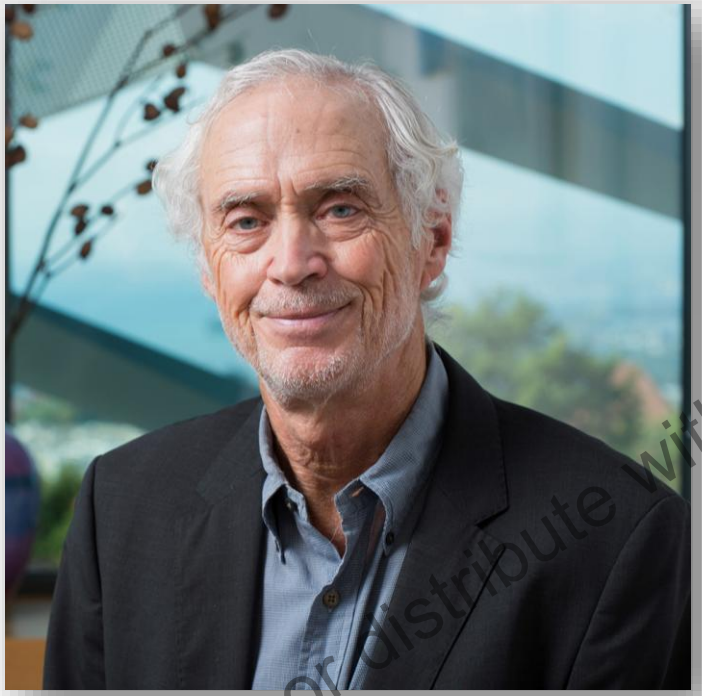


The hallmarks of cancer: Perspectives for cancer medicine

Douglas Hanahan

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European School of Oncology – Basic Principles in Oncology Course

The hallmarks of cancer: Perspectives for cancer medicine



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Douglas Hanahan

27 October 2022

LUDWIG CANCER RESEARCH
Lausanne

SWISS CANCER CENTER
LEMAN

ISREC
Institut Suisse de Recherche Expérimentale sur le Cancer @EPFL

EPFL

Part 1. The Conundrum of Cancer that led to the Hallmarks of Cancer

Cancer is a disease of extraordinary complexity, at all levels (genetic, histological, pathological, prognostic, therapeutic…)

Can we rationalize this complexity?

Are there common principles underlying this daunting diversity?

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We reasoned, perhaps naively trying to simplify the complexity of cancer:

- Might disparate cancers share fundamental qualities?

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We reasoned, perhaps naively trying to simplify the complexity of cancer:

- Might disparate cancers share fundamental qualities?

- Maybe this daunting complexity merely reflects different solutions to the same challenge?

Namely that *cancer cells must surmount multiple barriers and roadblocks used by the organism to prevent expansive cell proliferation, some of which differ mechanistically from organ to organ and cell type to cell type*

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What are hallmarks of cancer?

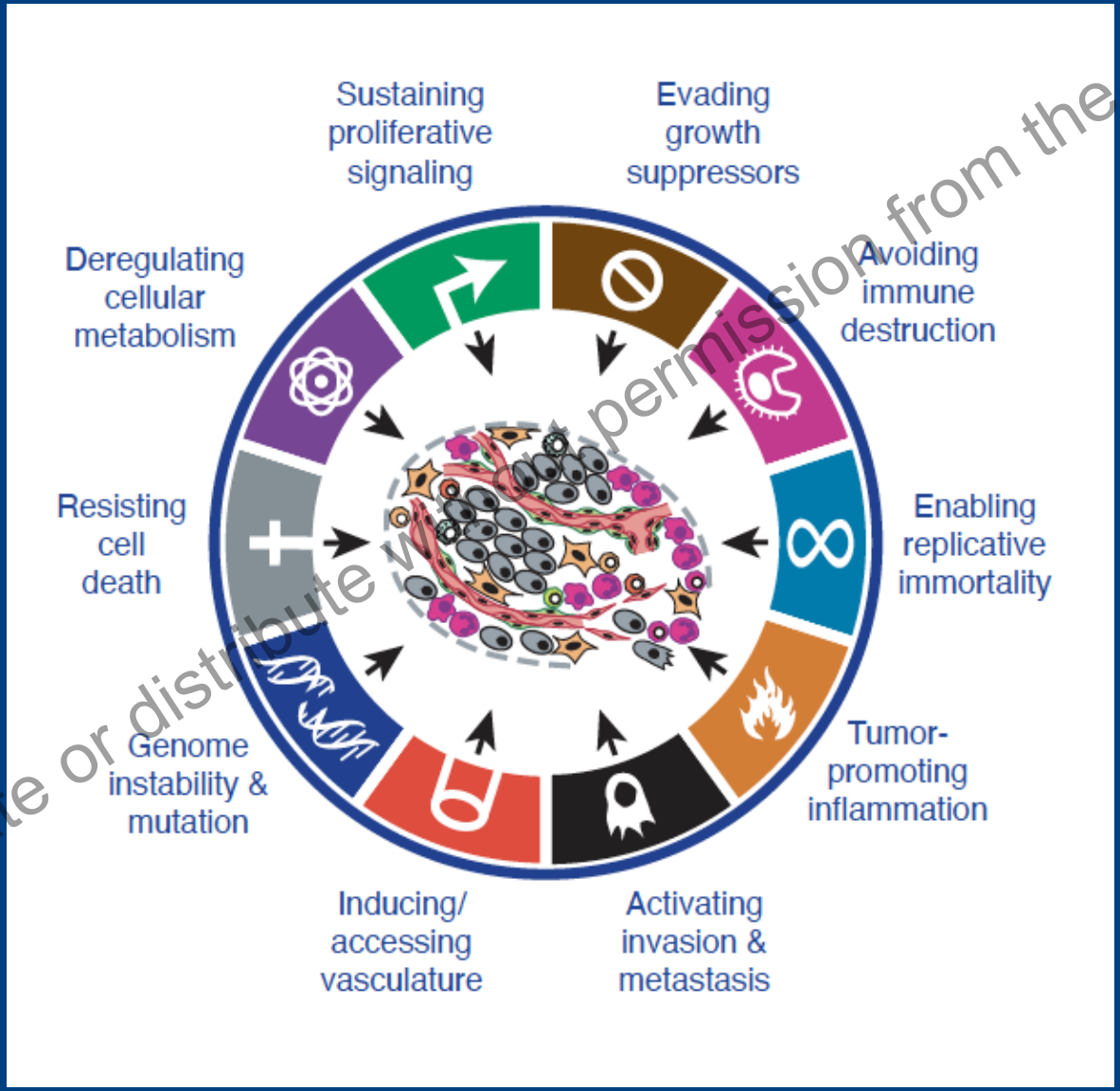
We defined hallmarks to be acquired functional capabilities, that allow tumors

-- to perform functions that contribute to manifestation of the disease

-- typically, to conduct these actions chronically, rather than during the carefully orchestrated tasks of cells and organs in the body

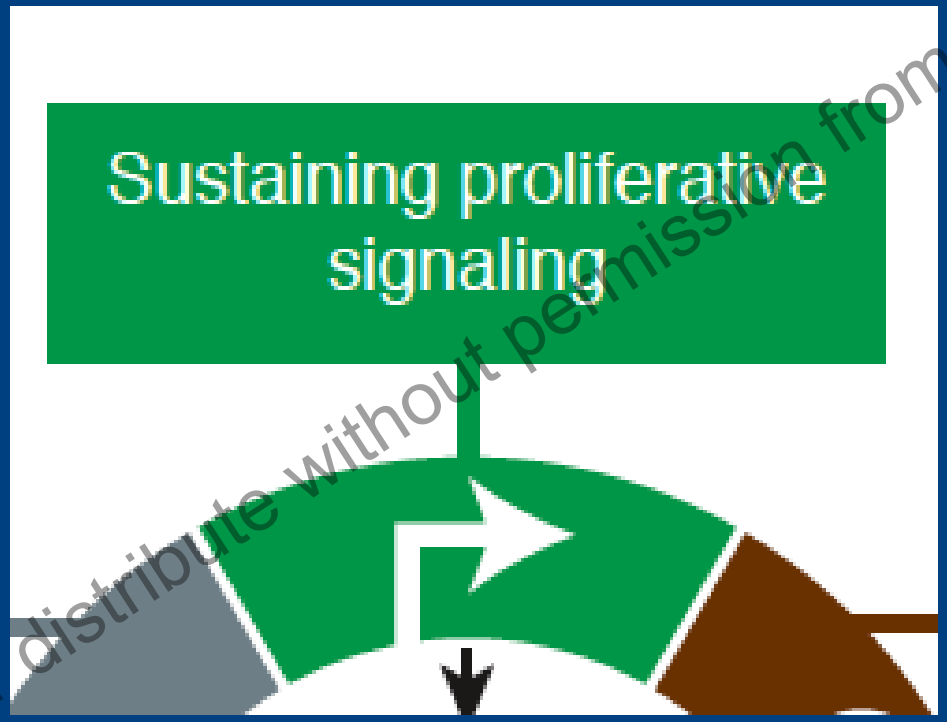
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The hypothesis:
Eight hallmarks of cancer are necessary and sufficient for cancer to arise



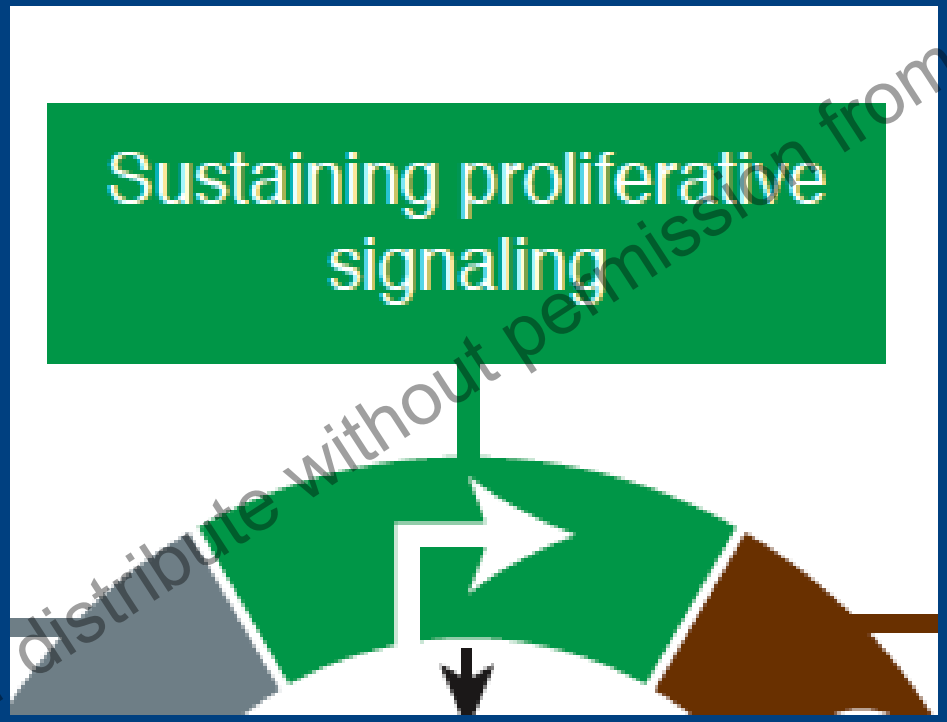
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The first hallmark



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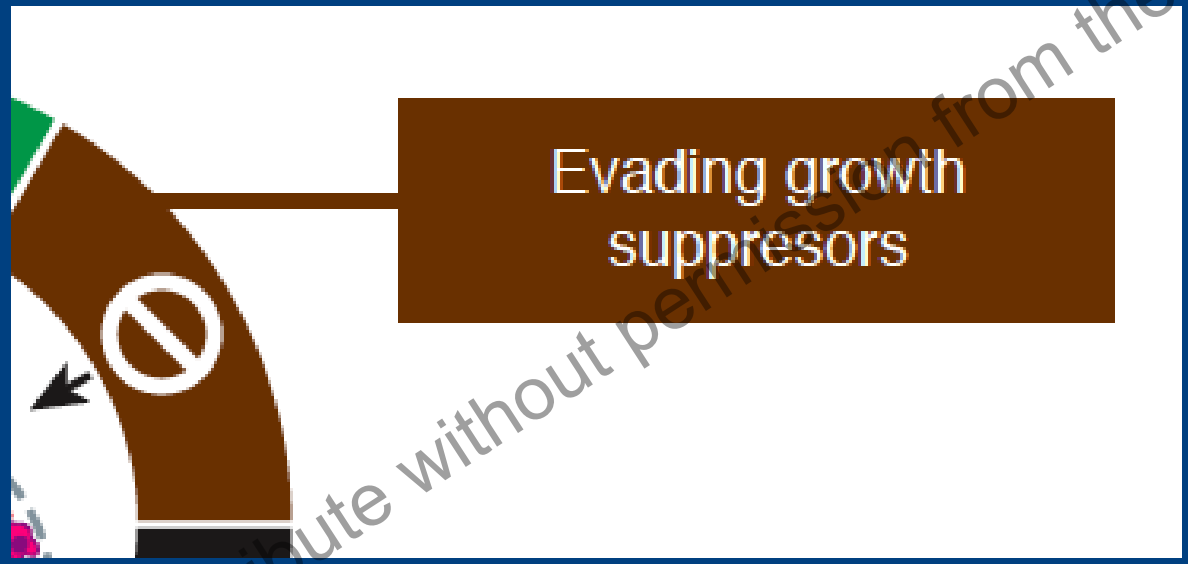
The first hallmark



