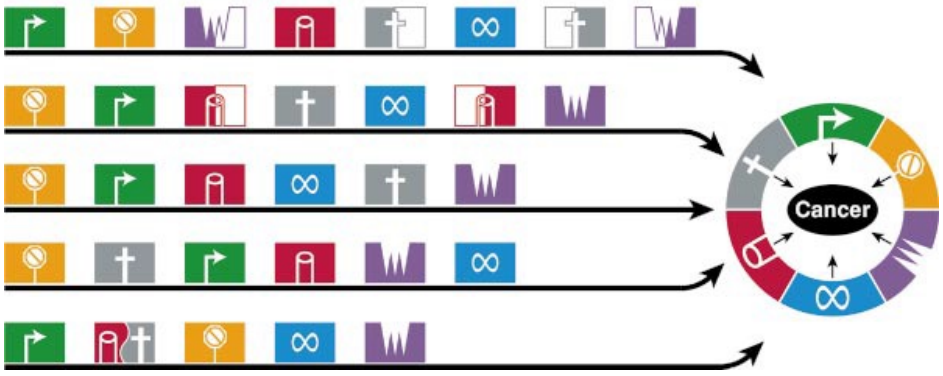
~~*'Emerging' hallmarks:*~~

In 2011: Not yet as firmly established as the "core" hallmarks.

Today, their broad relevance is equally accepted

Hanahan & Weinberg (Cell, 2011)

Alternative paths towards cancer



- the order in which the capabilities are acquired may vary
- in some tumors, a particular lesion can confer several capabilities simultaneously. For example, loss of function of p53 facilitates increased cell proliferation, resistance to apoptosis *and* increased angiogenesis

What are hallmarks of cancer?

- ***acquired capabilities*** that enable tumors to overcome *specific* barriers in healthy tissues
- ***acquired****:* i.e. they arise step-wise during tumor progression, by *various* molecular mechanisms, often in *variable* order
- in general, ***chronically*** *functional*, e.g.:
  - persistent inflammation (unlike acute infection)
  - sustained cell growth and proliferation (unlike regulated growth during normal tissue and organ development)

1. Sustained proliferative signaling

Specific barrier
supply of growth stimuli normally is too limited to support unlimited cell proliferation

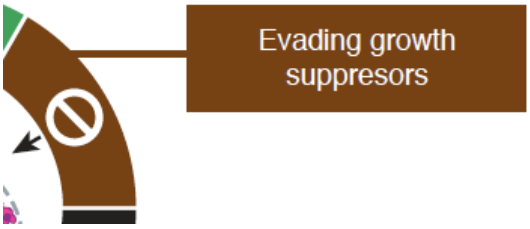
Acquired capability

Reduced dependence on physiological growth factors through:

- autocrine growth factors
- production of alternative extracellular stimuli
- de-regulation of intracellular signaling networks (circuits)
- altered cellular cross-talk

2. Evading growth suppressors

Specific barrier:
Cell cycle inhibitors prevent uncontrolled cell division



Acquired capability:

Loss of physiological cell cycle inhibitors such as RB1 allows escape from quiescent (G0) or postmitotic (G1) state

3. Resisting cell death

Specific barrier: Apoptosis
Induced cell death normally eliminates « outlaw » cells

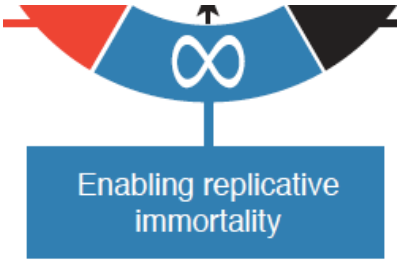
Acquired capability:

Resisting cell attrition (apoptosis) through

- inactivation of proapoptotic regulators (e.g. mutation of p53 in 50% of all cancers)
- activation of specific survival signals
- disruption of effectors downstream of sensors

4. Replicative immortality

Specific barrier
Replicative stress and cellular senescence (« wear and tear ») after hyperproliferation normally triggers cell cycle arrest



Acquired capability:
Evasion of stress signals and avoidance of telomere erosion
through inactivation of checkpoints and upregulation of telomerase activity

