ESMO 2012

The Hallmarks of Cancer:

Applications to Cancer Medicine?

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ISREC @EPFL
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EPFL
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Cancer

Cancer is a disease of extraordinary complexity, in terms of genetics, pathology, prognosis, and response to therapy

How can we rationalize this complexity?

Are there common principles underlying this daunting diversity and complexity?

A hypothesis for rationalizing the complexity of cancer

- Disparate cancers share fundamental qualities

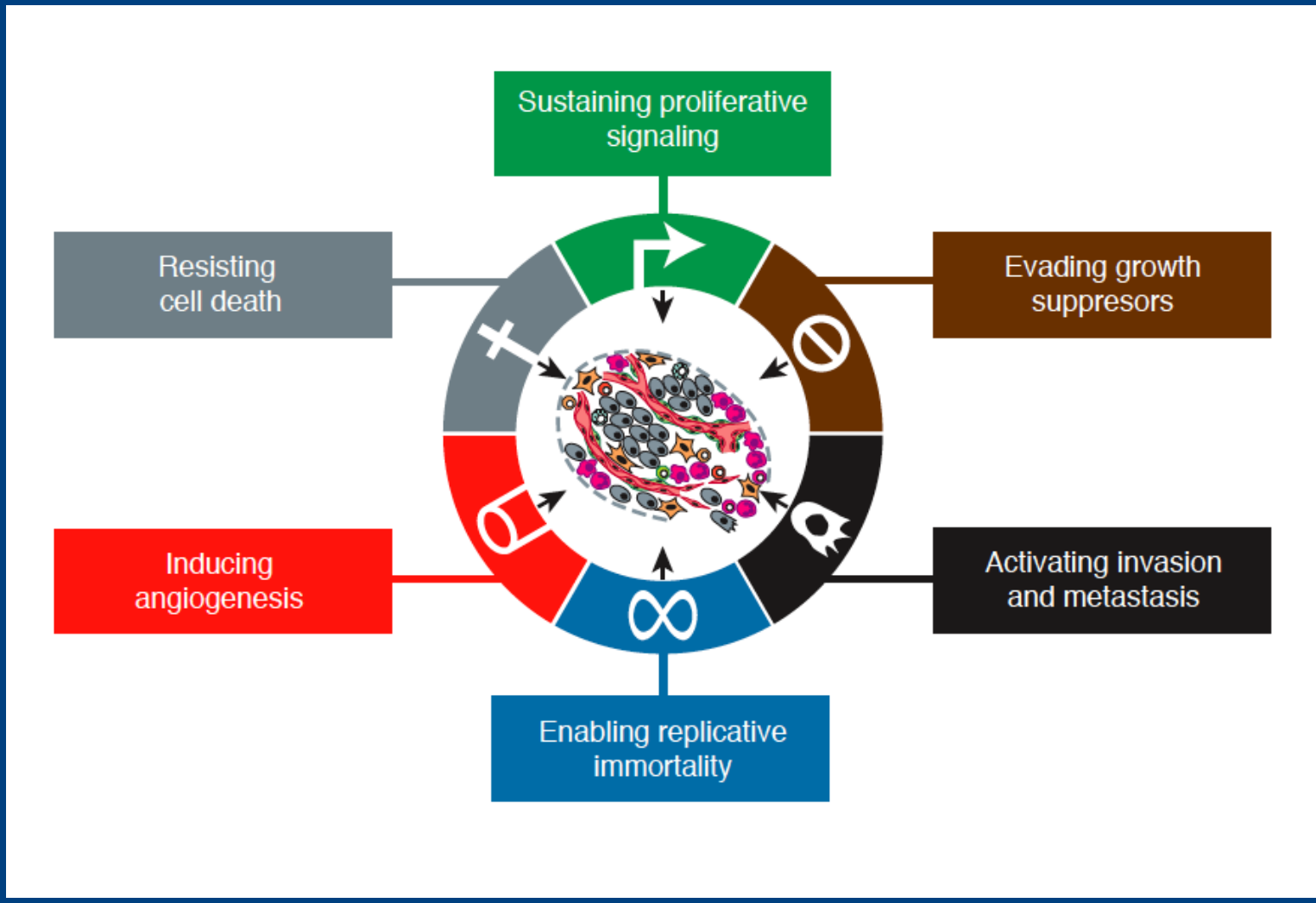
A hypothesis for rationalizing the complexity of cancer

- Disparate cancers share fundamental qualities

- This daunting complexity merely reflects different solutions to the same challenge:

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

A hypothesis for rationalizing the complexity of cancer



Posed by Douglas Hanahan and Robert Weinberg in 2000

What are hallmarks of cancer?

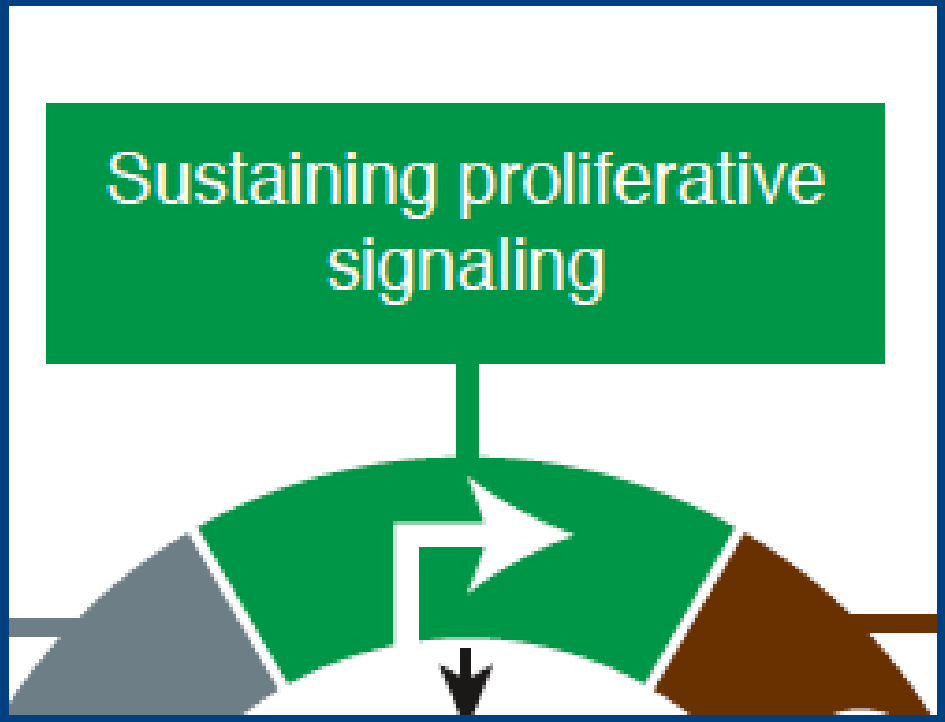
The hallmarks are acquired functional capabilities, that allow tumors to

-- do something active

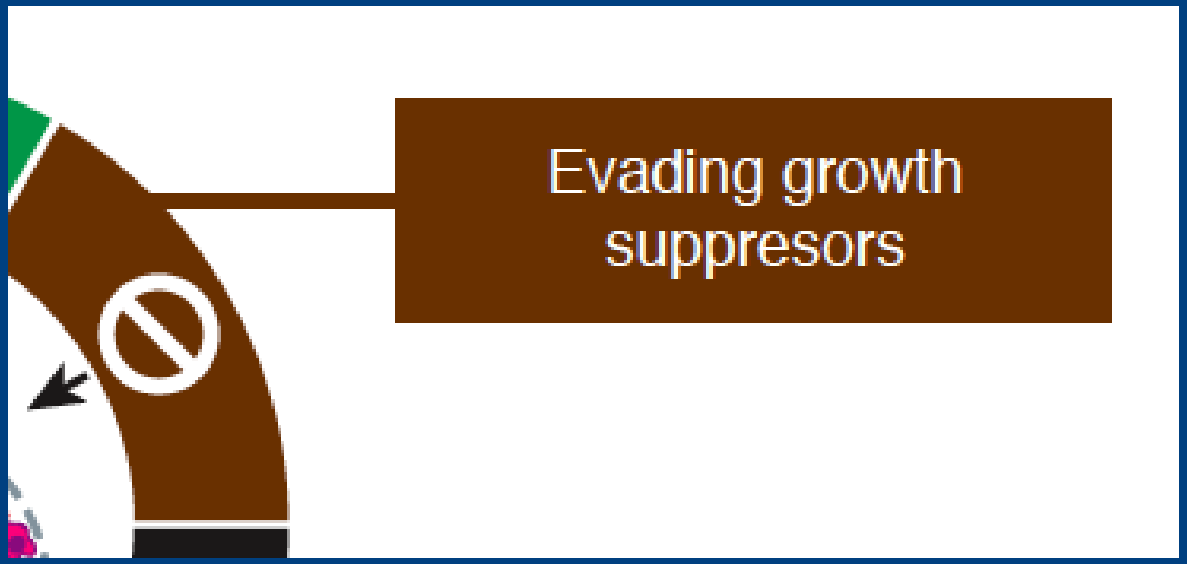
-- do things that normal cells should not

-- typically, to do them chronically, rather than during the carefully orchestrated activities of cells and organs in the body