The accelerator => driving the cell cycle, via signals that instruct cells to grow and divide chronically

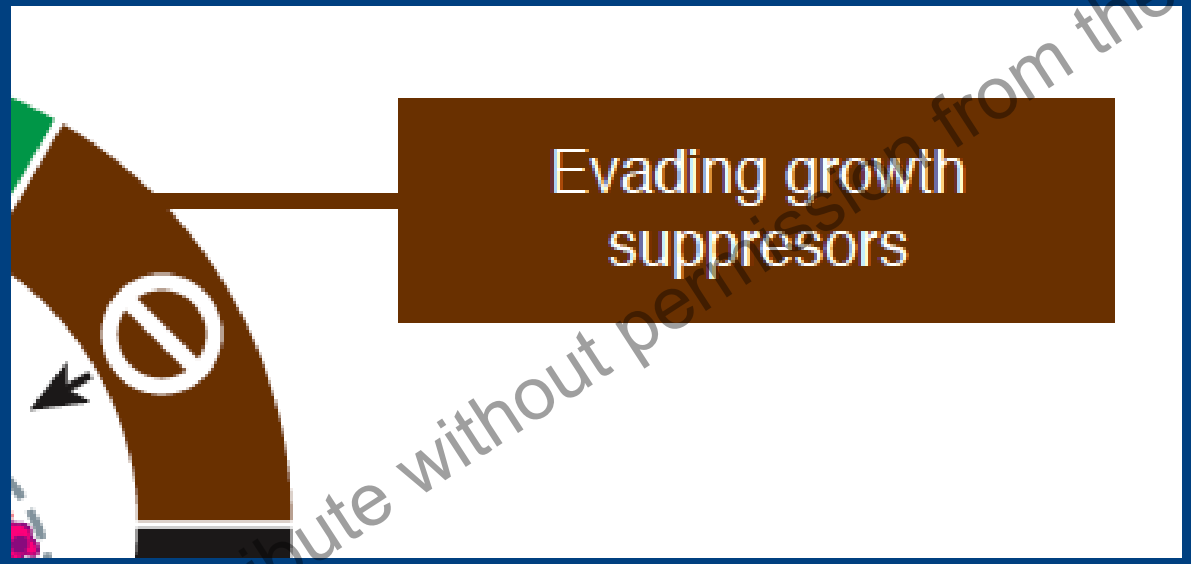
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The second hallmark



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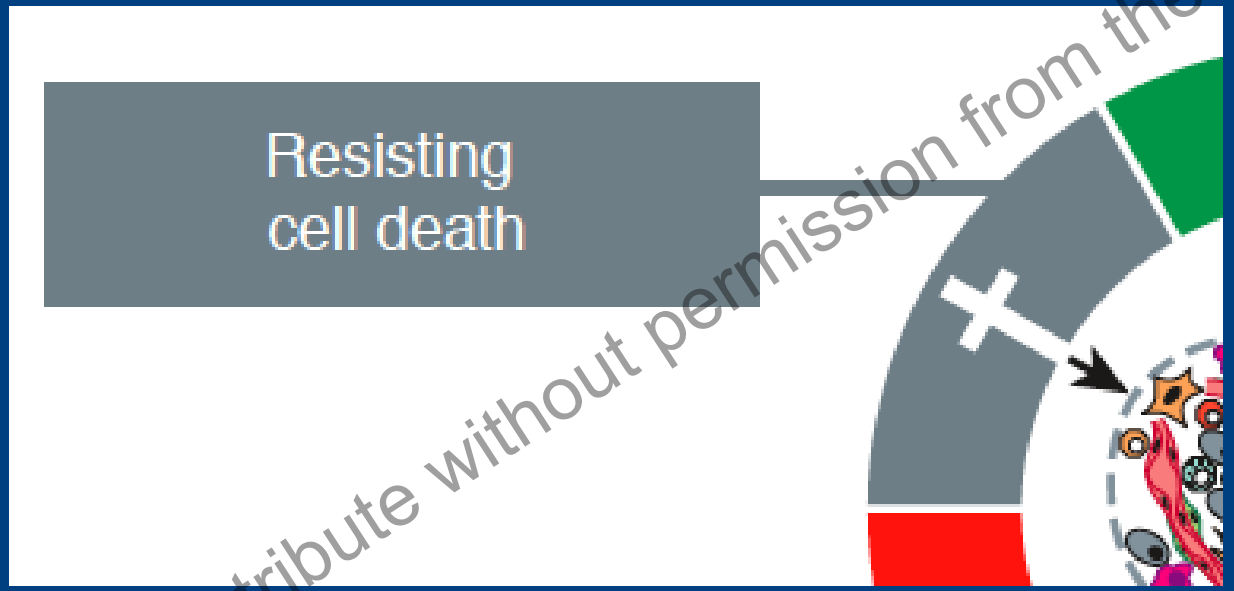
The second hallmark



Both cell-intrinsic and paracrine mechanisms that can shut off or block cell division are disabled

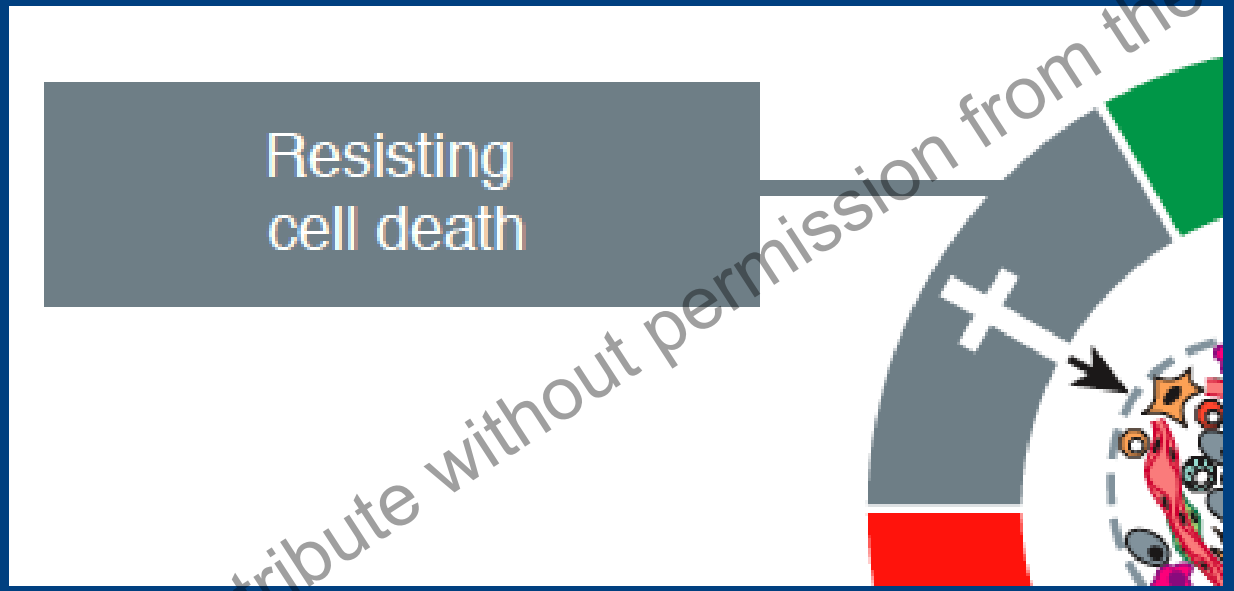
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The third hallmark



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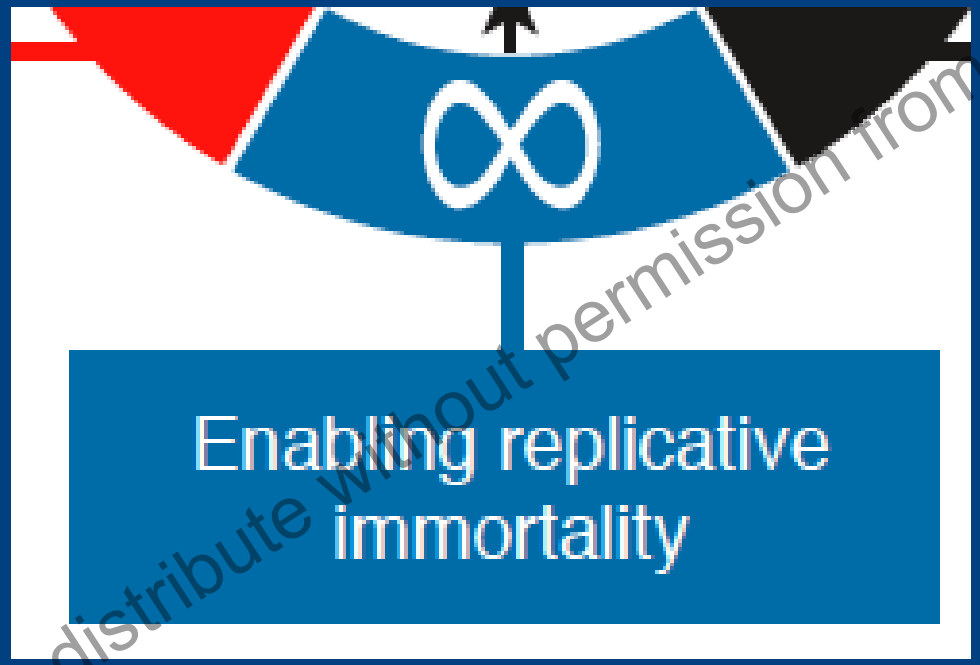
The third hallmark



Avoiding 'assisted suicide' of outlaw cells; abrogation of multiple mechanisms of programmed cell death intended to prevent unauthorized proliferation

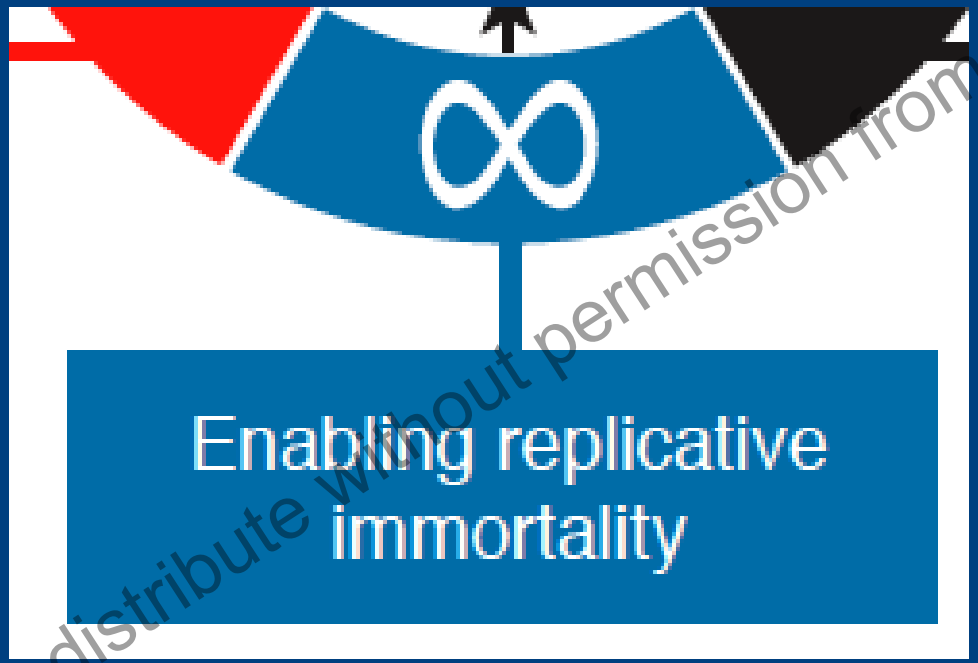
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The fourth hallmark



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The fourth hallmark



Circumventing a telomeric counting mechanism that blocks further cell division when a preset limit is reached

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The fifth hallmark



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The fifth hallmark



Turning on new blood vessel growth by angiogenesis or accessing it by invasive co-option of normal tissue vasculature so as to supply oxygen and nutrients that sustain lesional expansion