5. Inducing angiogenesis

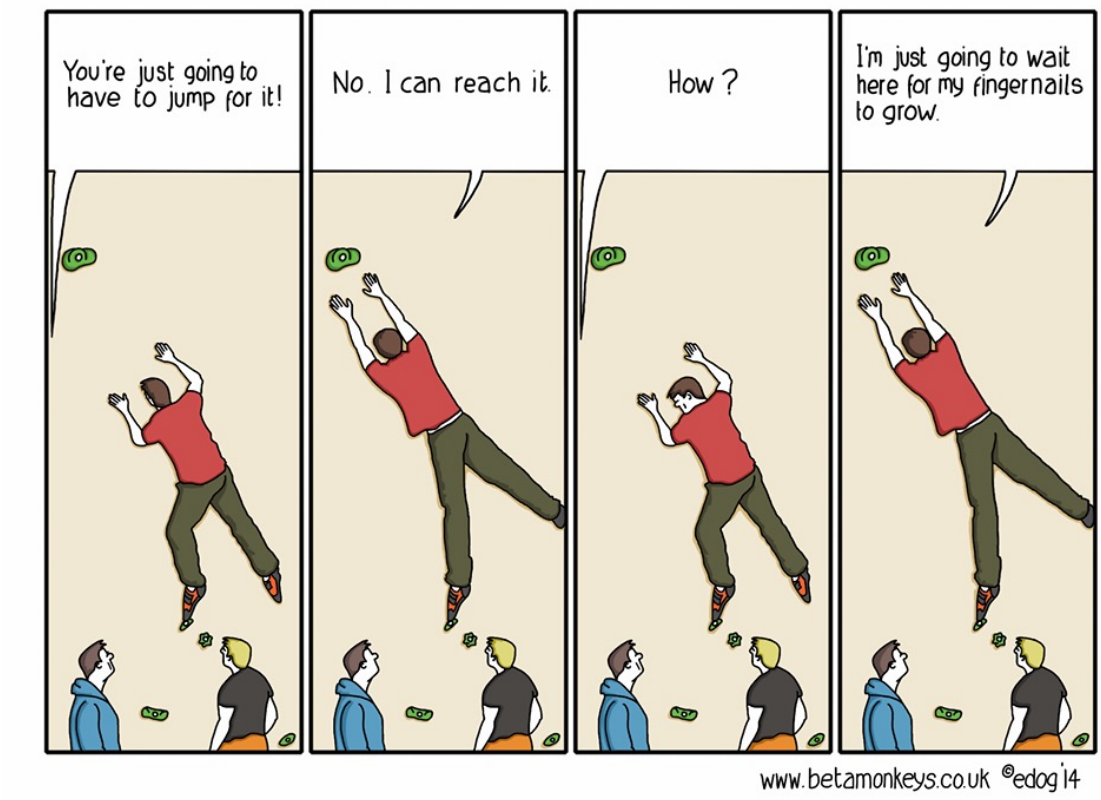
Specific barrier:
Supply of ***nutrients*** and ***oxygen*** by the vasculature is rate-limiting for tumor growth

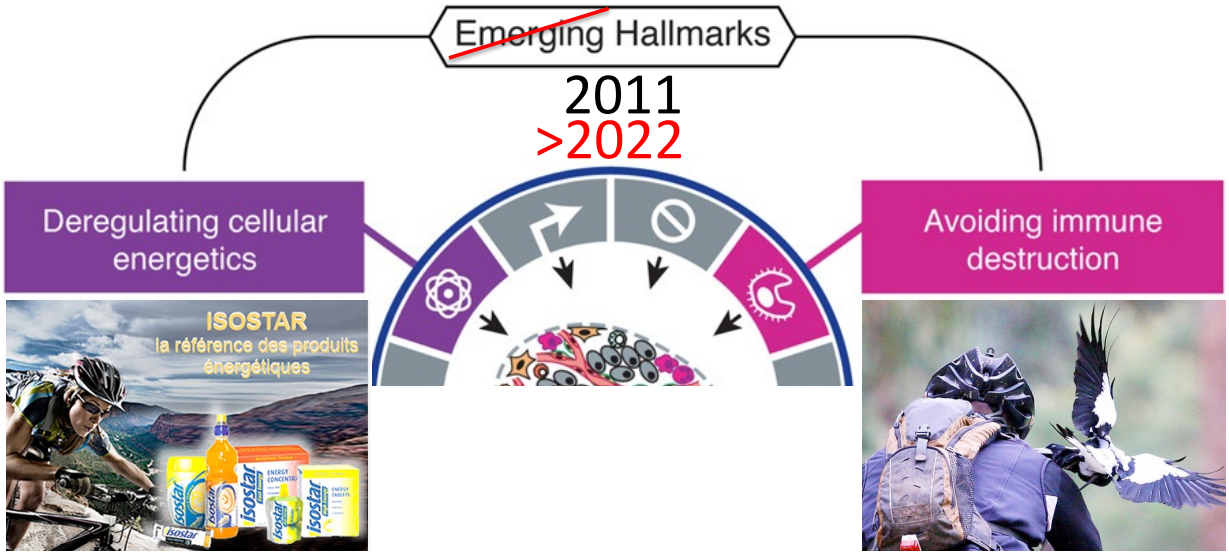
Acquired capability:
Recruitment of endothelial cells and vascular remodeling
through aberrant activation of signals that promote angiogenesis in development and during wound healing

6. Activating invasion & metastasis

Specific barrier:
Most cells types firmly adhere to their neighbors and cannot survive without adhesion to *extracullar matrix (ECM)*

Acquired capability:
Rewiring of multiple signaling circuits and remodeling of ECM
through reactivation of specific developmental programs and adaptation to new environments at distant sites