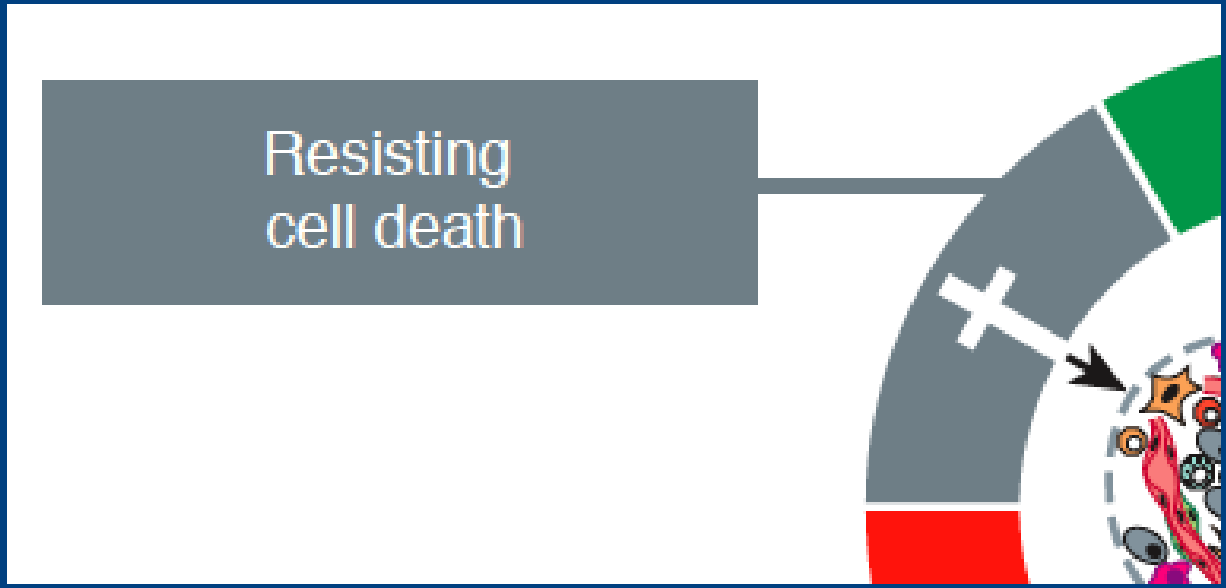
The first hallmark



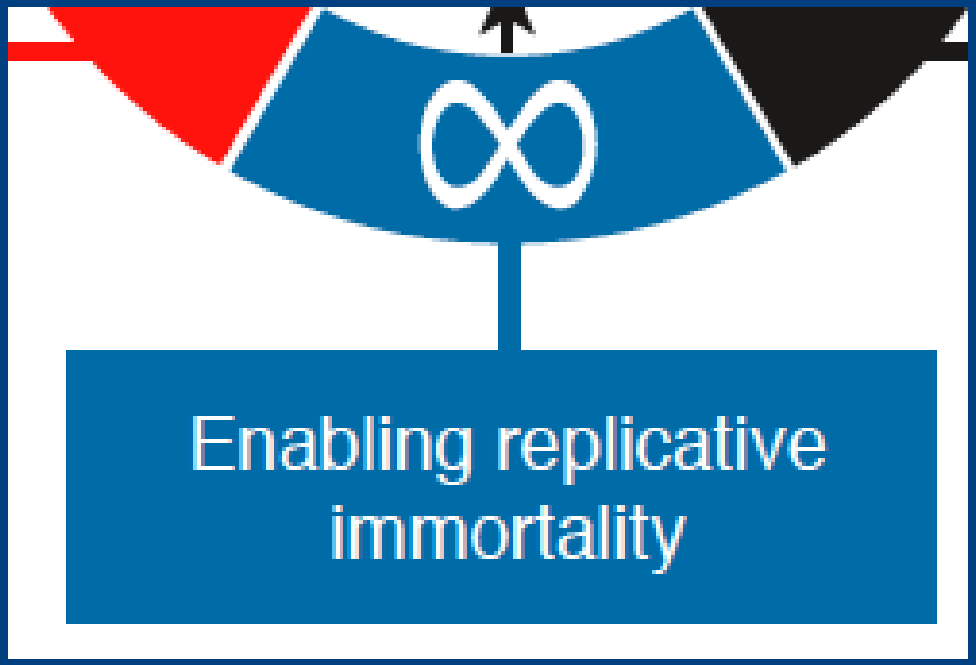
The second hallmark



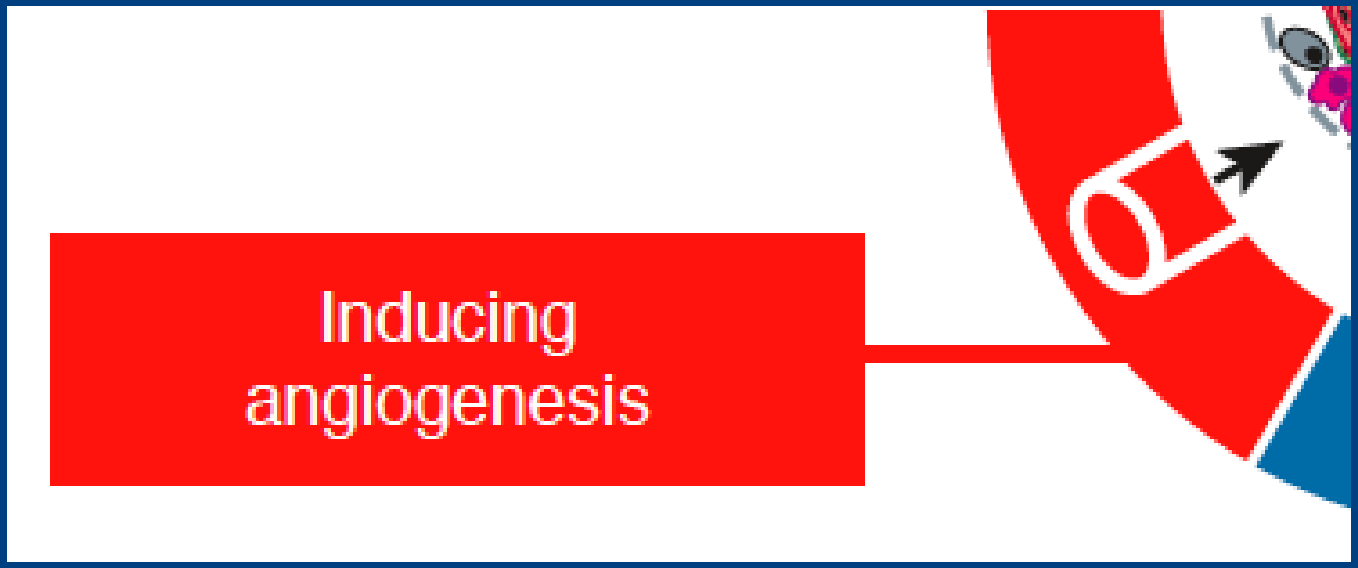
The third hallmark



The fourth hallmark

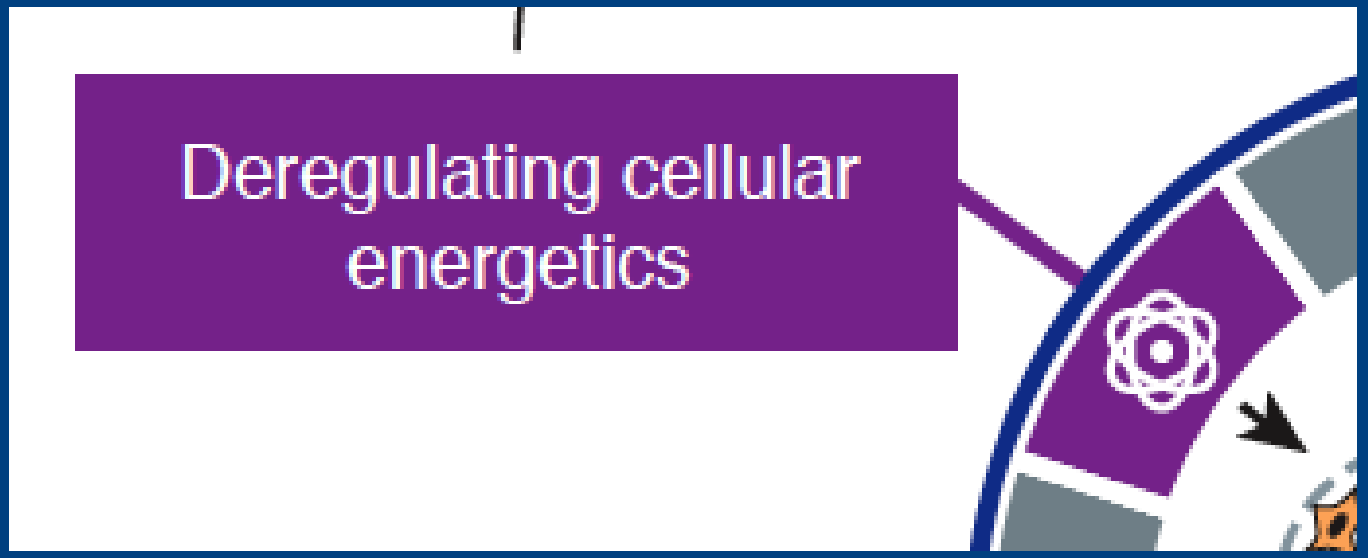


The fifth hallmark



The sixth hallmark

And, in 2011, two emerging hallmarks



And, in 2011, two emerging hallmarks

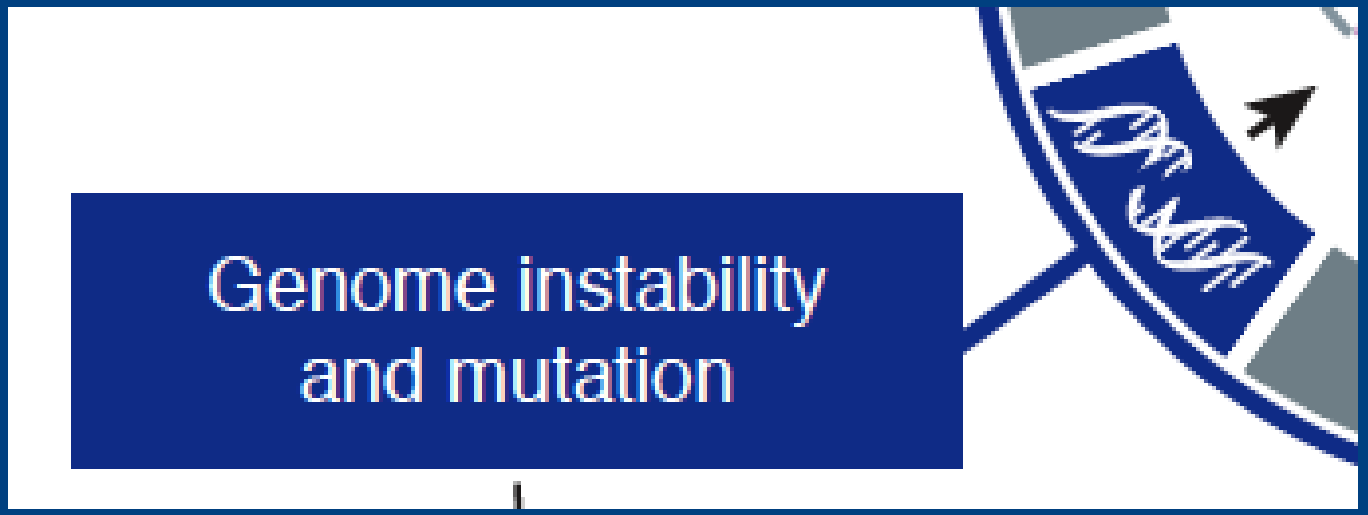
How are these hallmark capabilities acquired?

Via Enabling Characteristics

Enabling Characteristics are not functional capabilities per se, i.e. they are not actions performed by cancer cells and cancerous lesions