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The sixth hallmark



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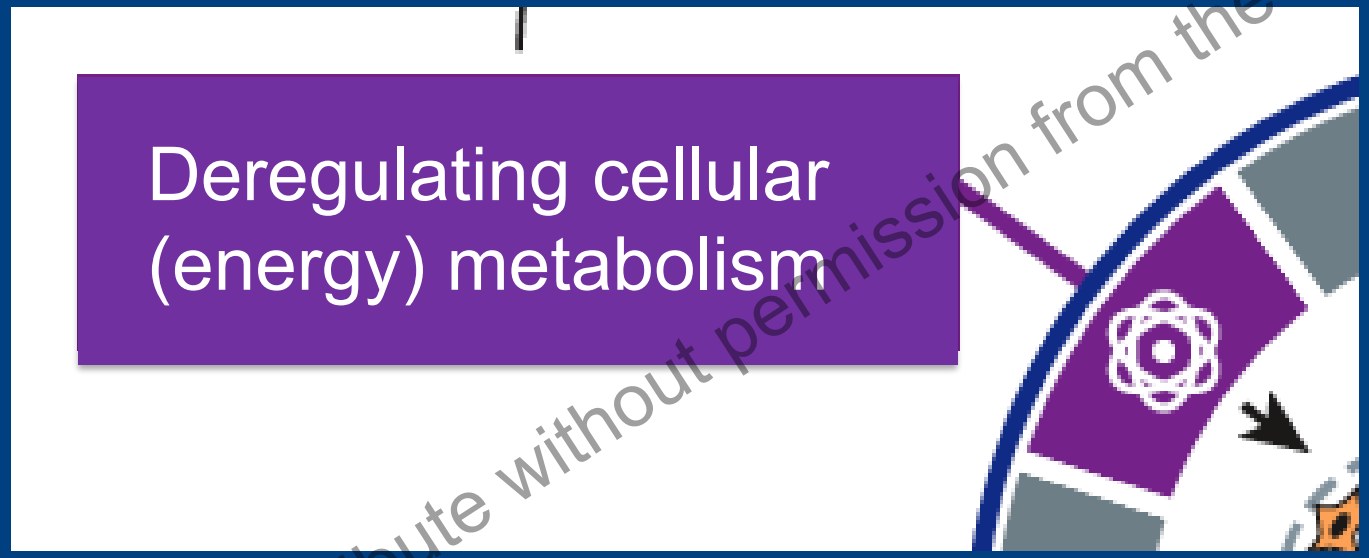
The sixth hallmark



Becoming 'guerilla cells' that grow by invading into normal organs, locally and throughout the body, 'living off the fertile land' of healthy tissues

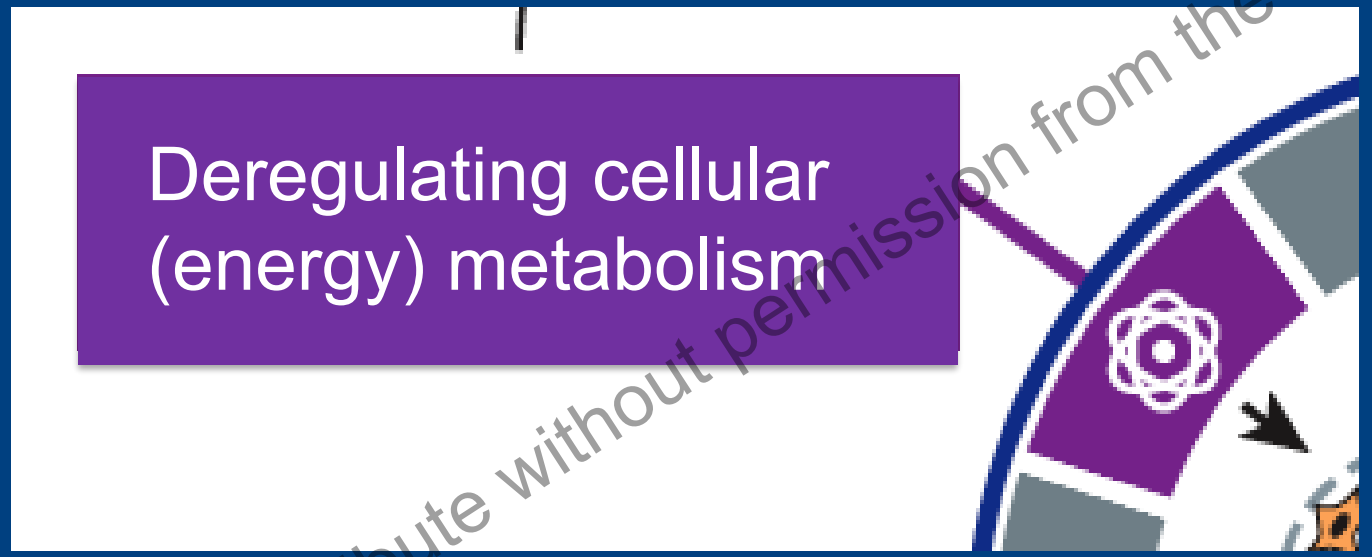
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The seventh hallmark



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In 2011, an emerging hallmark, now incorporated into the core



Tapping alternative energy sources to provide fuel for cell growth, producing in addition supplies of the cellular building blocks needed to generate new cancer cells

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The eighth hallmark



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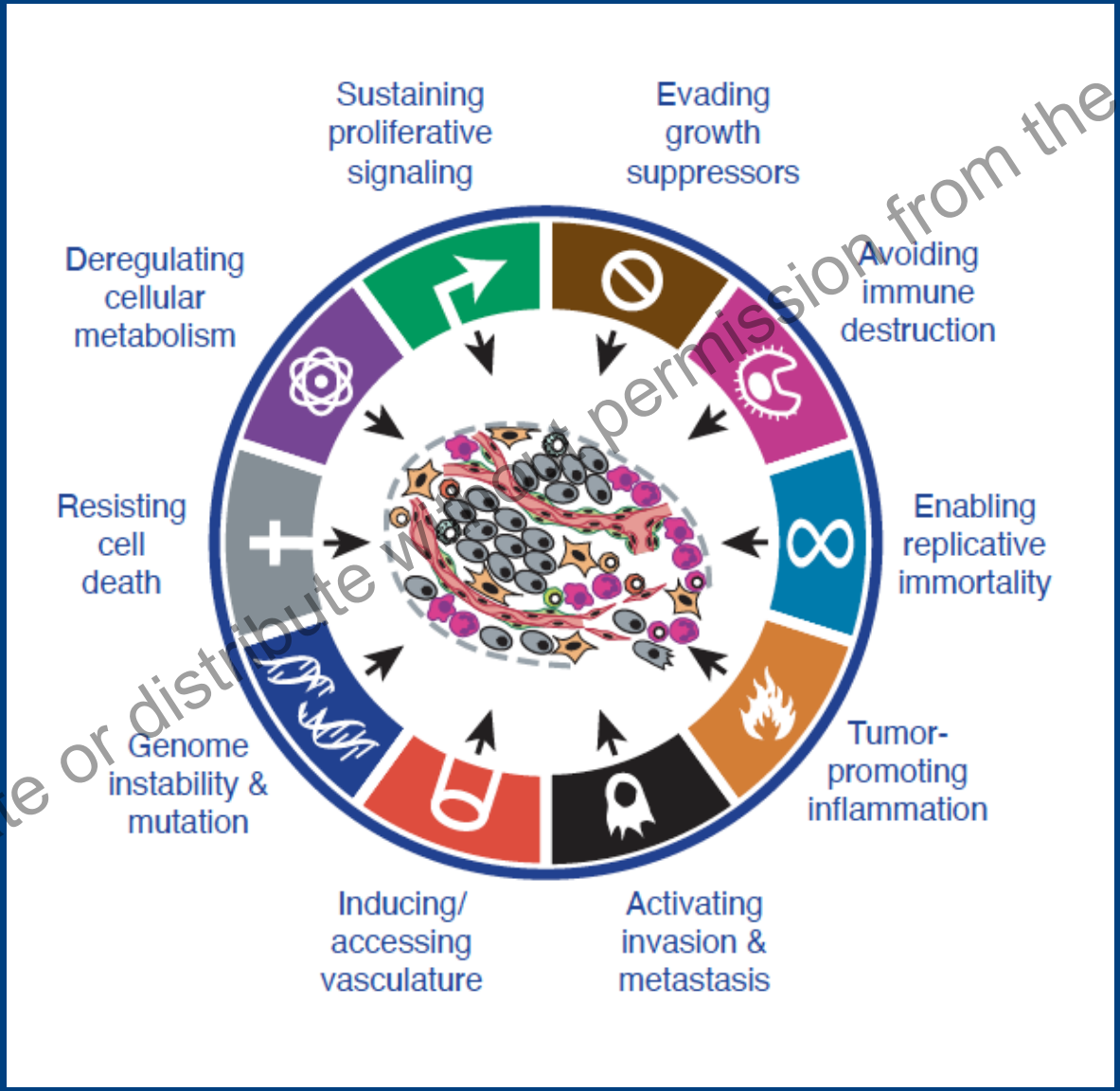
The eighth hallmark



In many cases, the immune system detects neoplasia and seeks *at some point during tumor development and progression* to kill cancer cells, an attack that lethal tumors learn to circumvent

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The hypothesis:
Eight hallmarks of cancer are necessary and sufficient for cancer to arise



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How are these hallmark capabilities acquired?

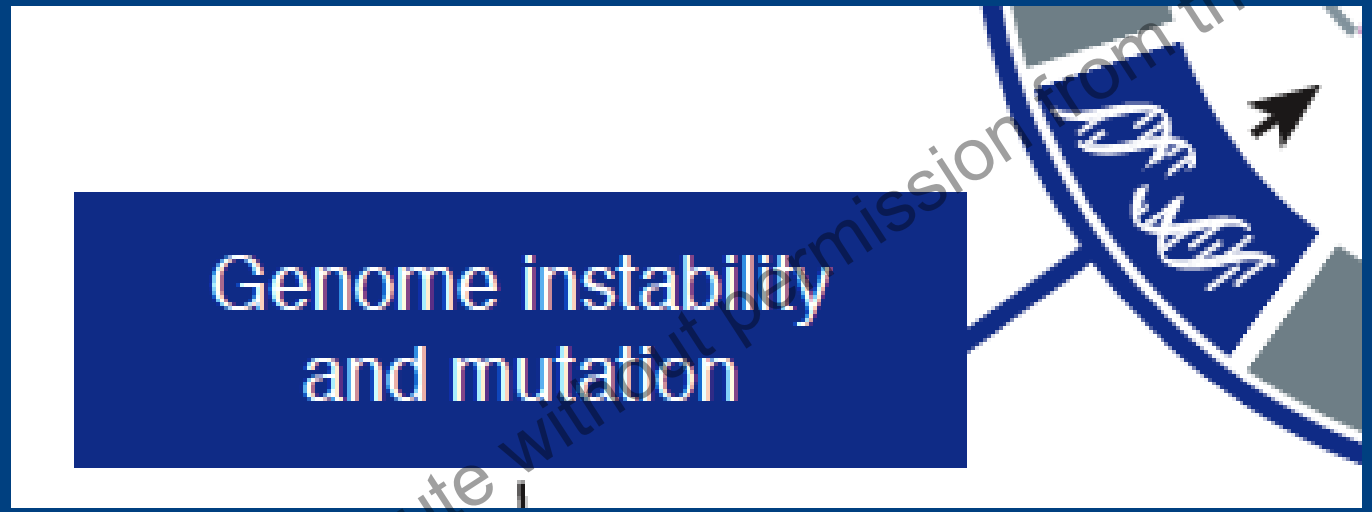
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How are these hallmark capabilities acquired?

Via Enabling Characteristics

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The key enabling characteristic for acquiring hallmarks



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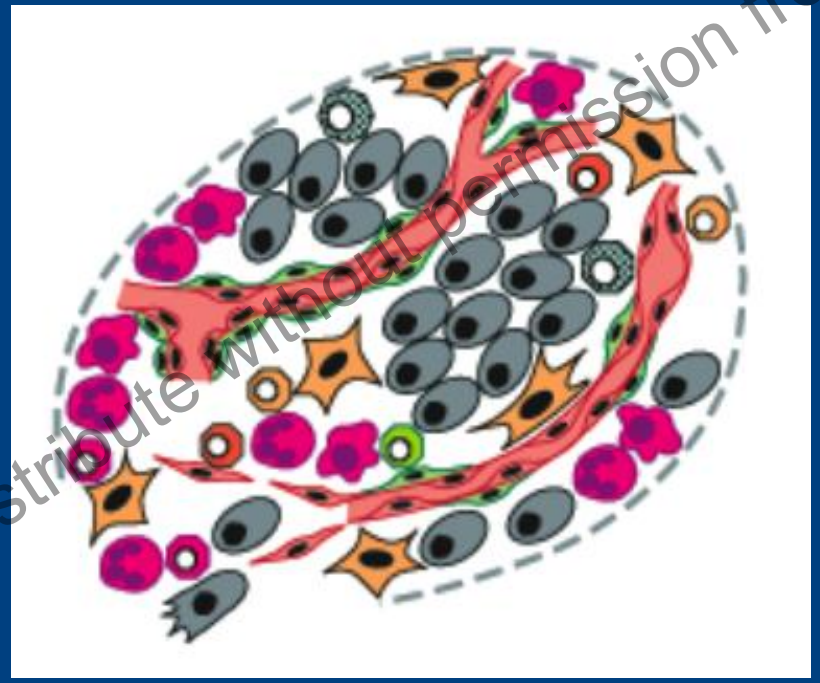
A 2nd enabling characteristics for acquiring hallmarks