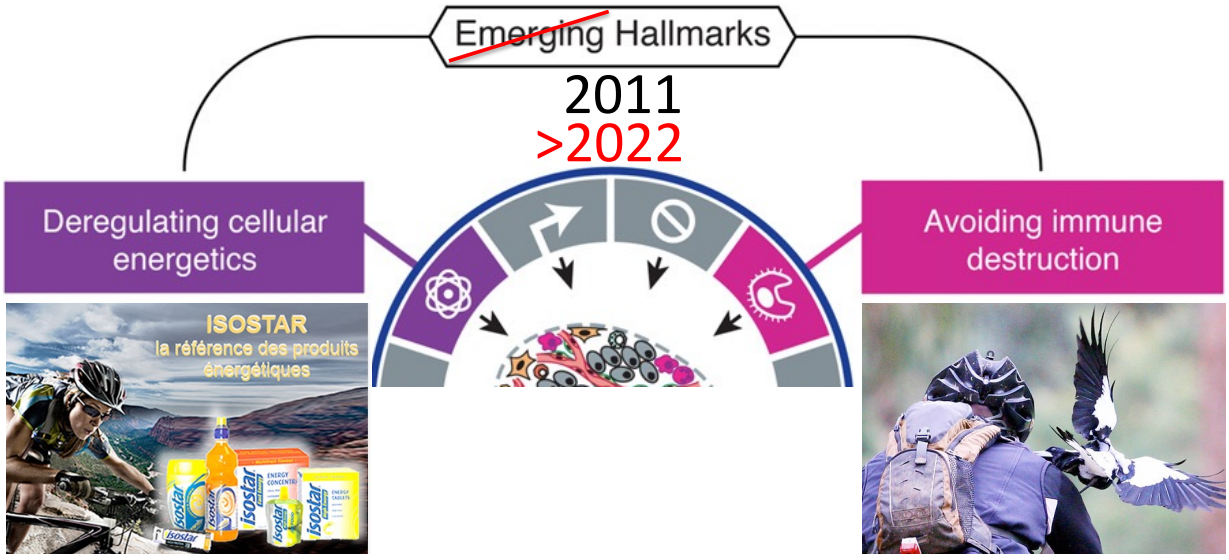


Barrier: Limited nutrient supply

Acquired capability:

O_2-independent energy boost

e.g. through increased glucose uptake and glycolysis (« Warburg effect »)



Barrier: Tumor-specific antigens can activate an immune response
Acquired capability:
Immune evasion by « immune checkpoint » activation, tolerance induction or « immunoediting »

Enabling characteristics

- do ***not directly*** by themselves provide a new capability
- however, ***they catalyze and thus accelerate*** the acquisition of hallmark capabilities

Barrier: Cell death induced by DNA damage is an important defense mechanism to eliminate premalignant cells

Defective genome maintenance and/or impaired DNA damage response **increase the impact of mutagenic agents and the frequency of permanent genetic alterations in tumor cells**

Catalyze hallmarks

Genome instability and mutation

Enabling Characteristics

Barrier: Inflammation normally helps to eliminate premalignant cells by stimulating an immune response against tumor antigens

Tumors can shift the balance among infiltrating immune effectors to instead promote e.g. angiogenesis, invasion, survival, and immune evasion through specific alterations in chemokines and specific immune modulatory factors