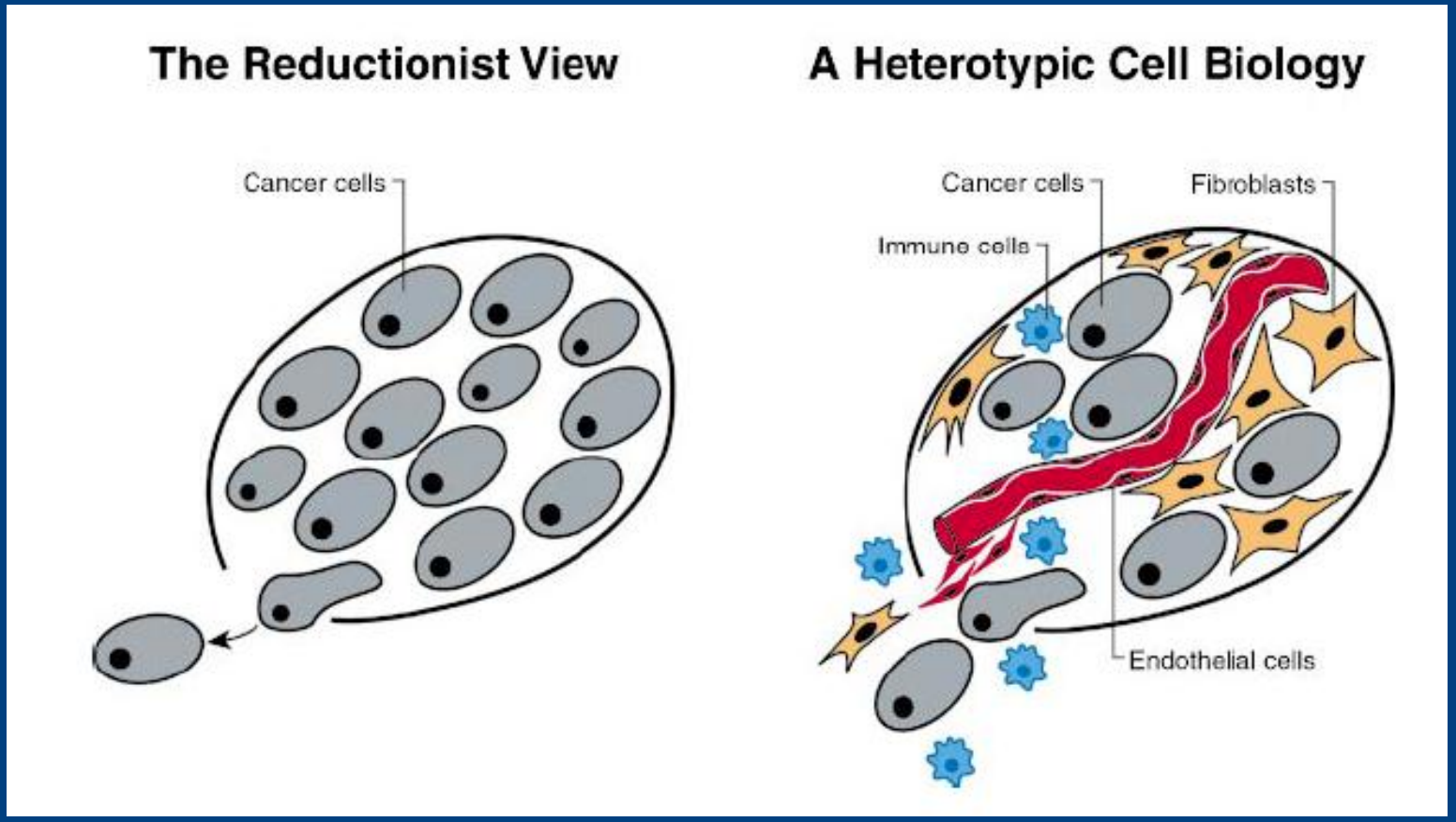
Rather, **Enabling Characteristics** are consequential effects that facilitate acquisition of the hallmark capabilities

An enabling characteristic for acquiring hallmarks

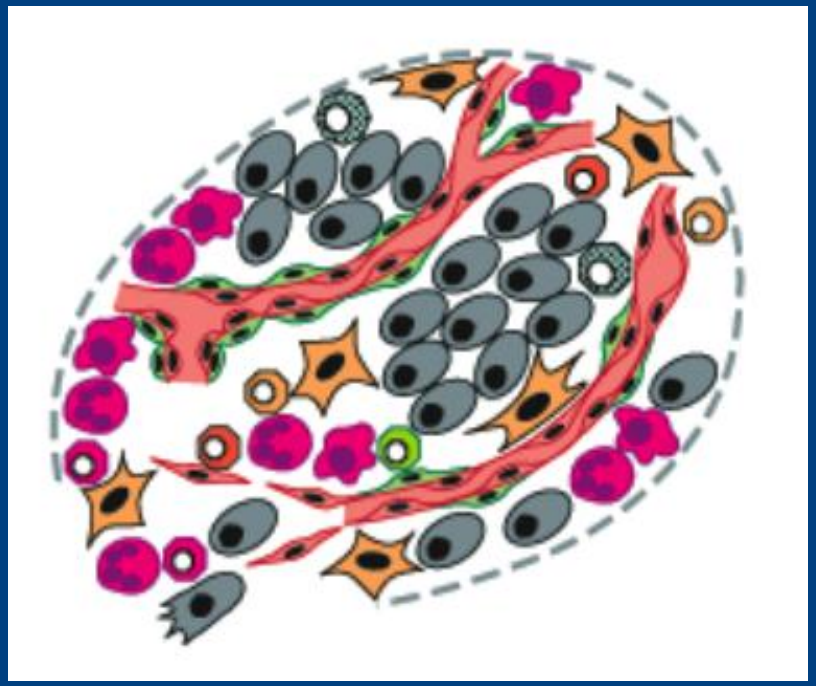


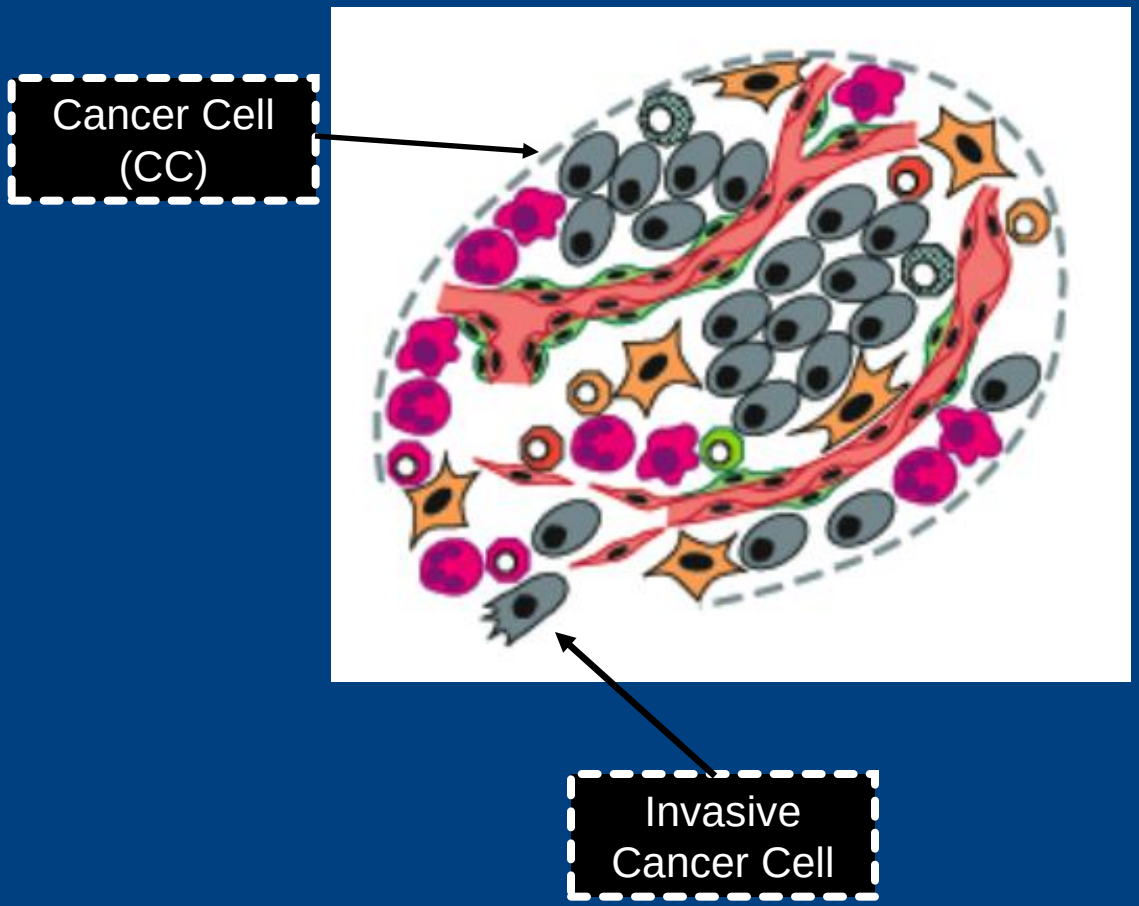
A second enabling characteristics for acquiring hallmarks

A related realization: tumors are not bags of cancer cells but rather outlaw organs



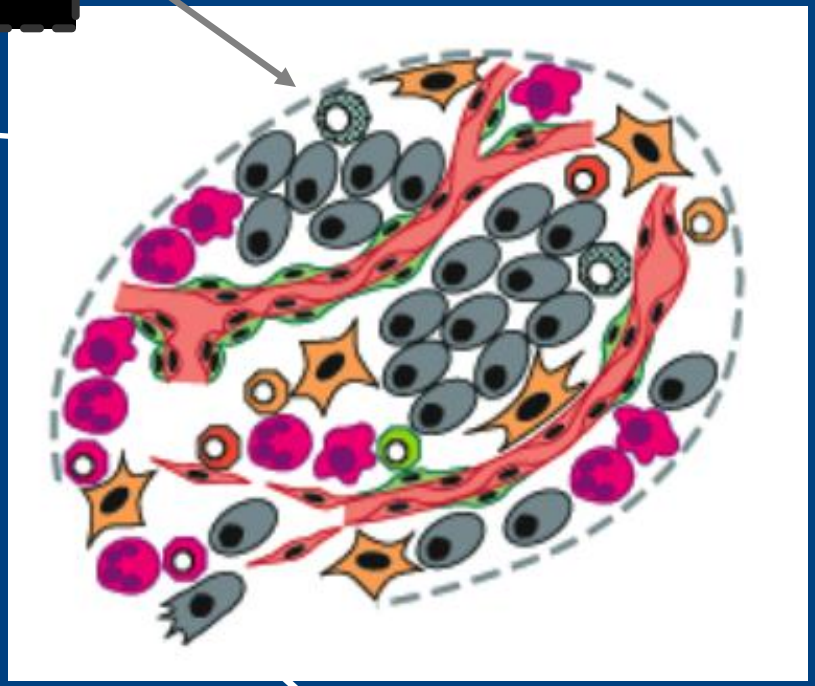
Tumors are composed of an assemblage of cell types that communicate and collaborate