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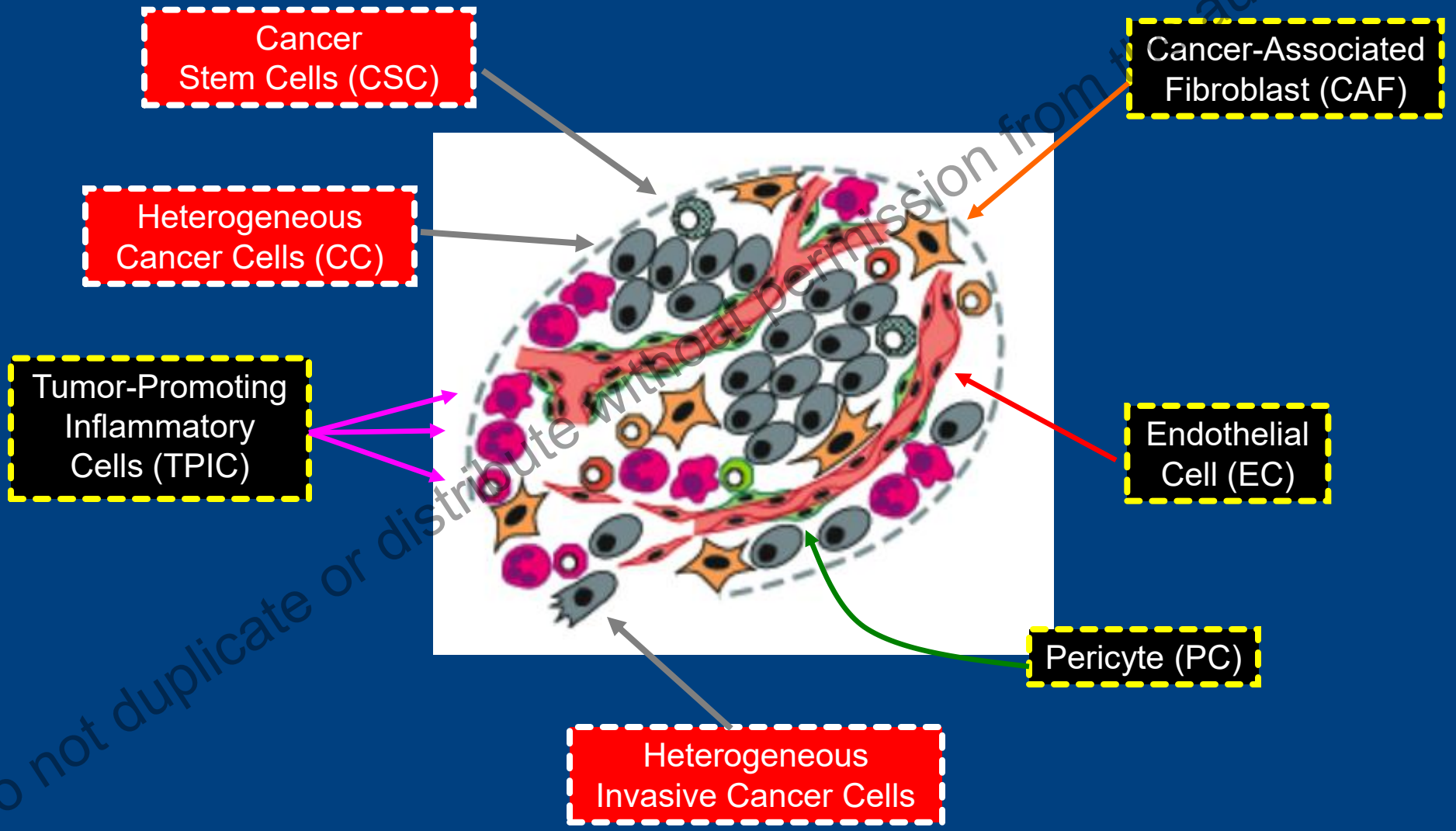
Beyond the foundation set by cancer cells are Outlaw Organs:

Tumors are assemblages of cell types that communicate and collaborate



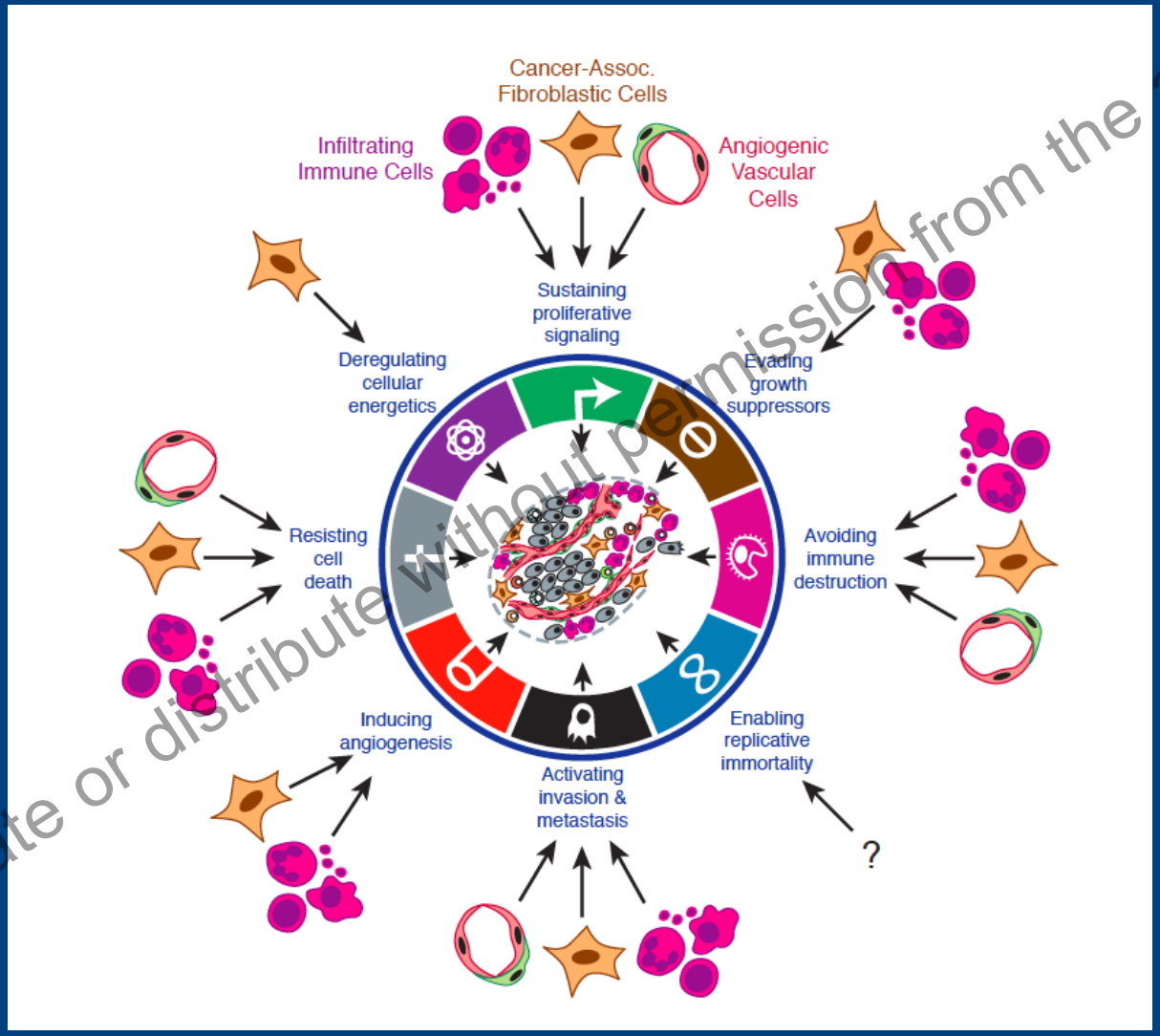
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Multiple normal and neoplastic cell types and subtypes are assembled to become components of tumors, helping to provide hallmark capabilities



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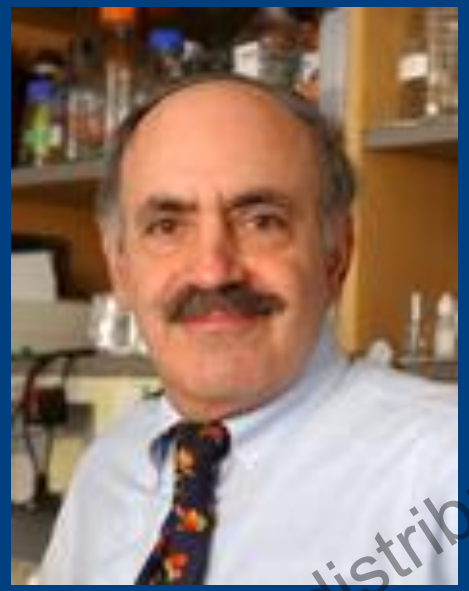
Accessory ('stromal') Cells recruited into the Tumor Microenvironment (TME) can demonstrably contribute functionally to 7 of the 8 hallmarks



Hanahan & Coussens (2012)

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Acknowledgement – a most unusual collaboration



Bob Weinberg!!!

(Whitehead Institute & MIT, Cambridge, MA, USA)

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Now, two perspectives beyond the core conceptualization

- Possible applications to cancer medicine?
- Provisional new facets to the conceptualization?

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Part 2. Hallmarks of Cancer:

Applications to Cancer Medicine?

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Hallmarks of Cancer:

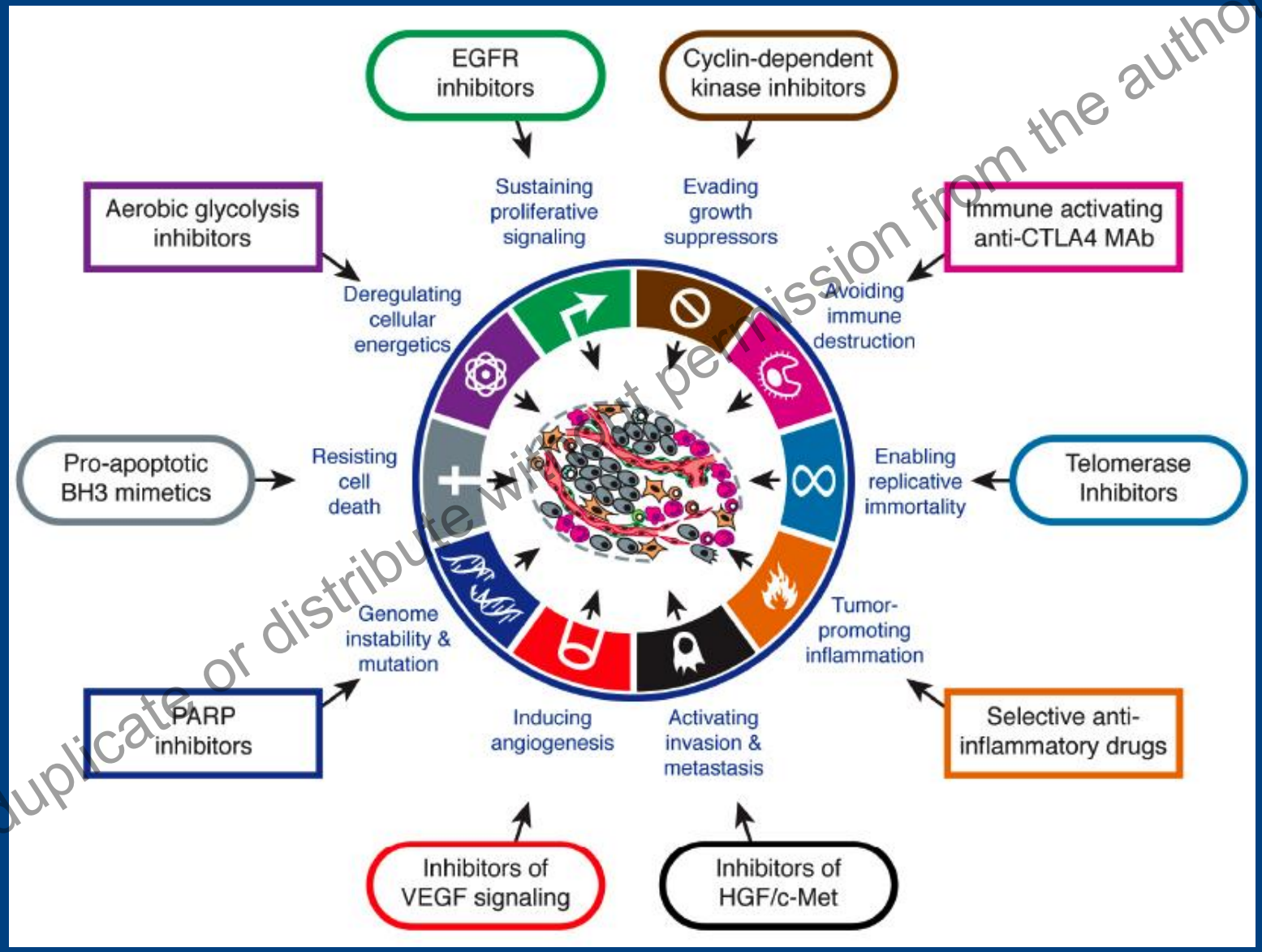
Applications to Cancer Medicine

- The hallmarks concept is helping to rationalize the wealth of new mechanistic data forthcoming from the cancer research community

- Is this concept applicable to the goal of more effectively treating human cancers?