Catalyze hallmarks

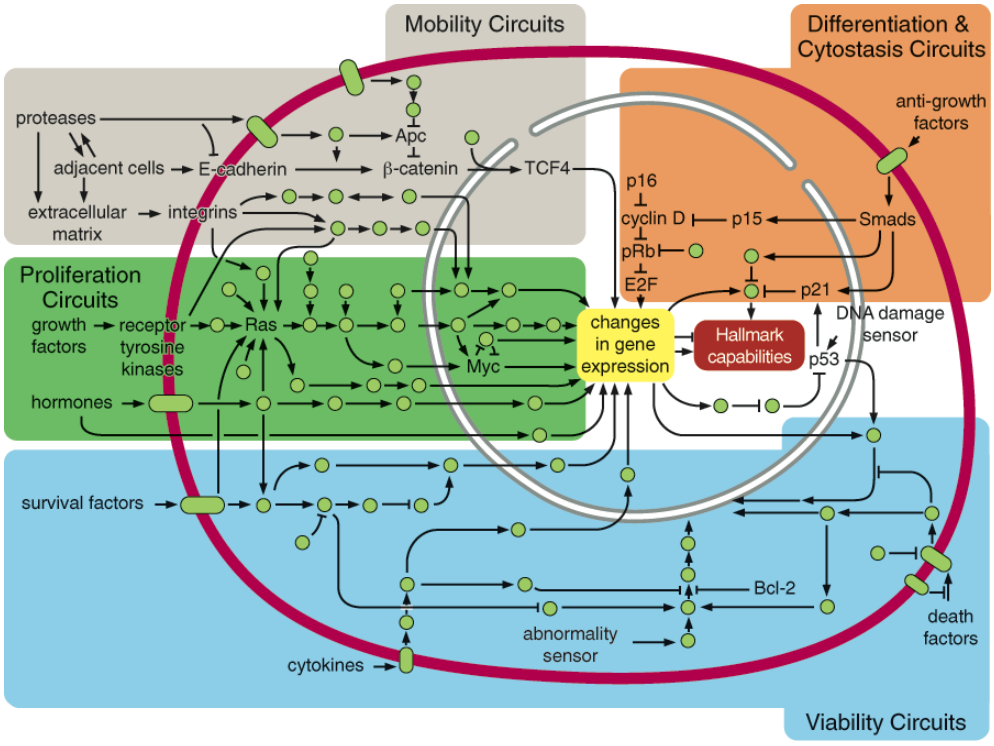
Tumor-promoting Inflammation

Enabling Characteristics

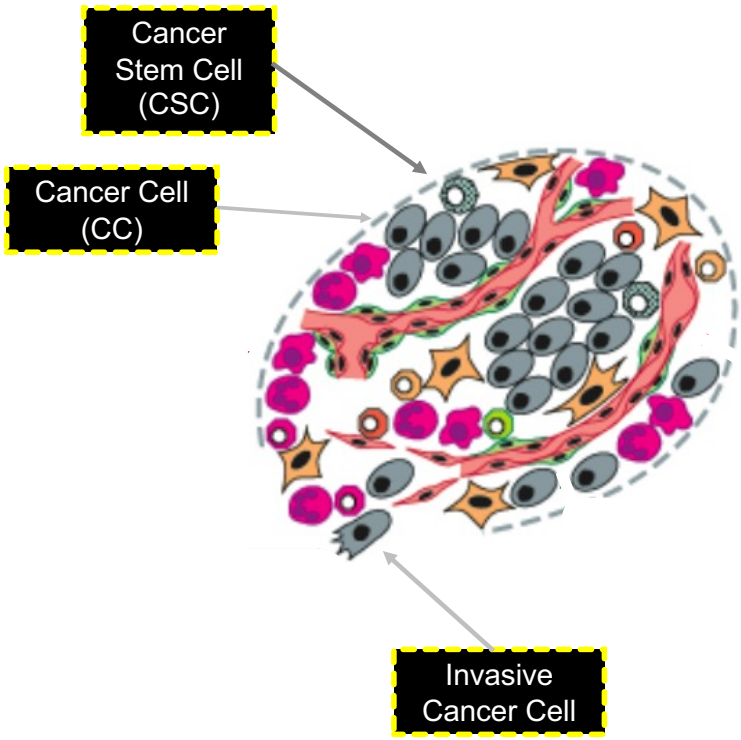
Cancer “hallmarks” are an “organizing principle” to “rationalize” the complexity of cancers

i.e. to help recognize and interpret meaningful patterns in seemingly chaotic tissue alterations

Hallmark capabilities reflect substantial reprogramming of intertwined signaling circuits in the cancer cells themselves

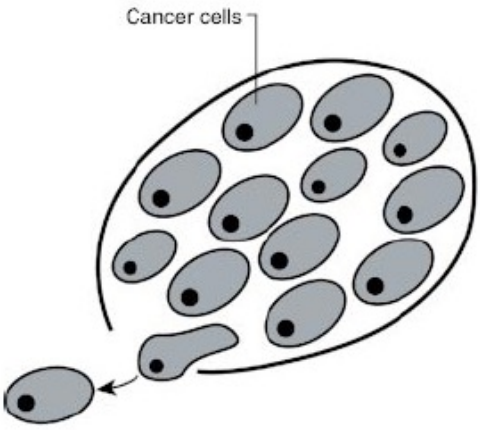


Genetic and epigenetic perturbations *within* cancerous cells or "cancer stem cells" clearly *can initiate* the process