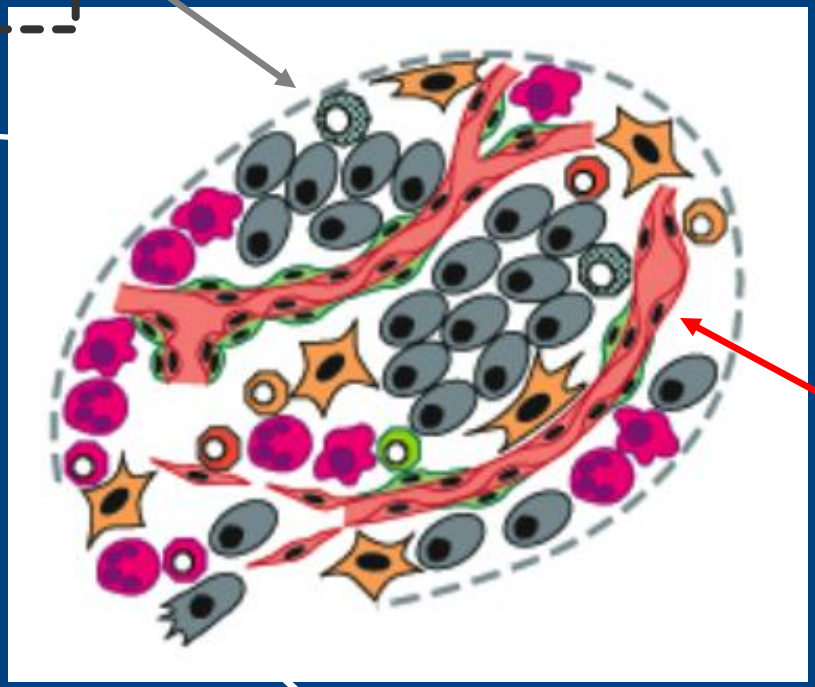

Cancer Cell
(CC)
Invasive
Cancer Cell

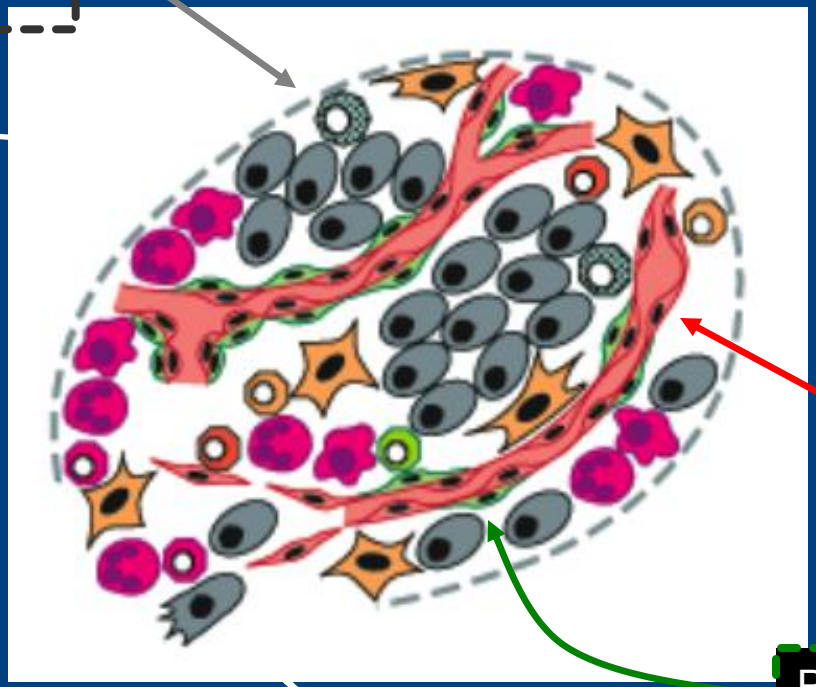
Cancer Stem Cell (CSC)

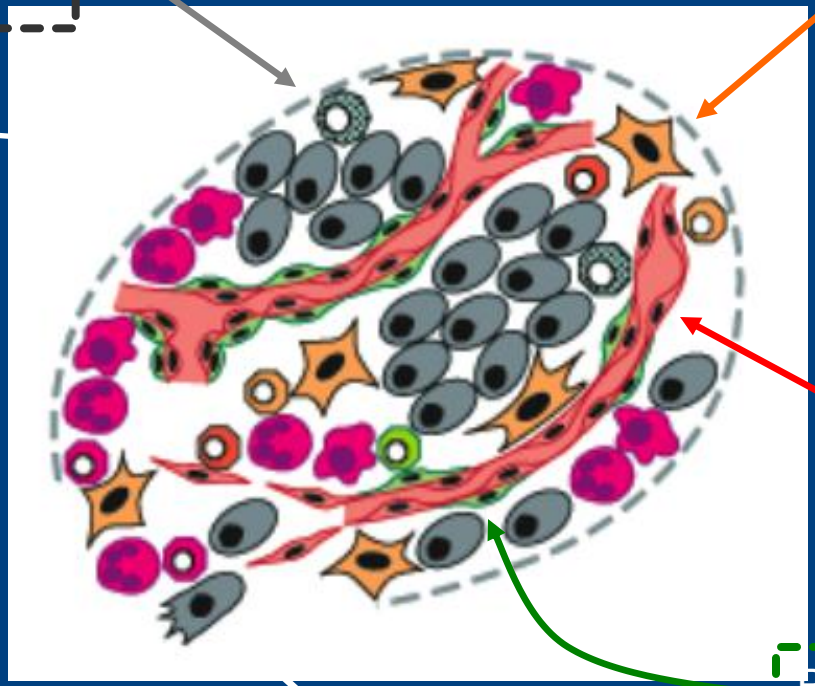
Cancer Cell (CC)

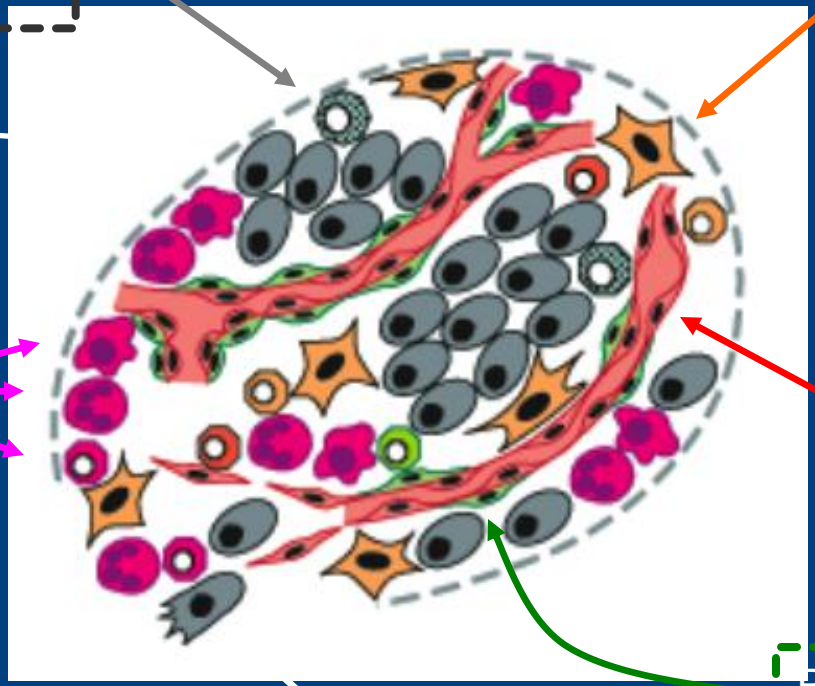


Invasive Cancer Cell

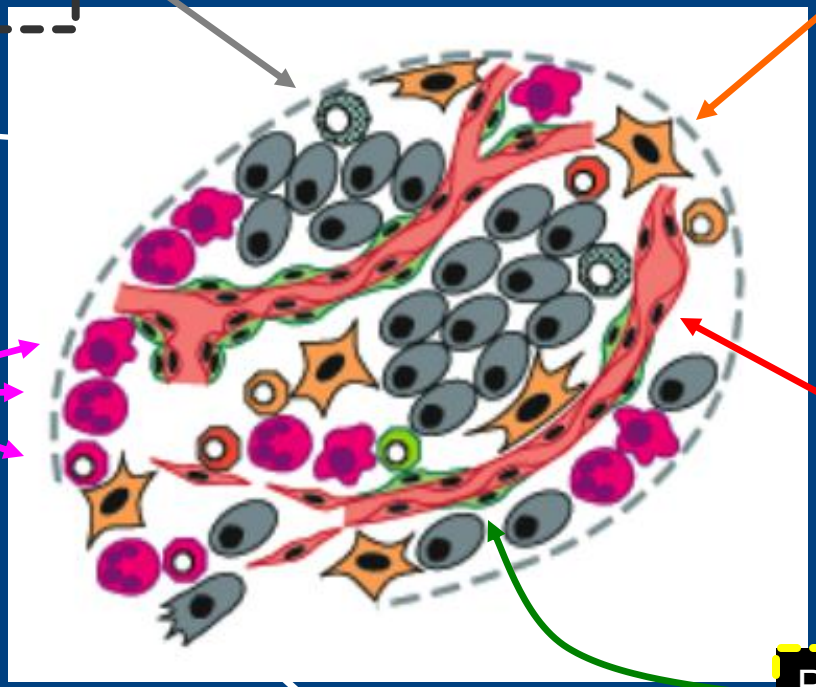

Cancer Stem Cell (CSC)
Cancer Cell (CC)
Endothelial Cell (EC)
Invasive Cancer Cell


Cancer Stem Cell (CSC)
Cancer Cell (CC)
Endothelial Cell (EC)
Pericyte (PC)
Invasive Cancer Cell


Cancer Stem Cell (CSC)
Cancer Cell (CC)
Cancer-Associated Fibroblast (CAF)
Endothelial Cell (EC)
Pericyte (PC)
Invasive Cancer Cell


Cancer Stem Cell (CSC)
Cancer-Associated Fibroblast (CAF)
Cancer Cell (CC)
Tumor-Promoting Inflammatory Cells (TPIC)
Endothelial Cell (EC)
Pericyte (PC)
Invasive Cancer Cell

Multiple normal cell types are recruited to become components of tumors, helping to provide hallmark capabilities



Cancer Stem Cell (CSC)

Cancer Cell (CC)

Tumor-Promoting Inflammatory Cells (TPIC)

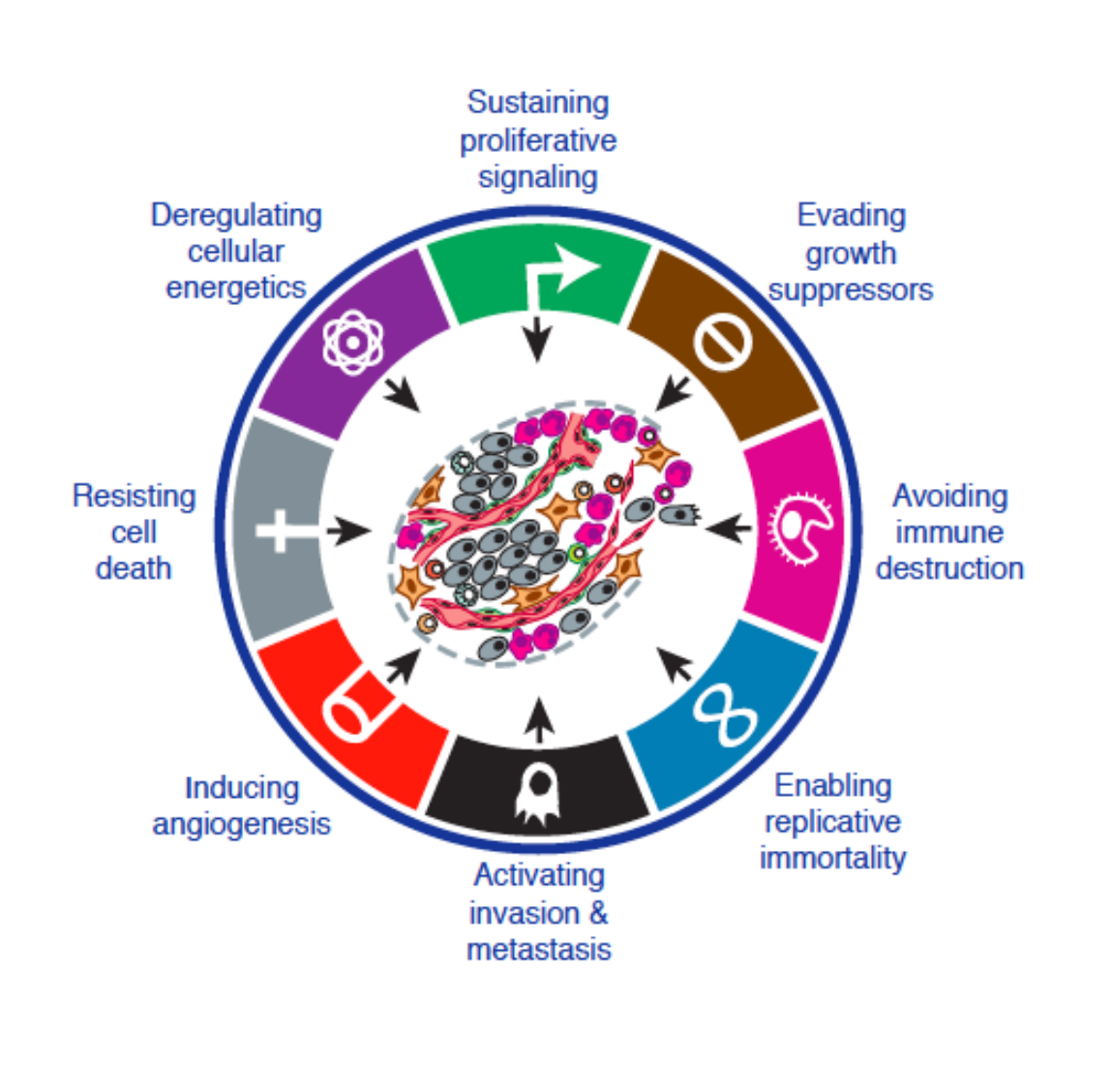
Invasive Cancer Cell

Cancer-Associated Fibroblast (CAF)