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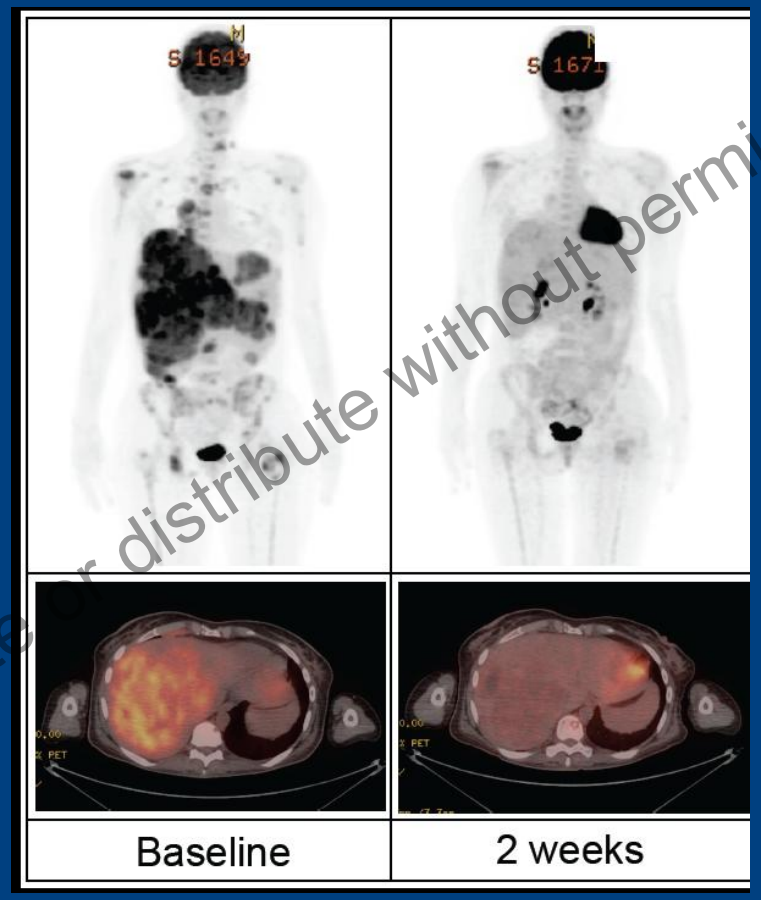
A growing armamentarium of 'smart drugs' can target each of the 8 hallmarks and their enablers



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Indeed, targeting single hallmarks can produce remarkable therapeutic responses – e.g. metastatic melanoma

Targeting mutant BRAF in metastatic melanoma with a drug (vemurafenib) targeting the proliferative hallmark

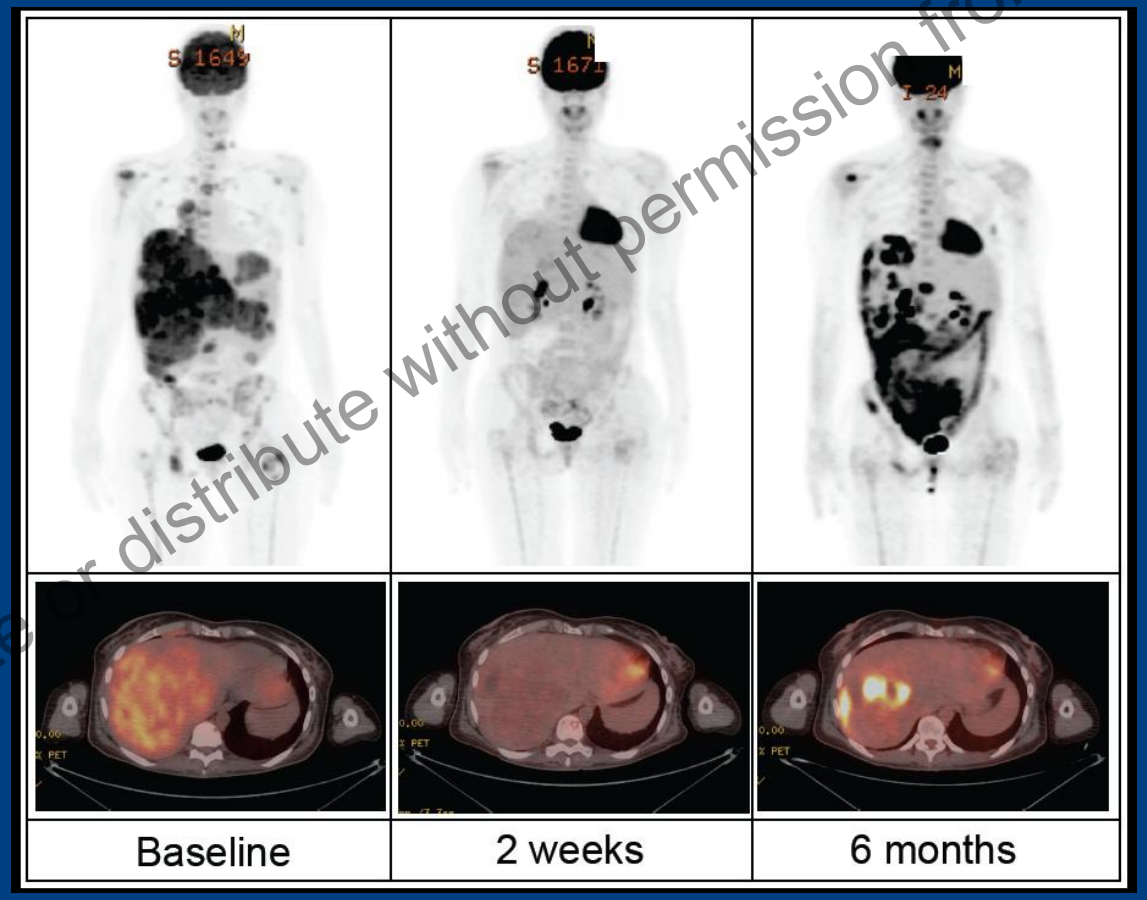


Finn et al
BMC Medicine
2012

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The reality check:
Targeting single hallmarks is most often transitory, followed by adaptive resistance and relapse

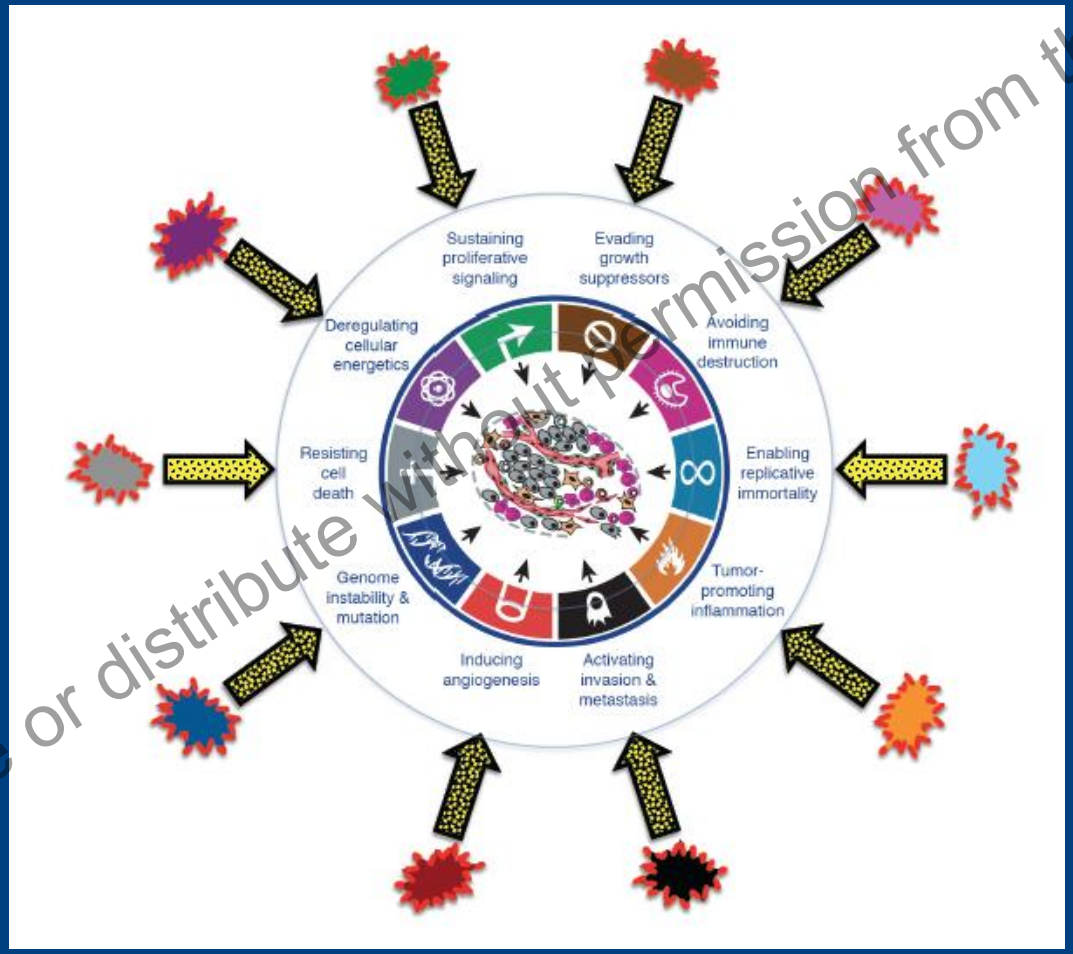
Targeting mutant BRAF in metastatic melanoma with a drug (vemurafenib) targeting the proliferative hallmark



Finn et al
BMC Medicine
2012

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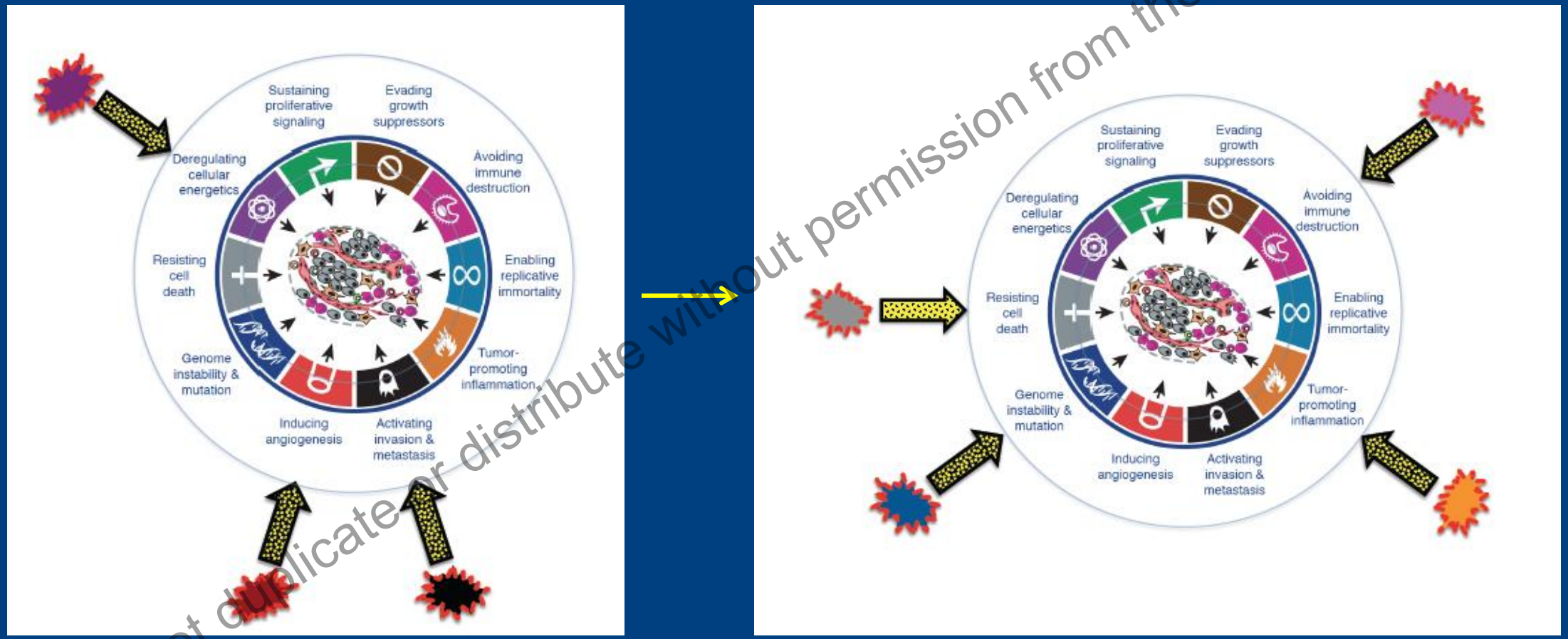
The dream scenario:
Attacking all of the hallmarks simultaneously, to stop tumors dead in their tracks



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A more realistic future of cancer therapy: combinations, layers, sequences

(a 'Hail Mary' attack will have too many side effects)



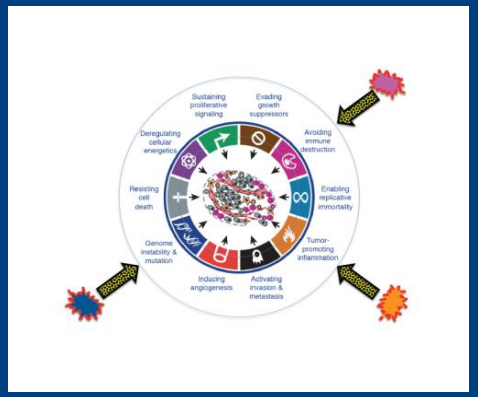
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Hanahan Lancet 2013