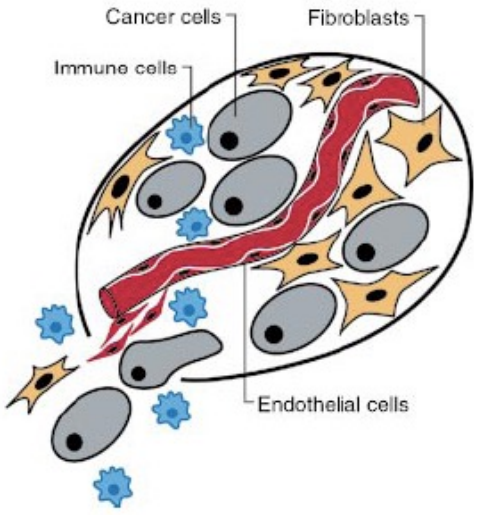


Realization: Tumors are not simply bags of cancer cells but rather outlaw organs

The Reductionist View

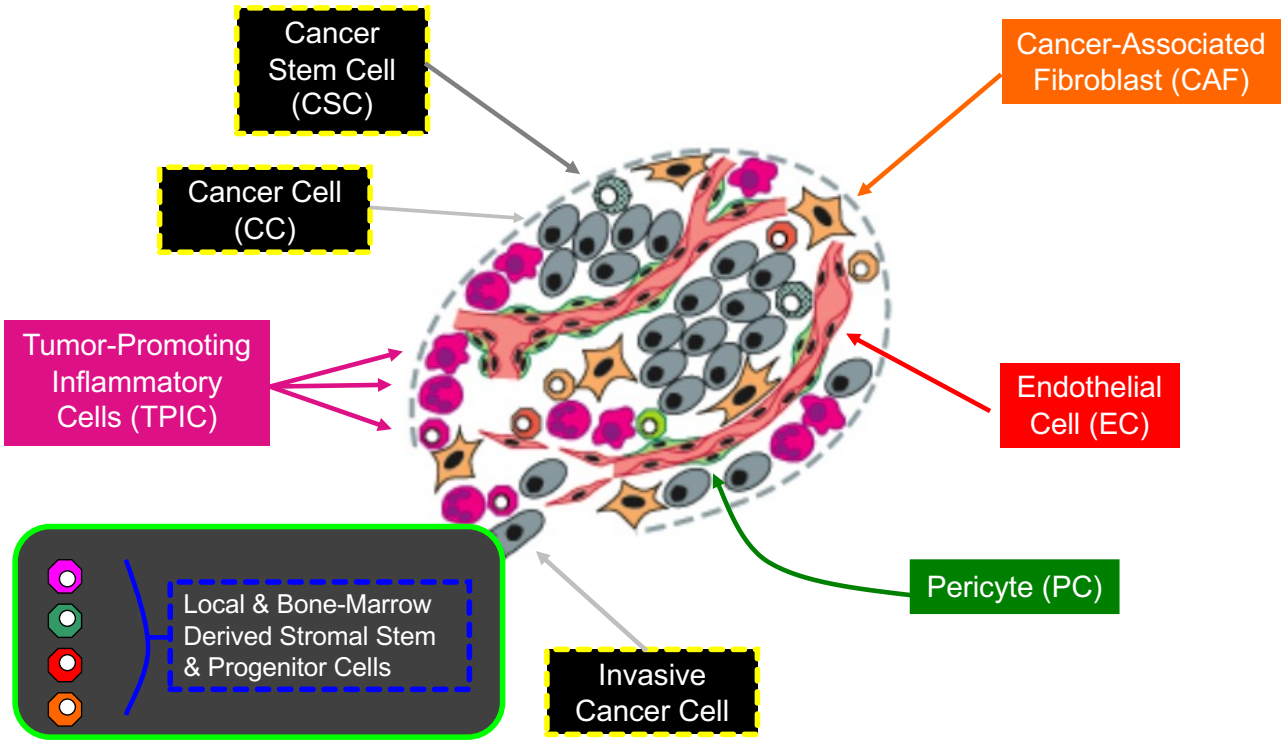


A Heterotypic Cell Biology

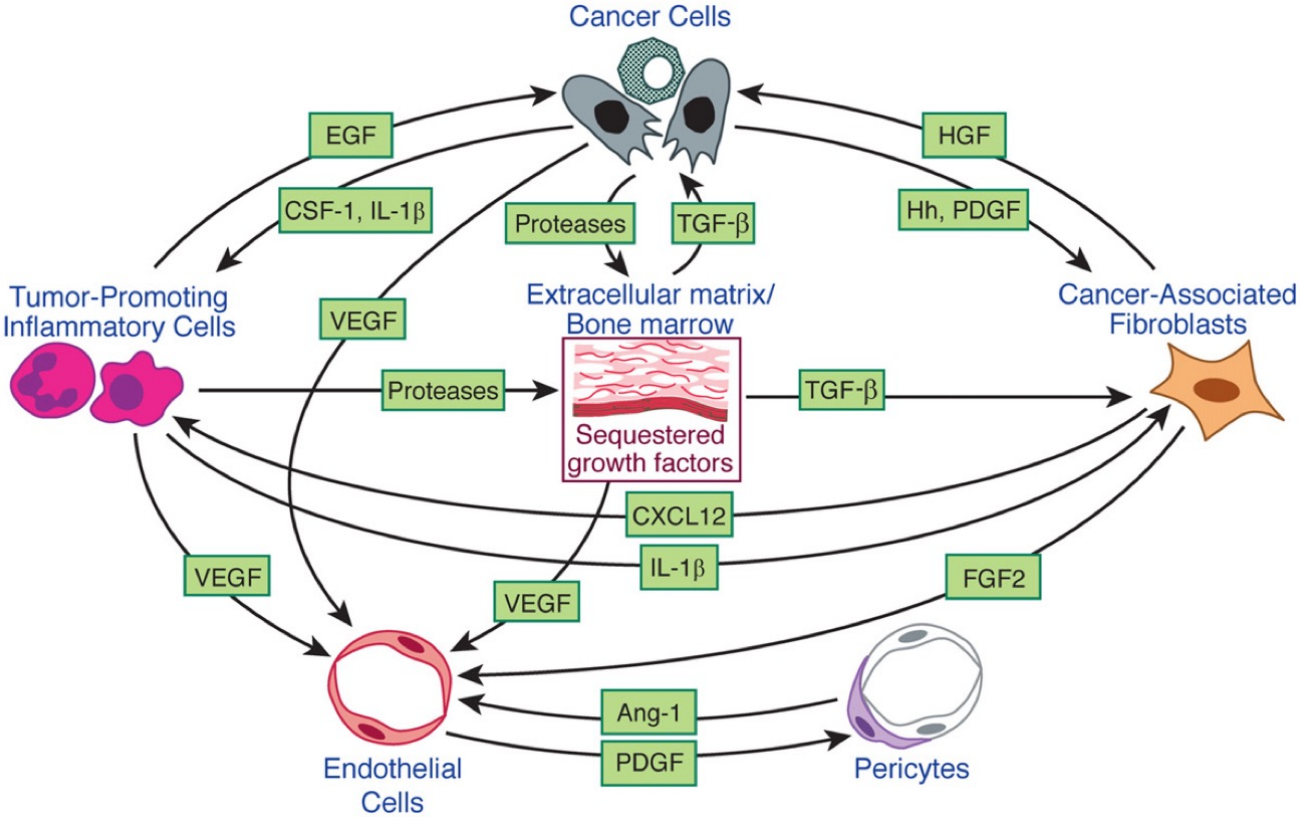


=> Which cell populations drive the acquisition of hallmark capabilities?