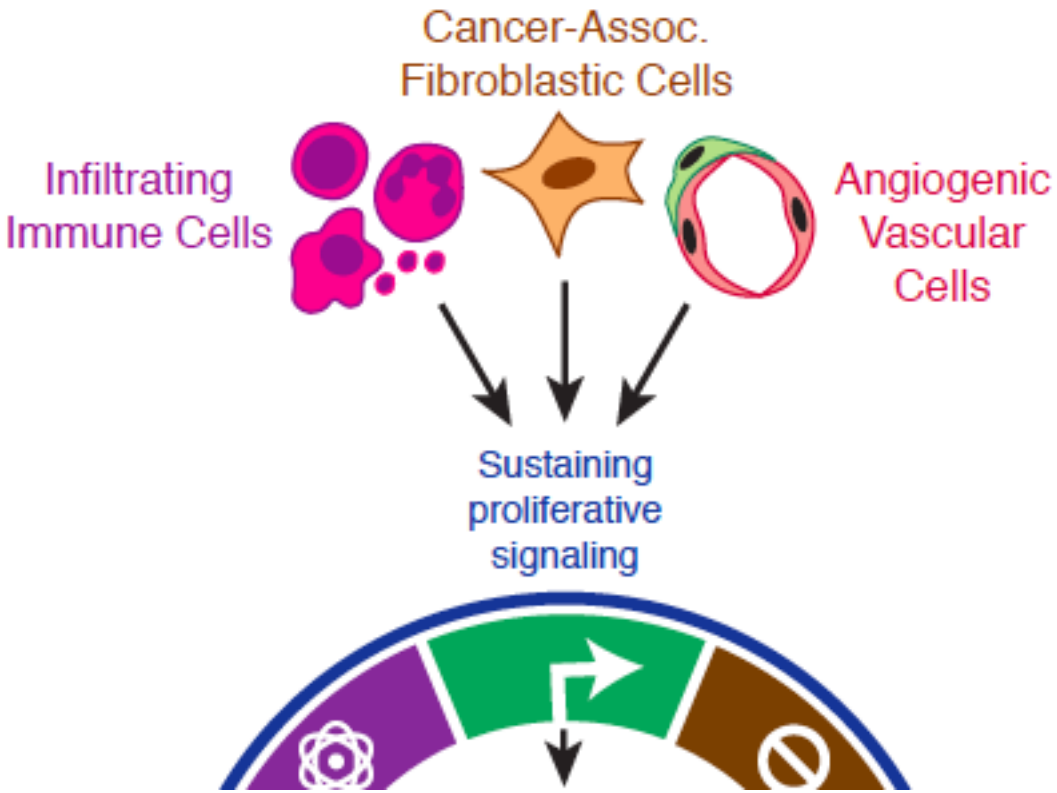
Endothelial Cell (EC)

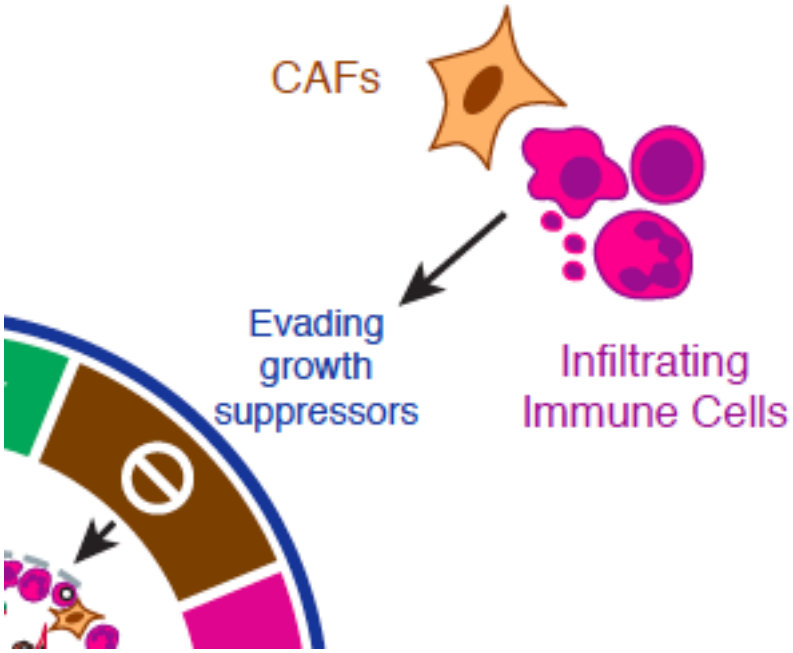
Pericyte (PC)

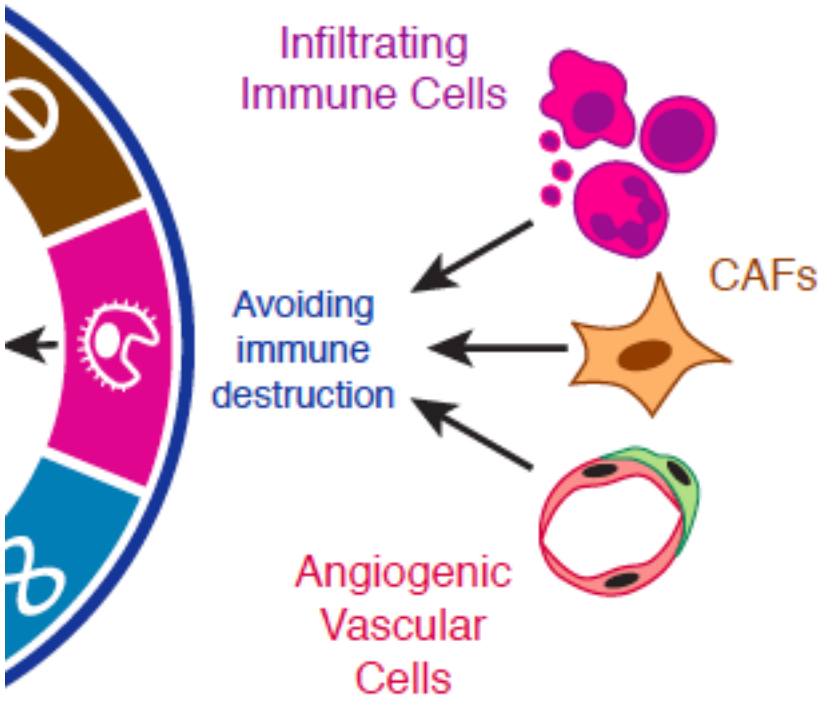
Stromal cells functionally contribute to multiple hallmarks

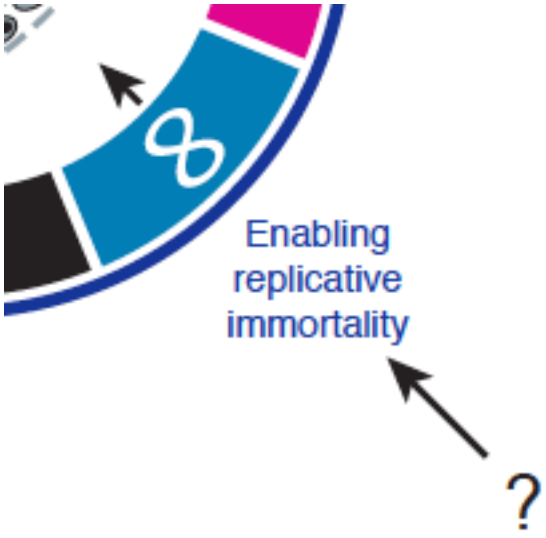


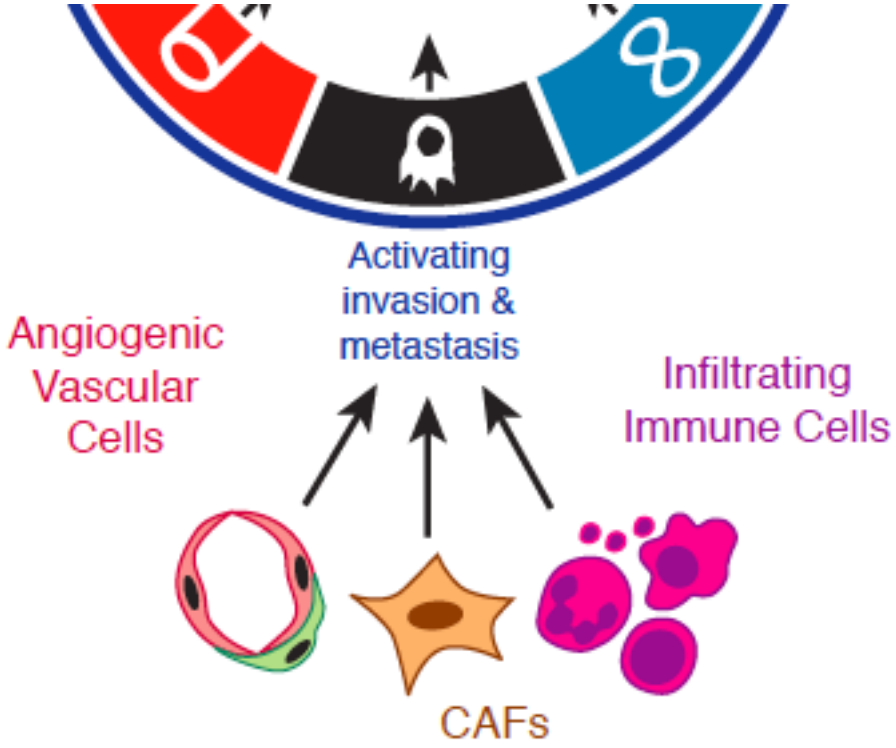
Hanahan & Weinberg (2011) Cell; Hanahan & Coussens (2012) Cancer Cell

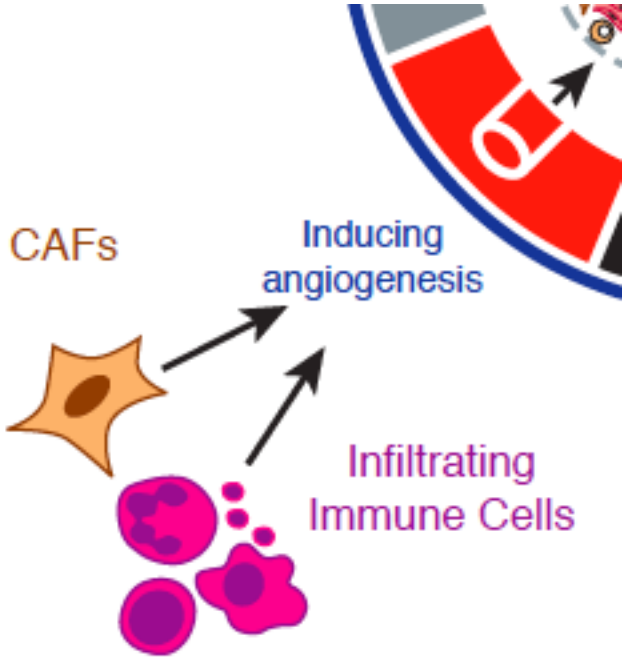

Cancer-Assoc.
Fibroblastic Cells
Infiltrating
Immune Cells
Angiogenic
Vascular
Cells
Sustaining
proliferative
signaling