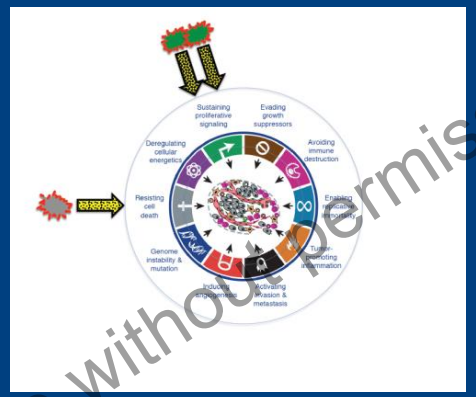
A futuristic 'battlespace' plan for the war on cancer:

Complex sequencing regimens, facilitated by 'war games' in pre-clinical trials using next-gen mouse models of cancer

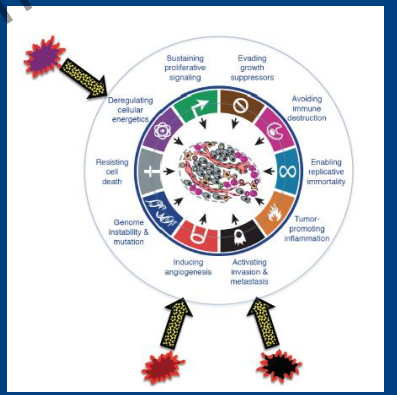
Immuno-



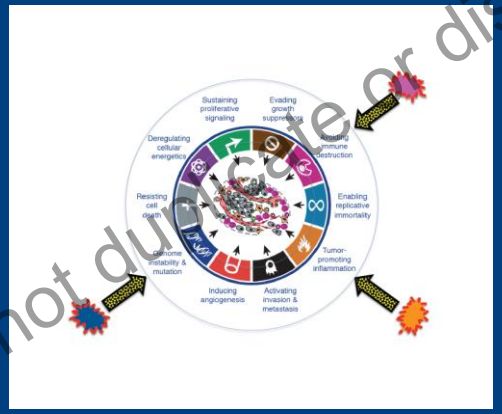
Onco-drivers



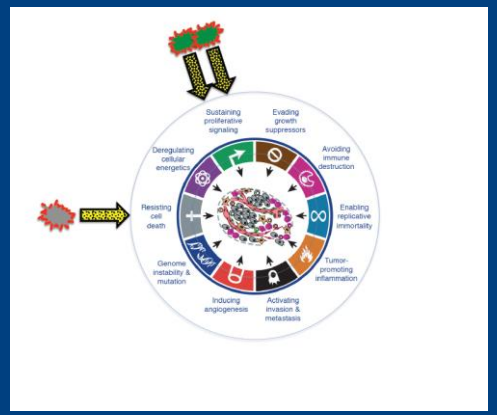
Angio & Metastasis



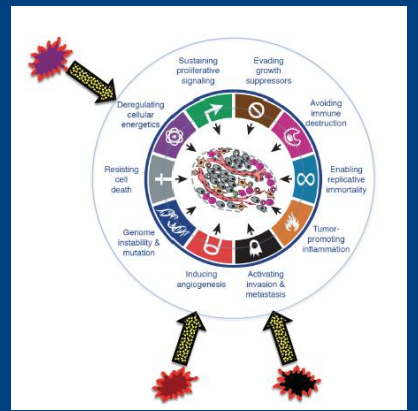
Immuno-



Onco-drivers



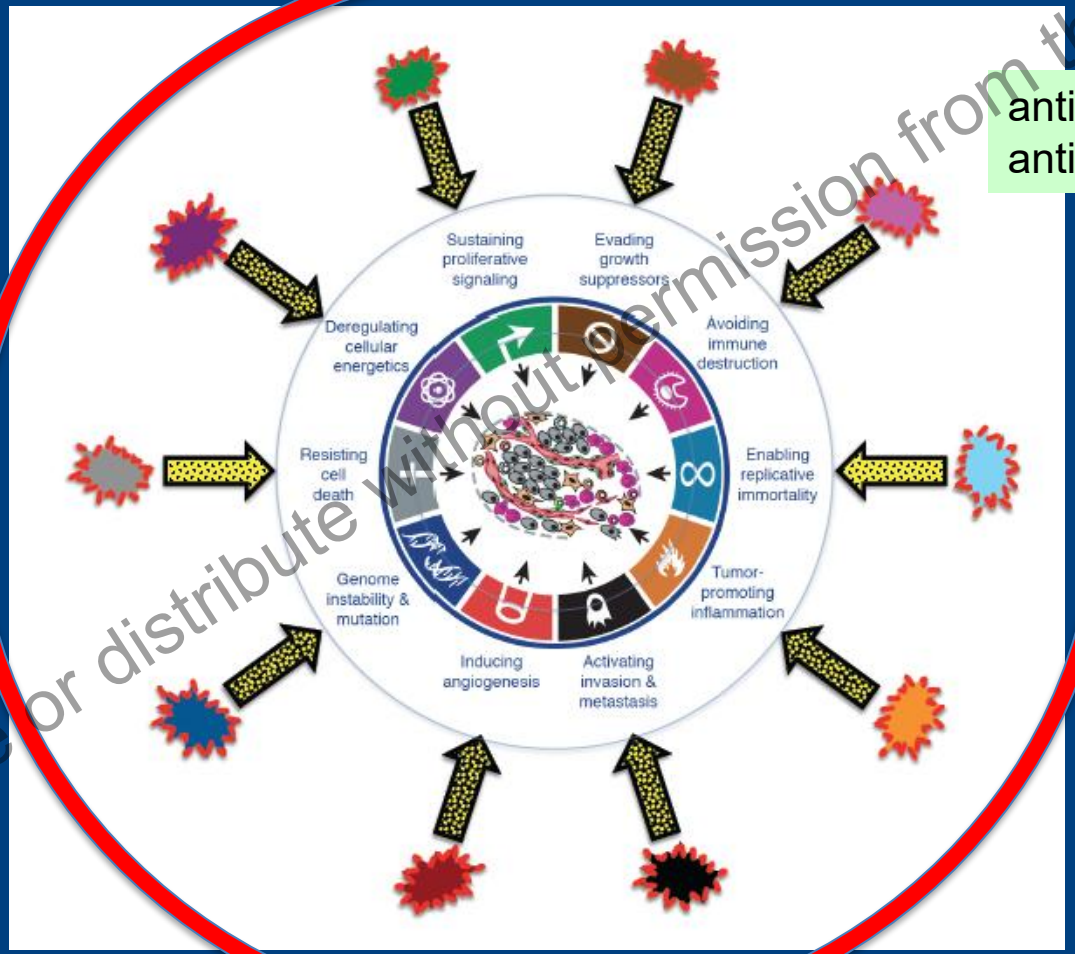
Angio & Metastasis



Hanahan
Lancet 2013

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For example, immune checkpoint inhibitors that disrupt immune evasion are being combined with other hallmark-targeting drugs



anti-PD1/PD-L1
anti-CTLA4

Anything and everything

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Signs of light: approved clinical trials involving hallmark co-targeting

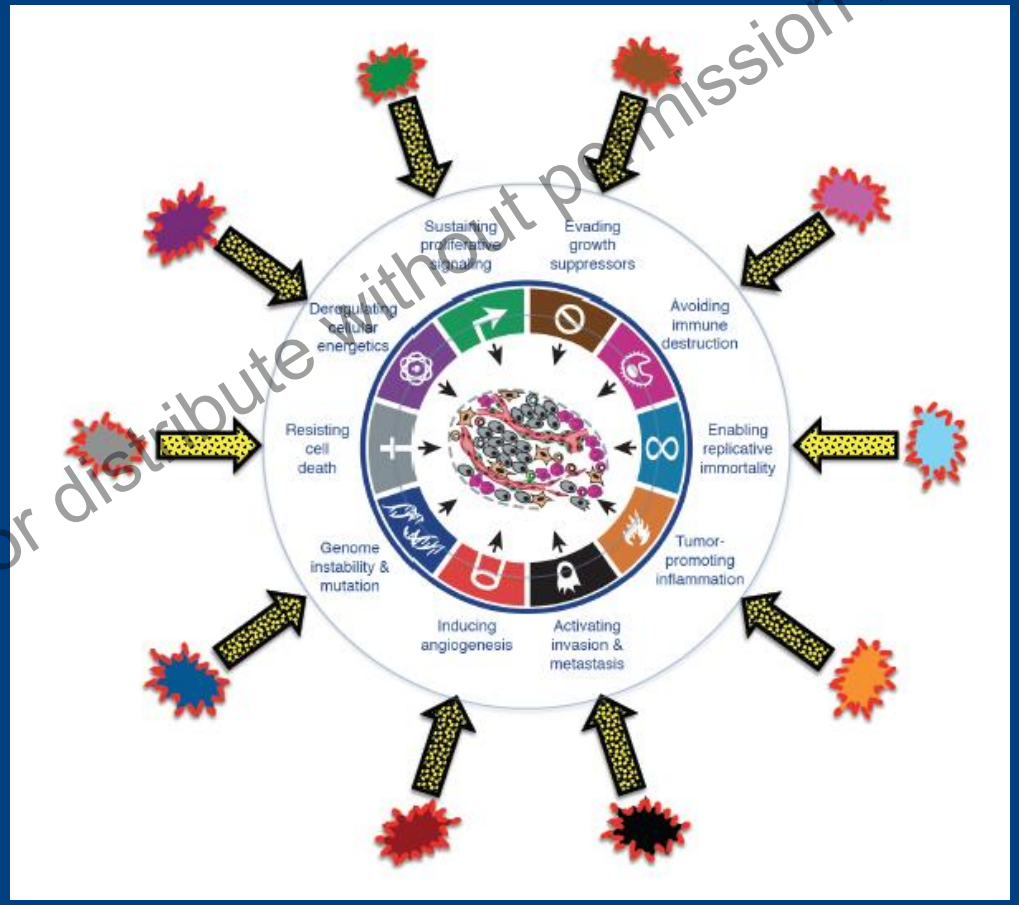
- atezolizumab (anti-PD-L1) plus cobimetinib (MEK-i) & vemurafenib (BRAF-i) approved for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma
- atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) approved for patients with unresectable or metastatic hepatocellular carcinoma
- Atezolizumab (anti-PD-L1) plus chemotherapy & bevacizumab (anti-VEGF) approved for first-line treatment of metastatic non-squamous lung cancer (NSCLC)
- pembrolizumab (anti-PD1) plus axitinib (VEGFR-i) approved for first-line treatment of patients with advanced renal cell carcinoma (RCC)
- pembrolizumab (anti-PD1) plus lenvatinib (VEGFR-i) approved for the treatment of patients with advanced endometrial carcinoma
- *In progress: various combos involving inhibitors of CDK4/6, Bcl2, and soon Kras, including ones co-targeting hallmarks beyond immune evasion*

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Will there prove to be long-term clinical benefit
from co-targeting multiple cancer hallmarks?

(*these case studies are encouraging but so far not dramatic or enduring*)

time will tell ….



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Part 3. Finally, an oft asked question:

Are there more facets to the Hallmarks Conceptualization?

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The oft asked question:

Are there more facets to the HoC Conceptualization?

Indeed, there are emerging parameters demonstrably operative in certain cancers that might in the future be generalized sufficiently to be incorporated into HoC 3.0

Several are posed to stimulate debate, discussion, and continuing experimental assessment

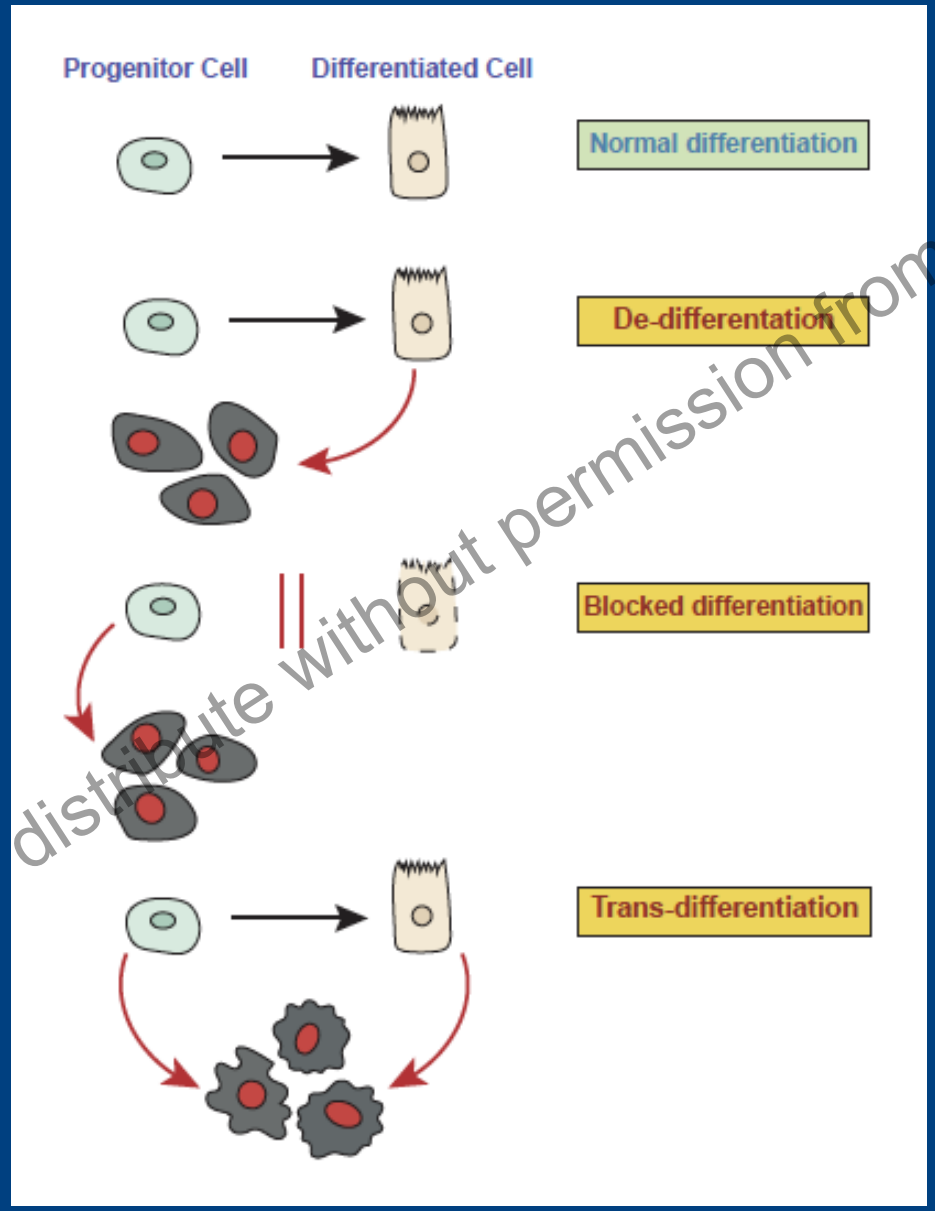
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Is unlocking phenotypic plasticity a new hallmark capability