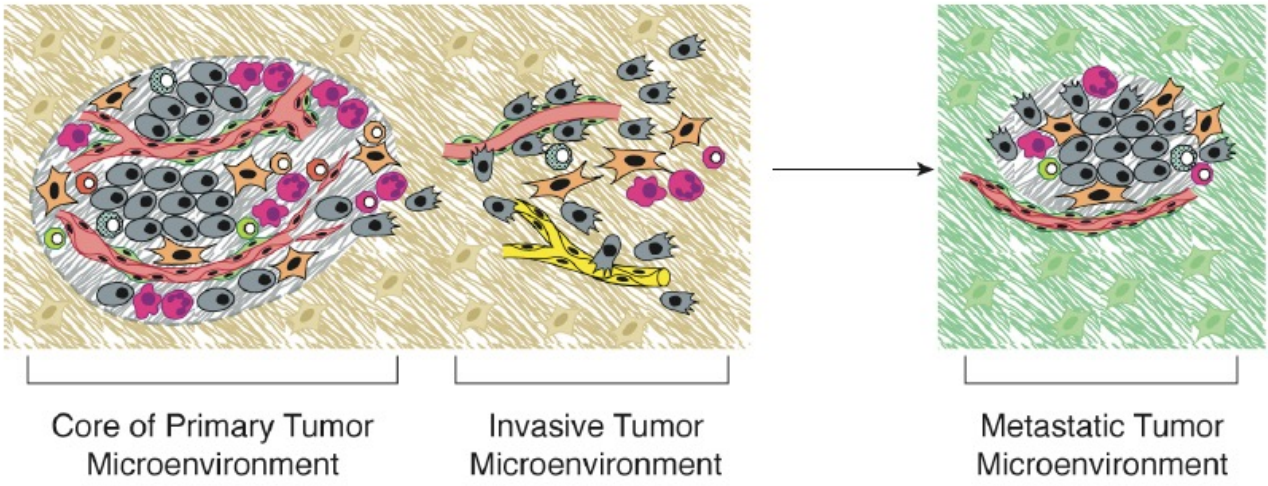
Multiple *normal* cell types become components of tumors and promote hallmark capabilities



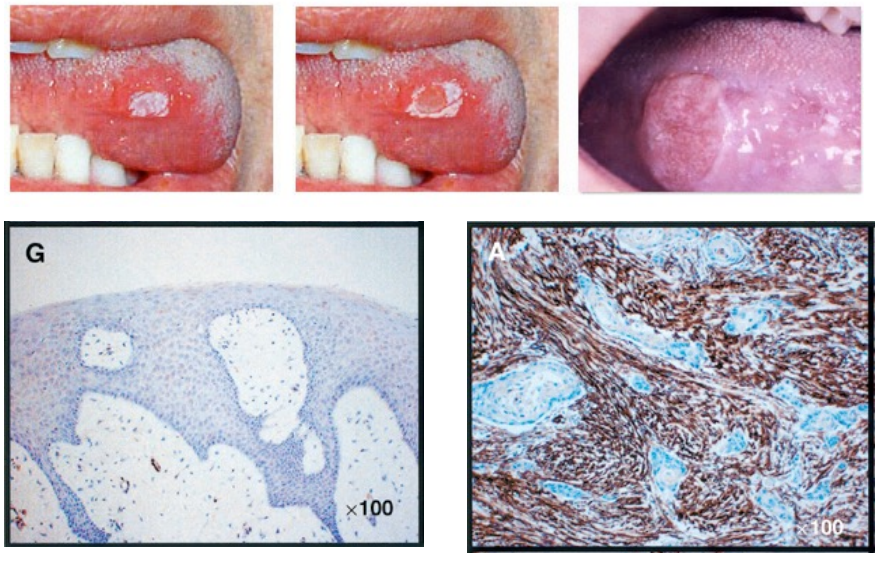
Some hallmark cabilities rely on altered signaling between cancer cells and *their microenvironment*