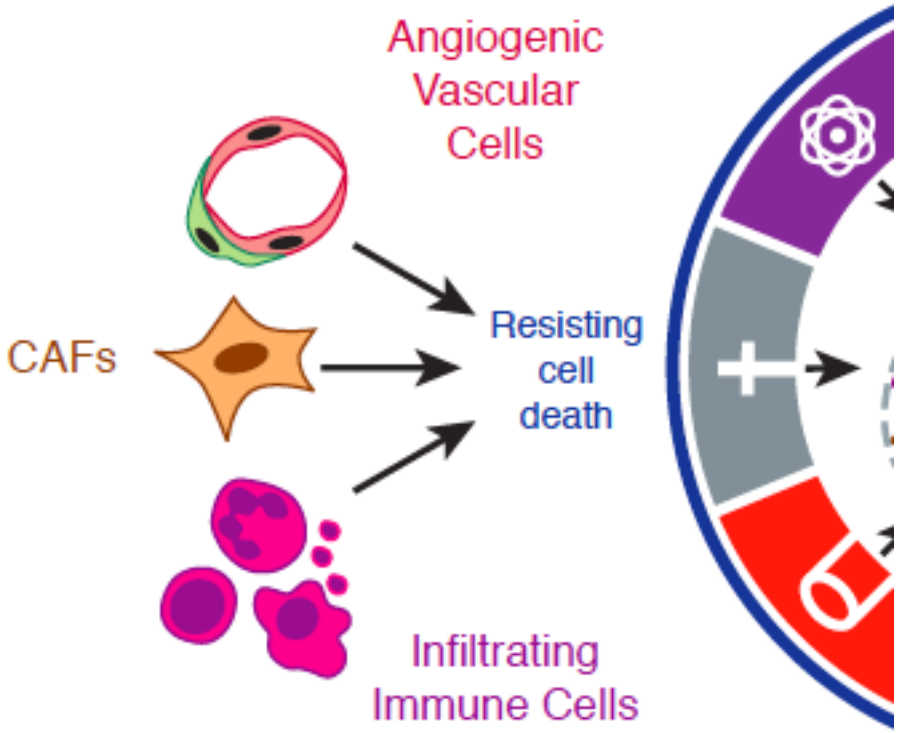

CAFs
Evading
growth
suppressors
Infiltrating
Immune Cells

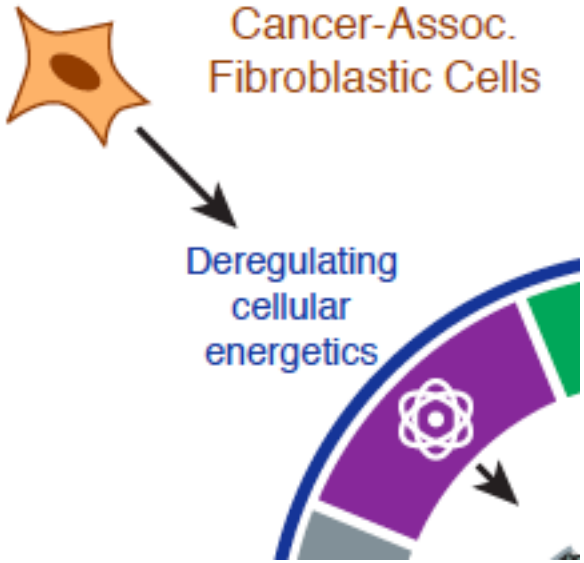

Infiltrating
Immune Cells
CAFs
Avoiding
immune
destruction
Angiogenic
Vascular
Cells


Enabling
replicative
immortality
?

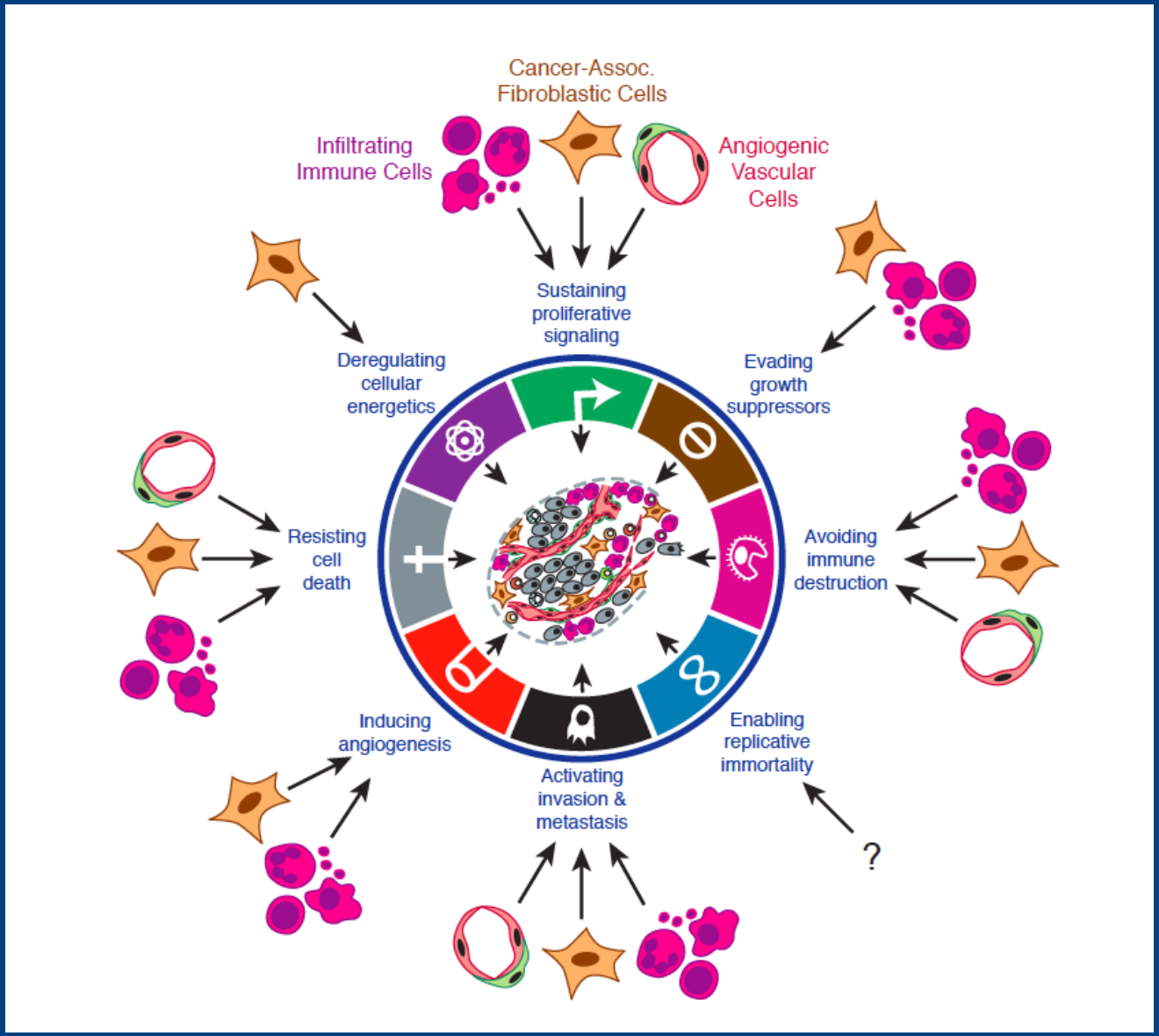

Activating
invasion &
metastasis
Angiogenic
Vascular
Cells
Infiltrating
Immune Cells
CAFs


CAFs
Inducing
angiogenesis
Infiltrating
Immune Cells


Angiogenic
Vascular
Cells
CAFs
Resisting
cell
death
Infiltrating
Immune Cells

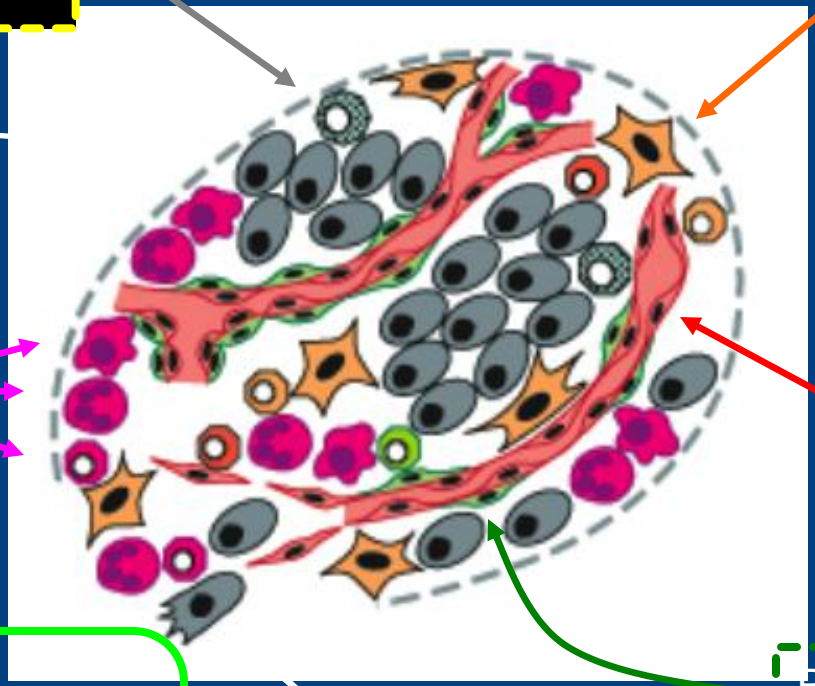

Cancer-Assoc.
Fibroblastic Cells
Deregulating
cellular
energetics

Stromal cells functionally contribute to 7 of 8 hallmarks



Hanahan & Coussens (2012) Cancer Cell

Yet, the basis remains the cancer cells, now including variable populations of 'cancer stem cells' – whose corruptions are being revealed by genome re-sequencing and charting the epigenome



Cancer Stem Cell (CSC)

Cancer Cell (CC)

Tumor-Promoting Inflammatory Cells (TPIC)