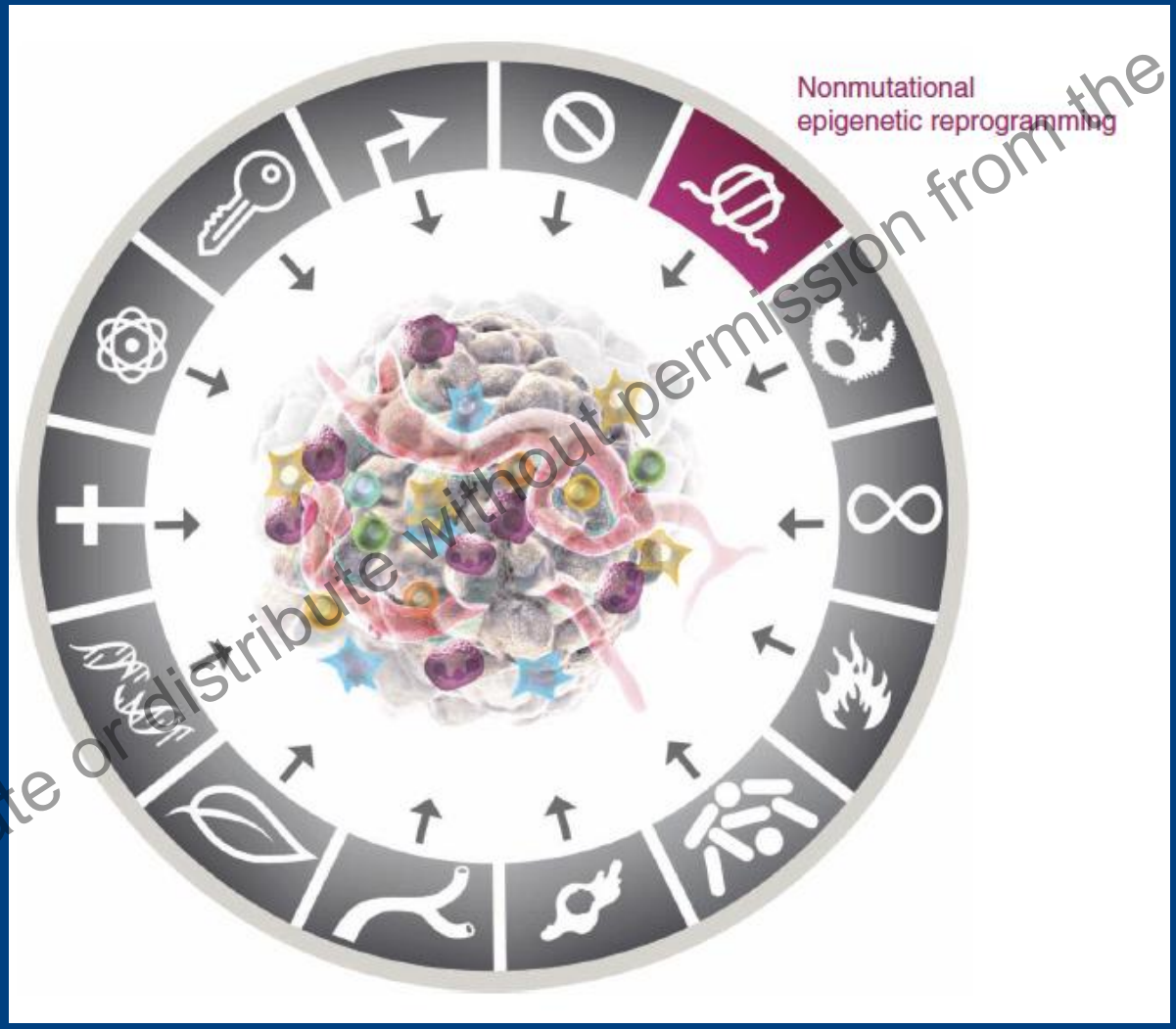
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Three modes of phenotypic plasticity



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Is non-mutational epigenetic reprogramming a discrete enabling capability?



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Is non-mutational epigenetic reprogramming a discrete enabling capability?

Embryonic development and differentiation, learning & memory, etc.,
are orchestrated by
non-mutational epigenetic reprogramming

By analogy,

in addition to mutational reprogramming (incl. of epigenetic modifiers),

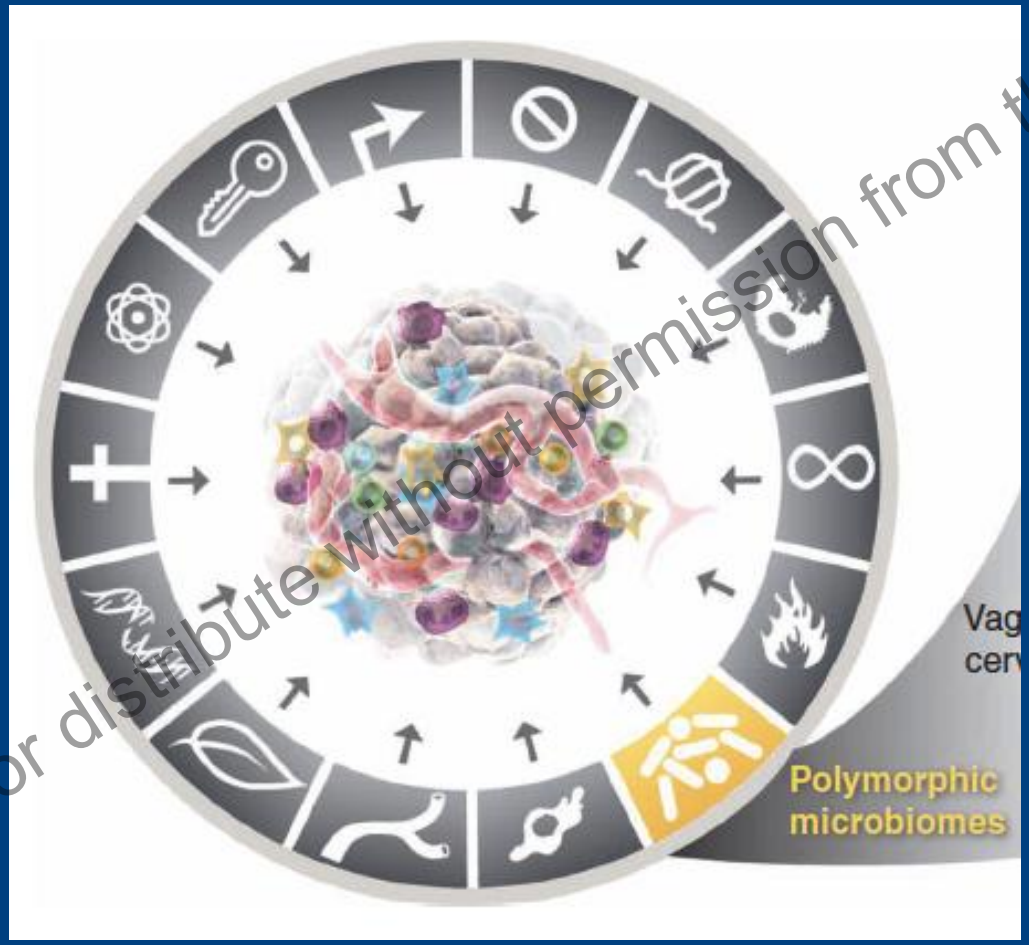
the evidence increasingly suggests that

purely epigenetic mechanisms contribute to the aberrant activities

of cancer cells and the (genomically stable) cells of the TME

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Are polymorphic microbiomes a separable and general enabling capability?



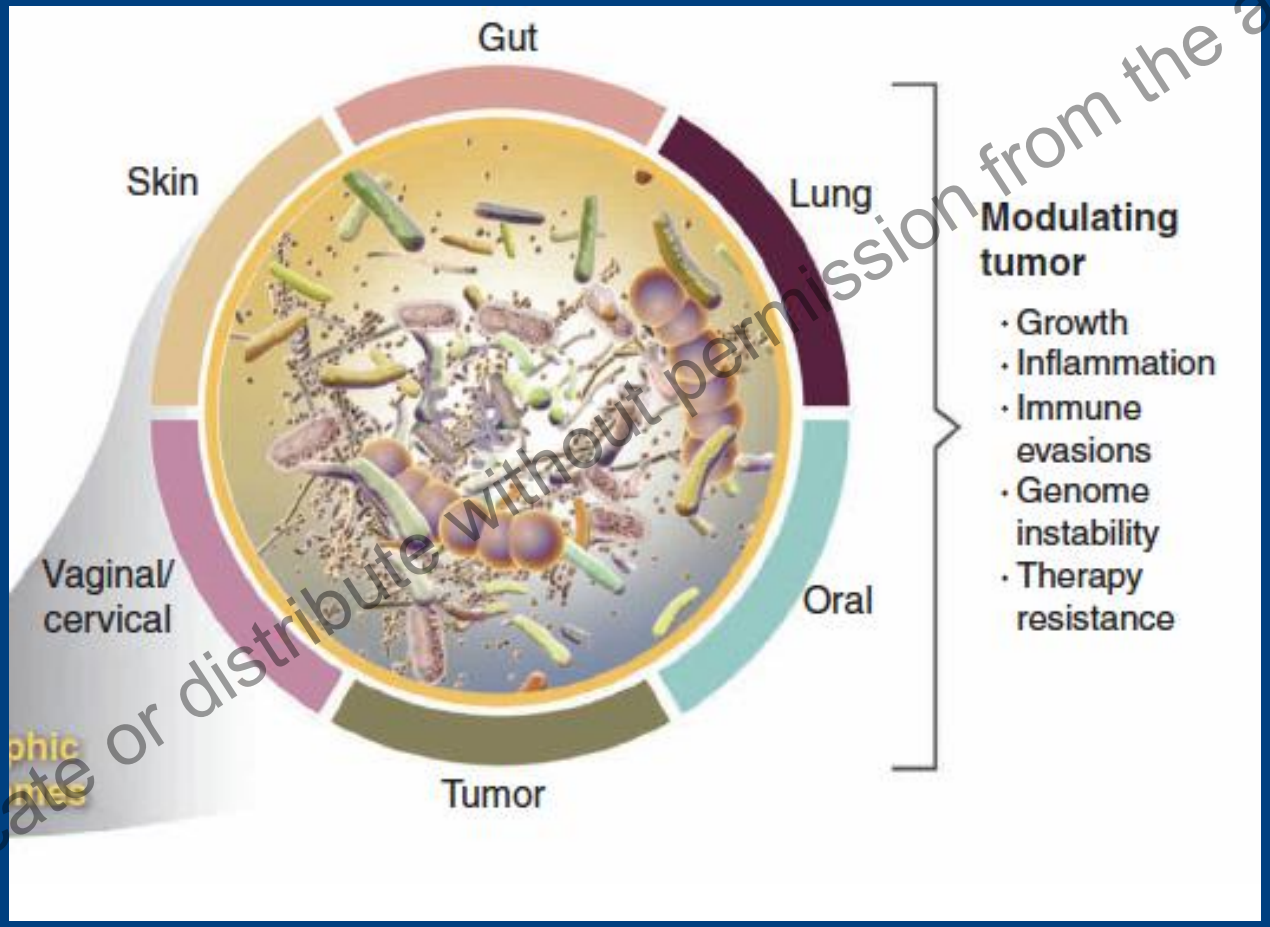
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Are polymorphic microbiomes a separable and general enabling capability?