The tumor microenvironment *changes* during malignant progression



Example: Myofibroblasts in oral squamous cell carcinoma progression



benign hyperplasia Oral SCC

Brown: α-smooth muscle actin (α-SMA) positive "myofibroblasts"

British Journal of Cancer (2004) **90**, 822–832.

Hallmarks of Cancer: Applications to Cancer Medicine?

- The hallmarks conceptualization helps to rationalize the wealth of new mechanistic data from cancer research
- Are there applications of the concept to treating human cancers?

Why is this prediction so important?

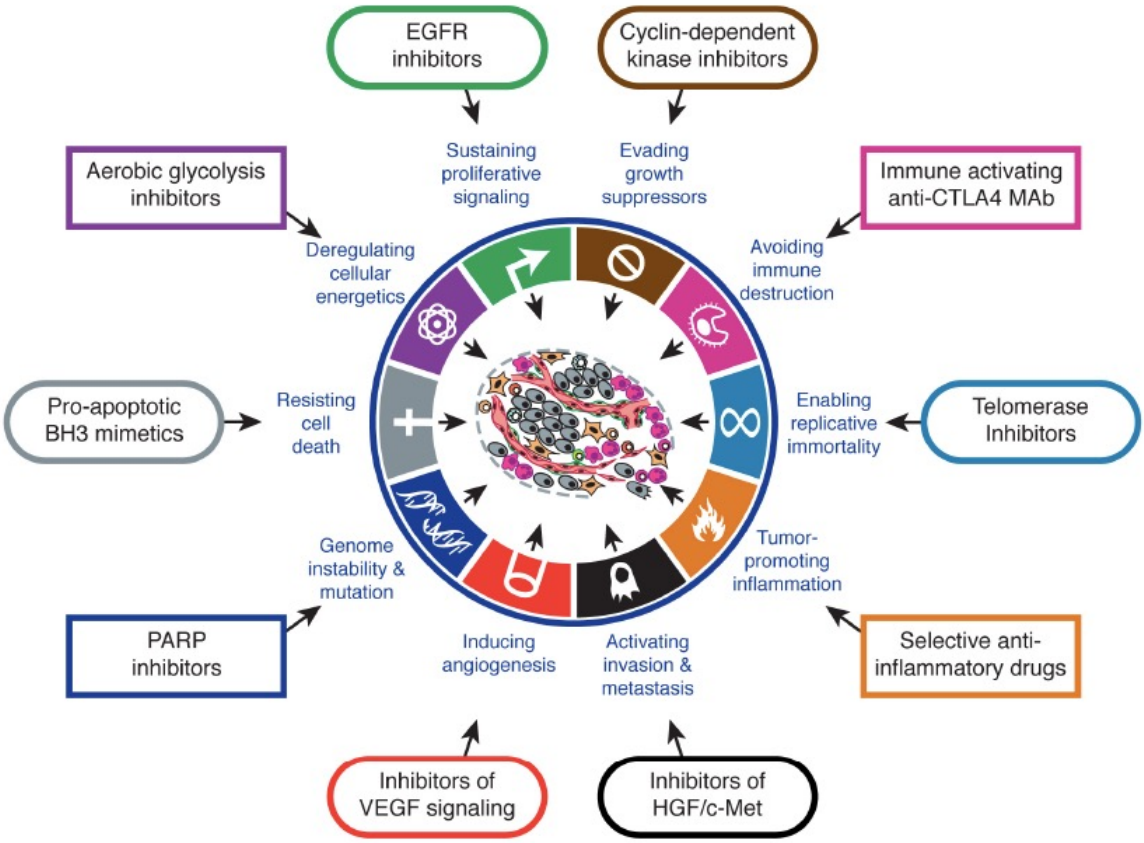
Classification of tumors based on hallmarks?

- molecular diagnosis ?
- tumor staging ?
- prognosis ?

Choice of alternative targeted therapies based on hallmarks?