Local & Bone-Marrow Derived Stromal Stem & Progenitor cells

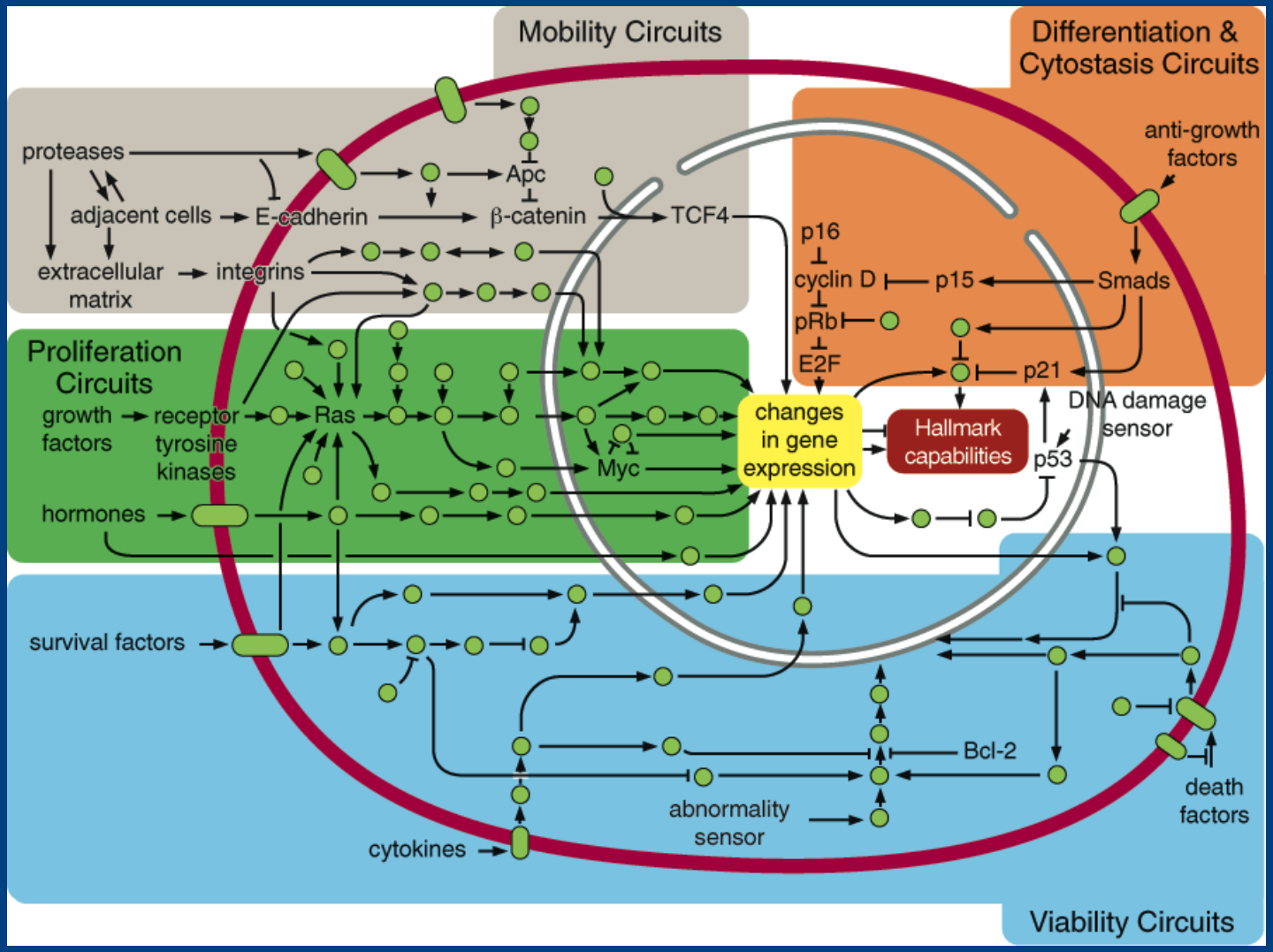
Invasive Cancer Cell

Pericyte (PC)

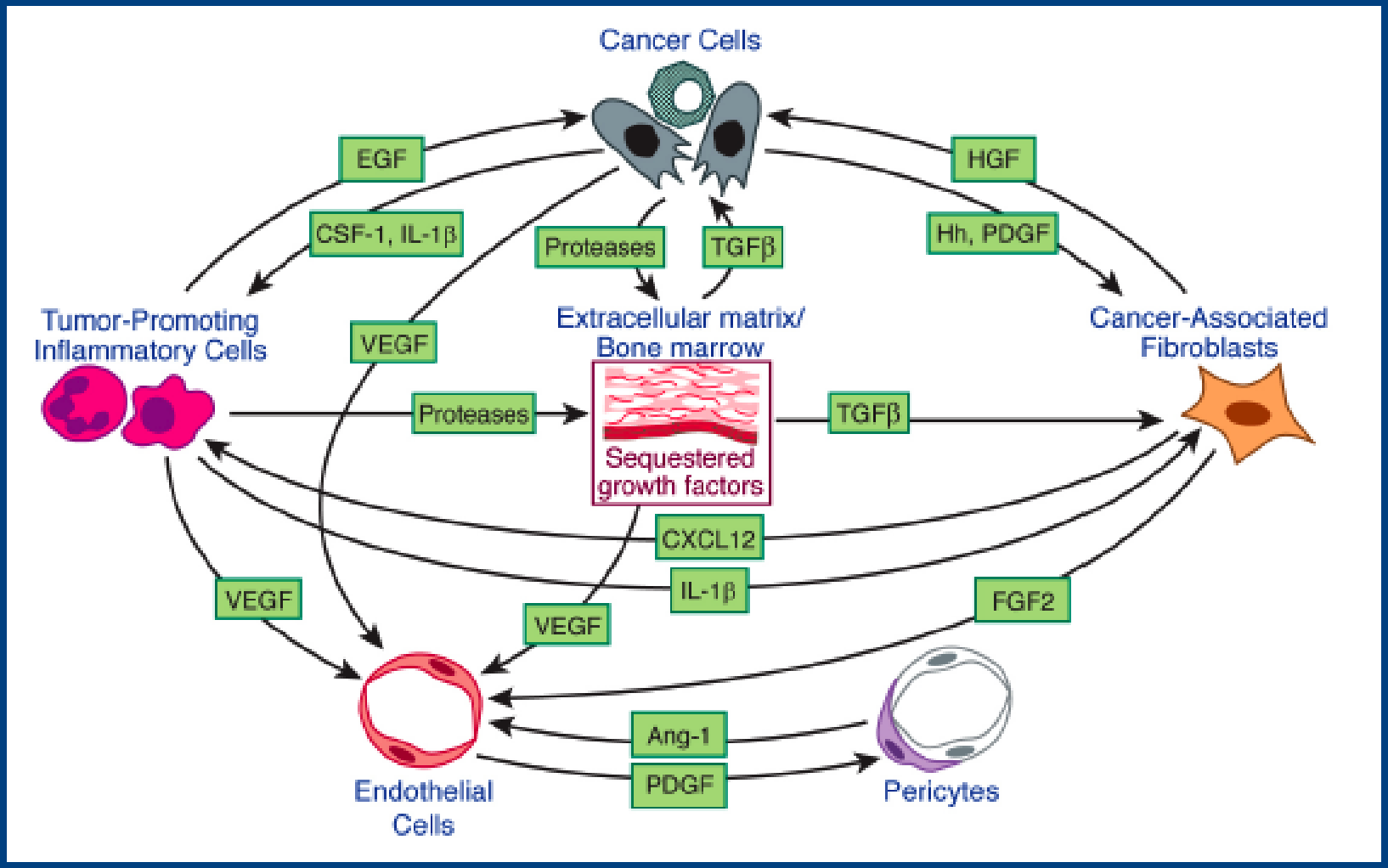
Endothelial Cell (EC)

Cancer-Associated Fibroblast (CAF)

The disease is regulated in part by the integrated signaling circuit of the cancer cell



Plus an even bigger network: the signals transmitted between the various cells of the tumor microenvironment

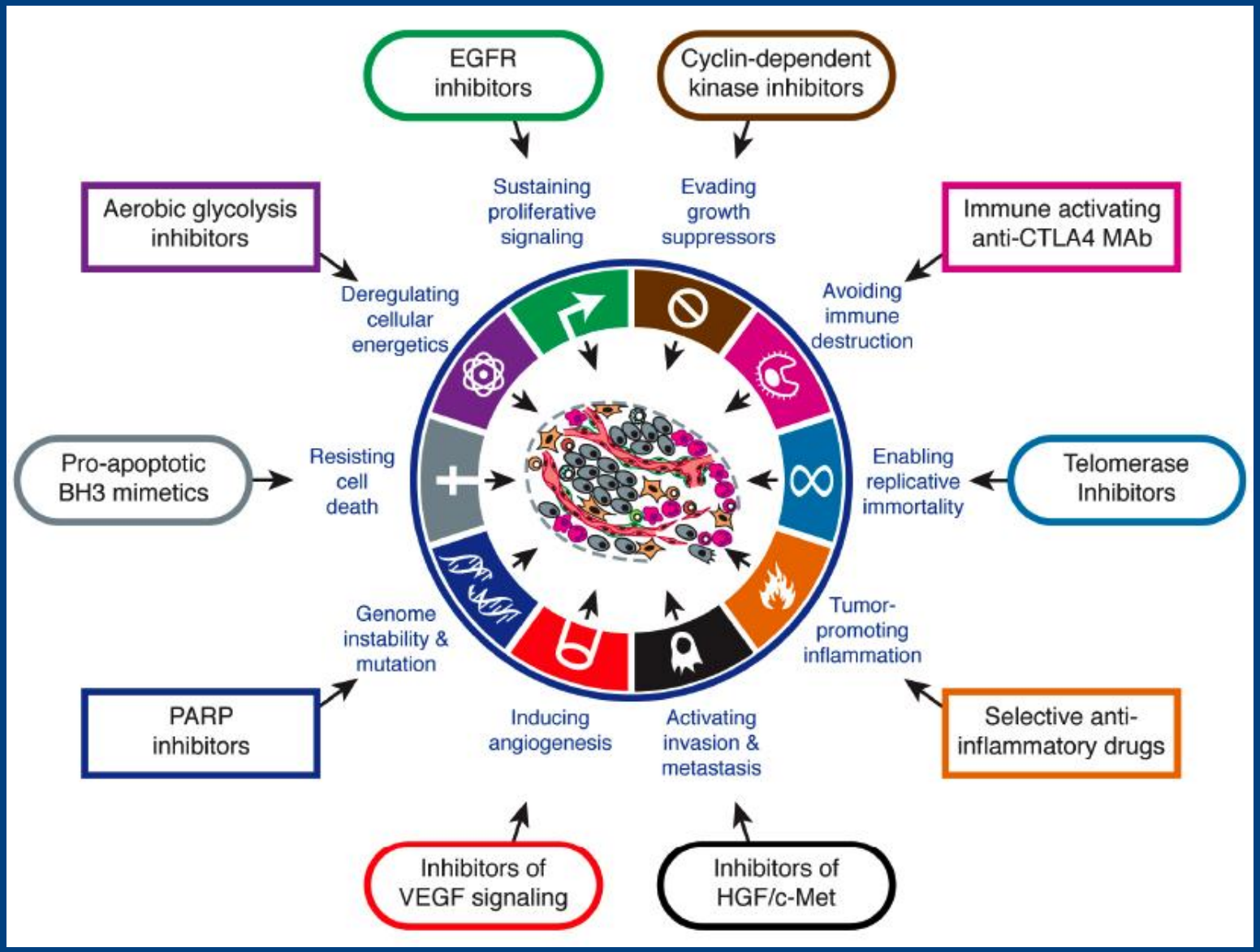


Hallmarks of Cancer:

Applications to Cancer Medicine?