- The gut microbiome is variably and convincingly implicated as alternatively protective or tumor-promoting
- Epidermal and mucosal microbiomes, in some cases distinguishable from the gut microbiome, are on the radar
- So too are intra-tumoral microbiomes

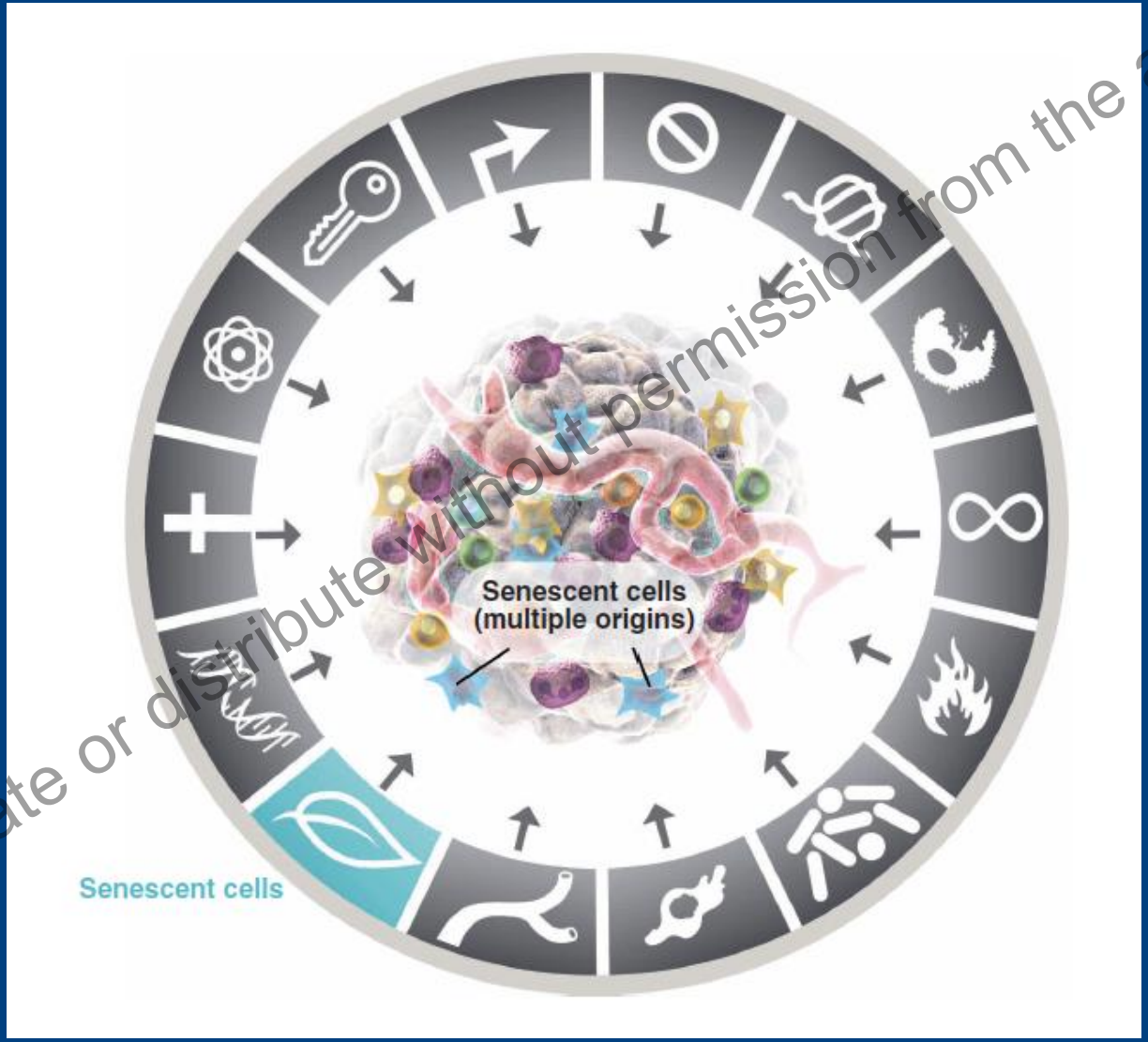
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Are polymorphic microbiomes a separable and general enabling capability?



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Are senescent cells important constituents of the tumor microenvironment?



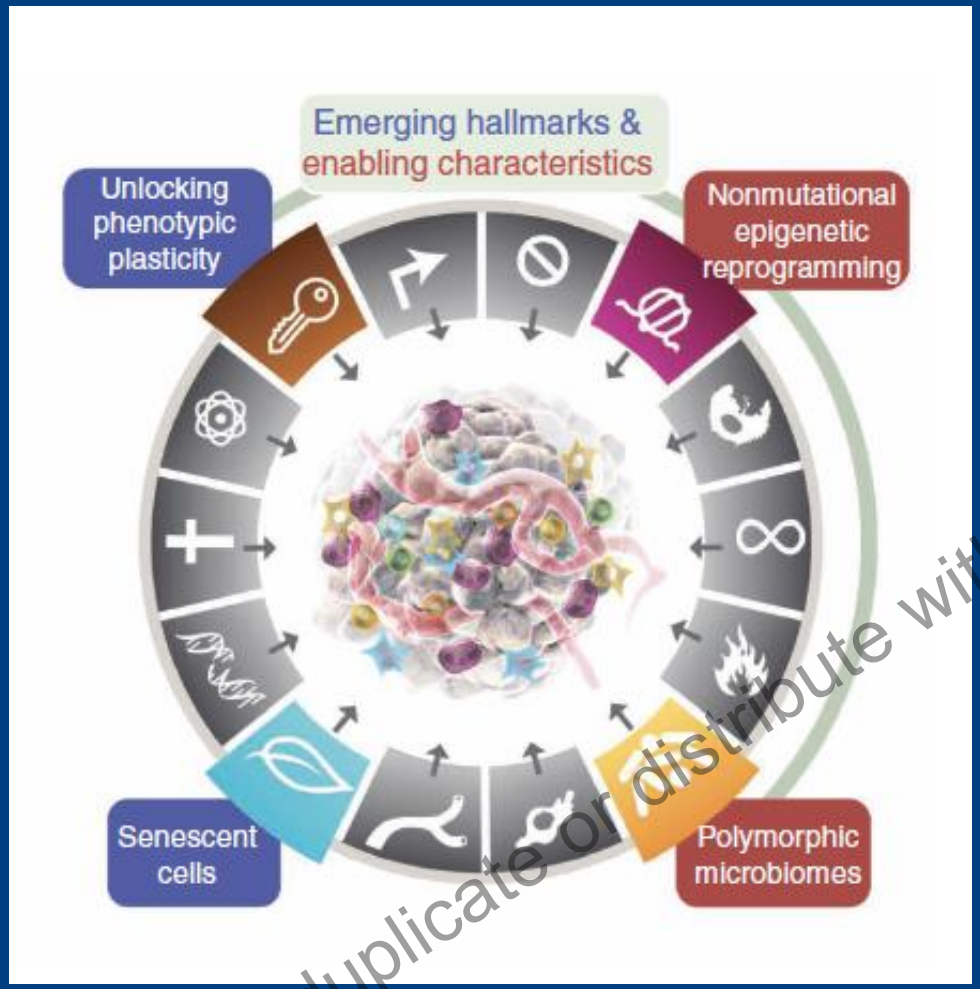
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Are senescent cells important constituents of the tumor microenvironment?

- The variable senescence-associated secretory program (SASP) has potent capabilities to alternatively promote or antagonize tumor development and progression
- Senescent cancer cells are well documented
- Cells of the TME, including CAFs and endothelial cells, have been functionally implicated in case studies

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Provisional parameters, beyond the core?



REVIEW

Hallmarks of Cancer: New Dimensions

Douglas Hanahan

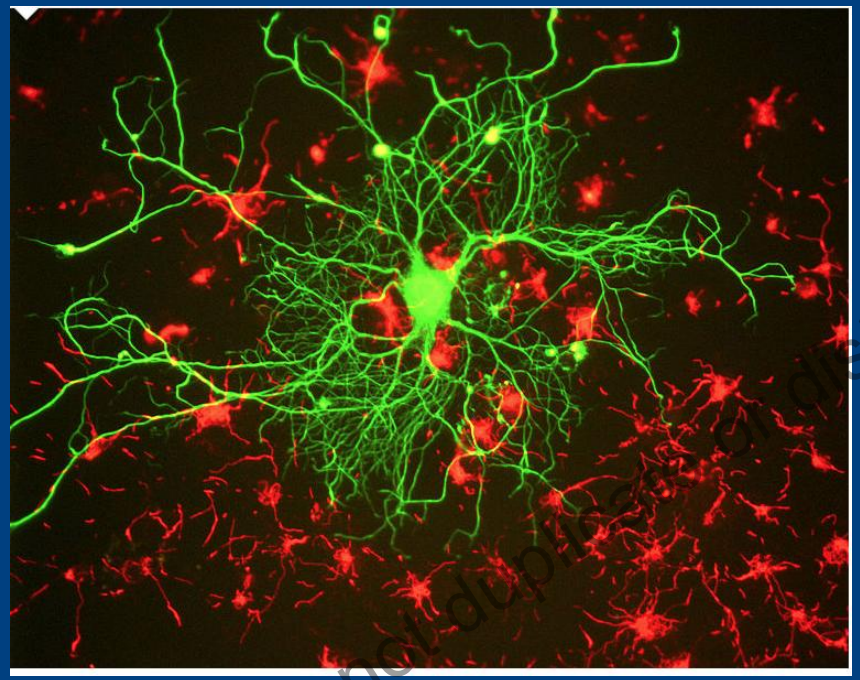
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Cancer Neuro-Biology: A provisional new parameter, way beyond the core?

Additionally: the increasingly appreciated engagement of the nervous system and its signaling circuits in cancer hallmarks!

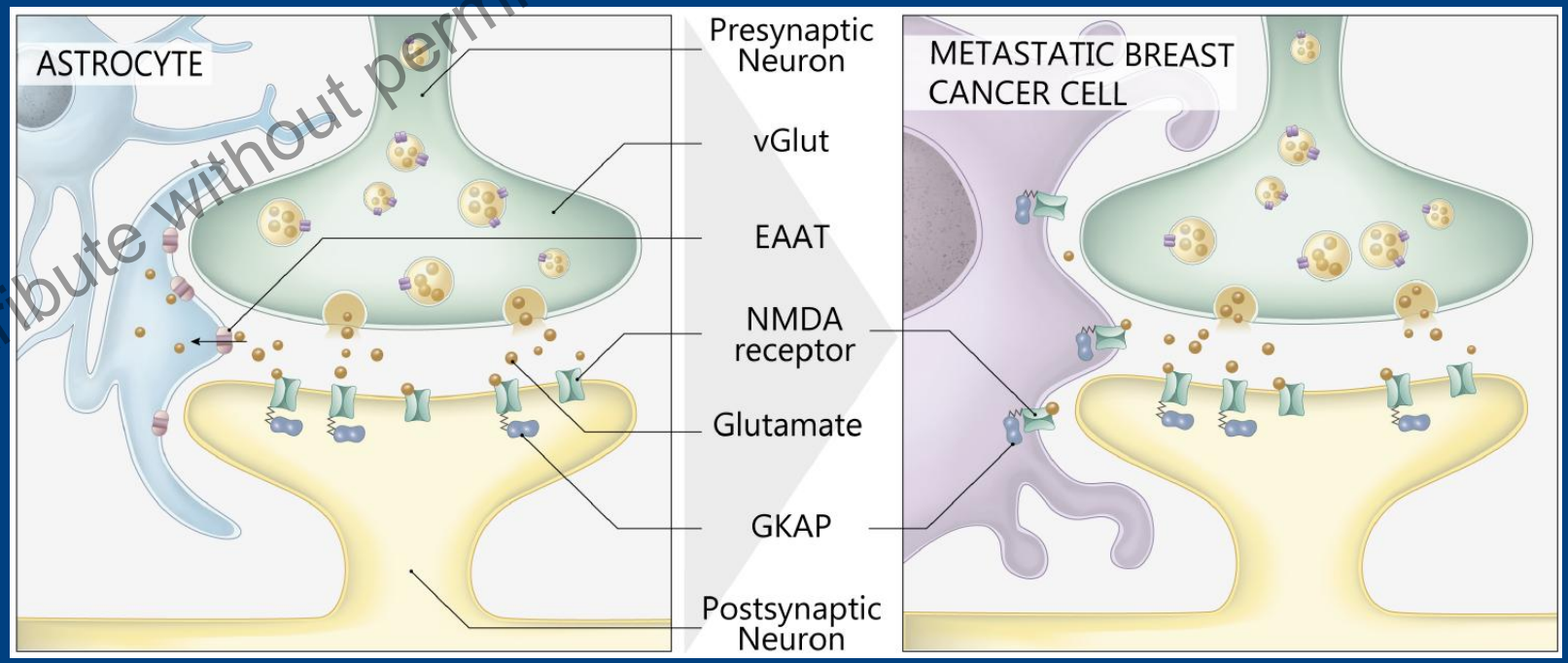
Innervation contributing to glioblastoma



Venkatesh, et al. (Monje). "Electrical and Synaptic Integration of Glioma into Neural Circuits." *Nature* 2019

Signaling during synaptic transmission

Parasitized synaptic signaling in brain-metastatic breast cancer



Zeng, et al (Hanahan). "Synaptic proximity enables NMDAR signaling to promote brain metastasis. Nature, 573: 526-531.." *Nature* 2019

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