- drug combinations to target more than one

Targeting hallmark capabilities for cancer therapy



Mouse models of human cancer

- It is now possible to genetically engineer mice to develop cancers in most of the organs of the body
- Such mouse models can reflect (or model) the genetic foundations and/or histo-pathological progression of the corresponding human cancers

Mouse models of human cancer

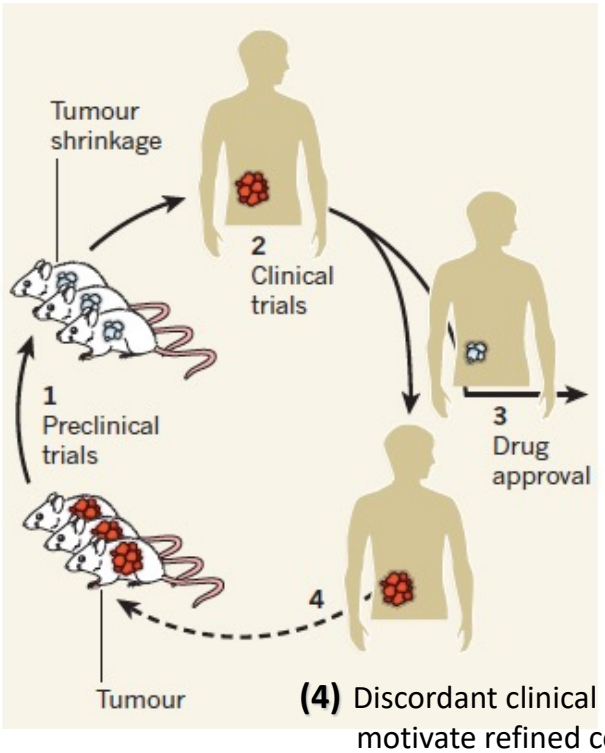
- Genetically engineered mouse models (GEMM) of human cancer have been used to elucidate cancer mechanisms, and contributed to the formulation of the hallmarks concept

- Are mouse models of human cancer important to test new therapies? Why or why not?

Interspecies Translational Therapeutic Oncology

(2) Efficacy in mouse model motivates clinical trials

(1) Pre/Co-clinical trials in mice modeling a human cancer

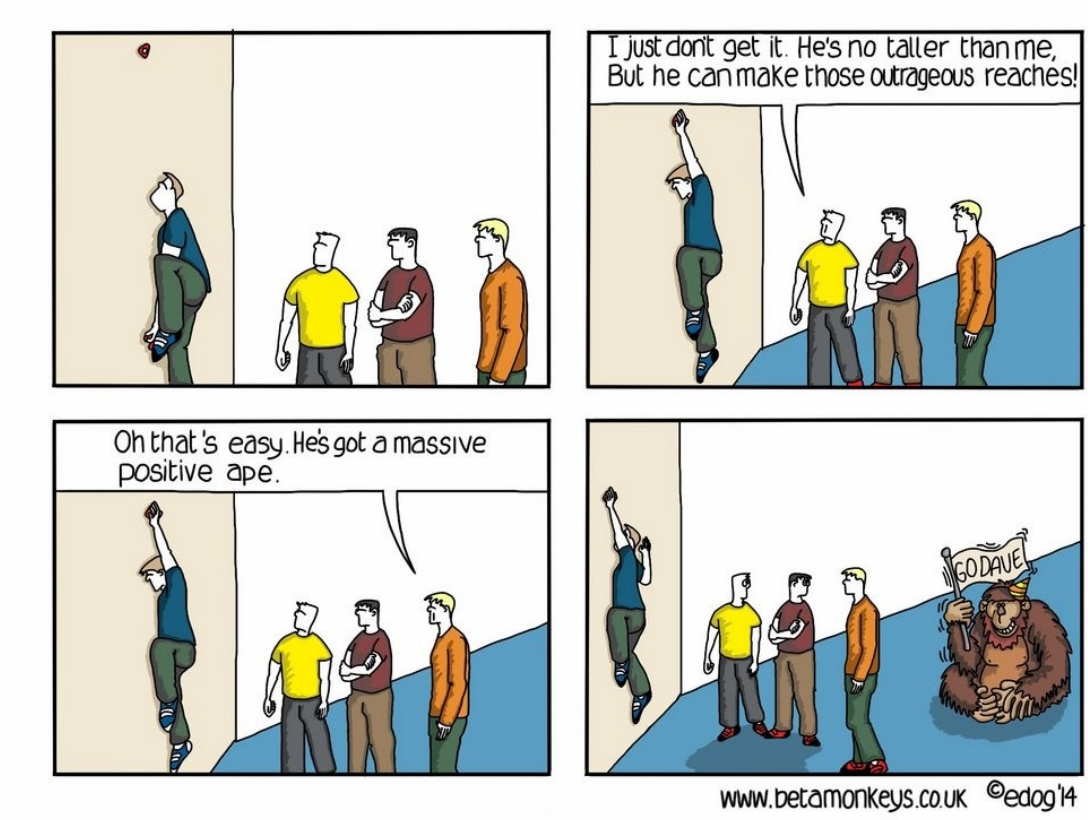


(3) Positive clinical results support drug approval

(4) Discordant clinical results and *resistance* motivate refined co-clinical trial designs

Tuveson & Hanahan 2011

Questions?


I just don't get it. He's no taller than me, But he can make those outrageous reaches!
Oh that's easy. He's got a massive positive ape.
GO DAVE
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