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

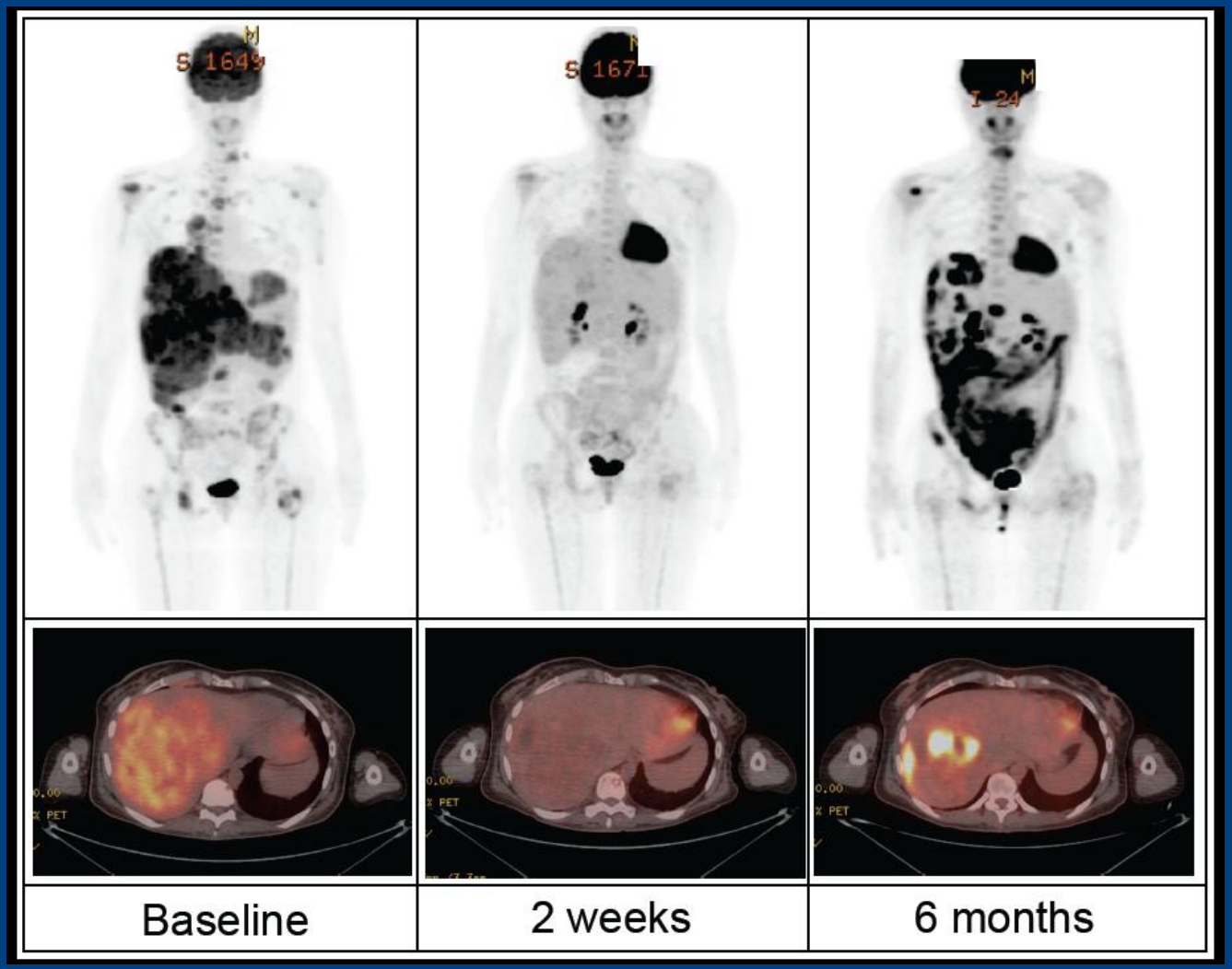
Therapeutic applications: all of the hallmarks are being targeted



The reality check: Targeting individual hallmark capabilities is not working so well

Typically, therapeutic targeting of individual hallmark capabilities produces initial responses and clinical benefit, followed by relapse to progressive disease

Remarkable, but often transitory responses in patients with metastatic melanoma treated with the B-Raf inhibitor vemurafenib



Finn et al
BMC Medicine
2012

Targeting individual hallmark capabilities is not working so well

including:

vemurafenib

erlotinib, et al

bevacuzimab

sunitinib, sorafenib, et al

One line of approach

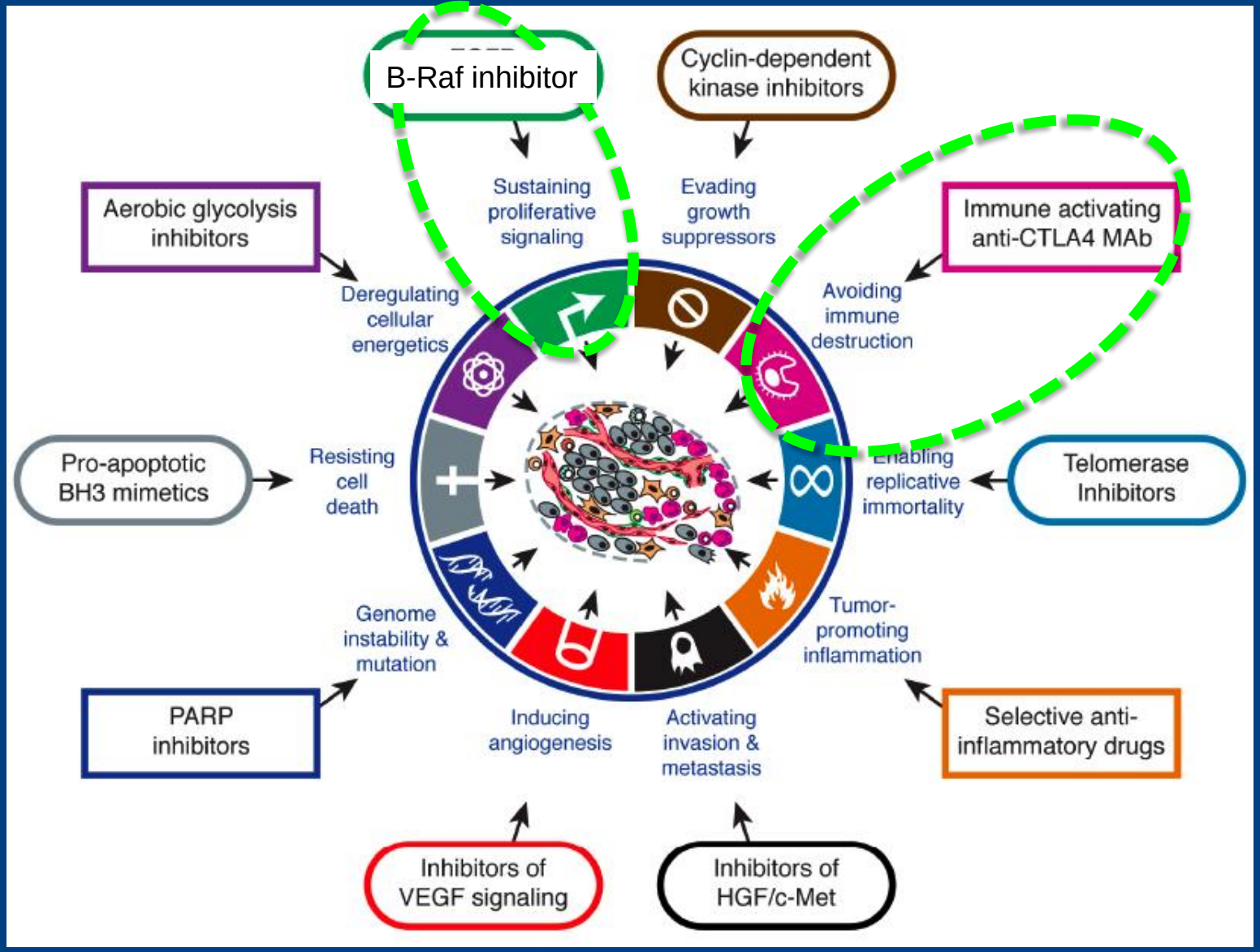
Hitting individual hallmarks even harder, at multiple nodes

An alternative approach

Co-targeting multiple hallmarks

Perhaps, by co-targeting multiple hallmarks, it will be more difficult for tumors to adapt, resulting in more enduring responses

For example, combining vemurafenib and ipilimumab in melanoma – clinical trials are ongoing



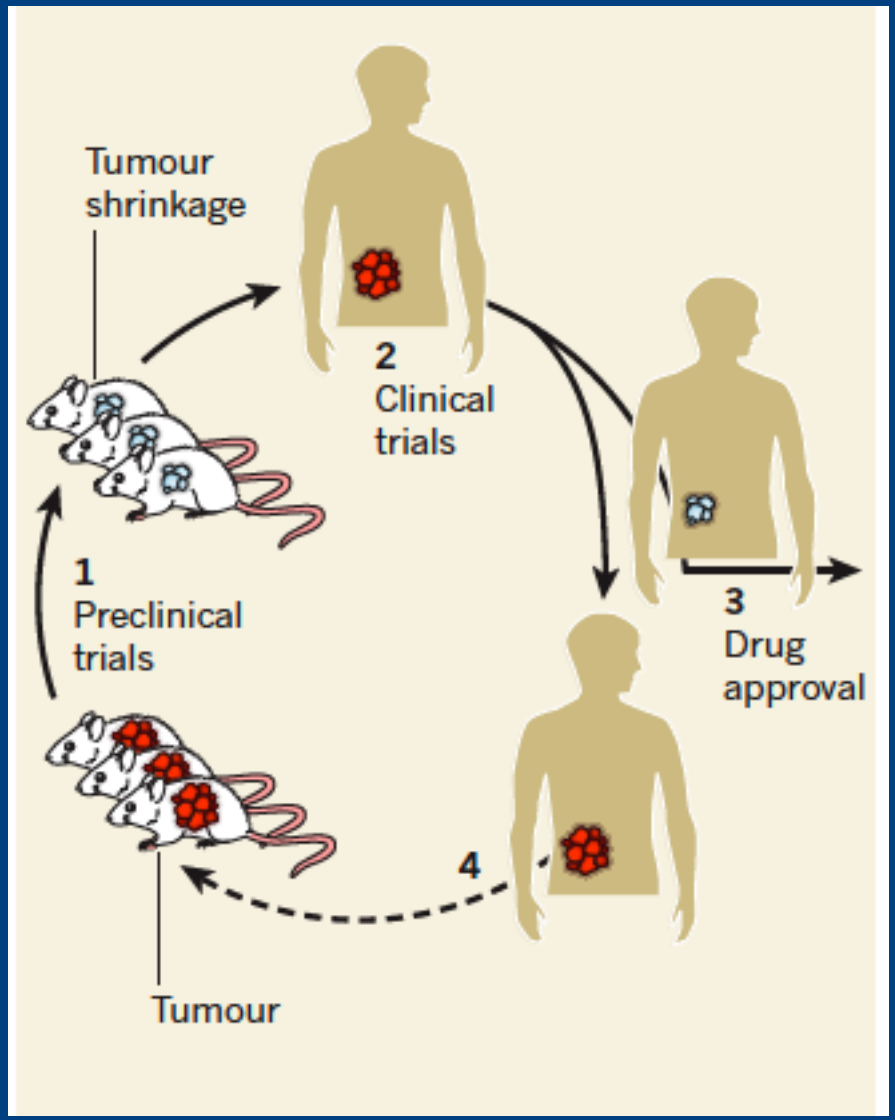
Exploring hallmark multi-targeting using mouse models of human cancer

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

- Mouse models of human cancer are increasingly being used to test new cancer therapies

Using mouse models in pre-clinical trials to guide clinical trials

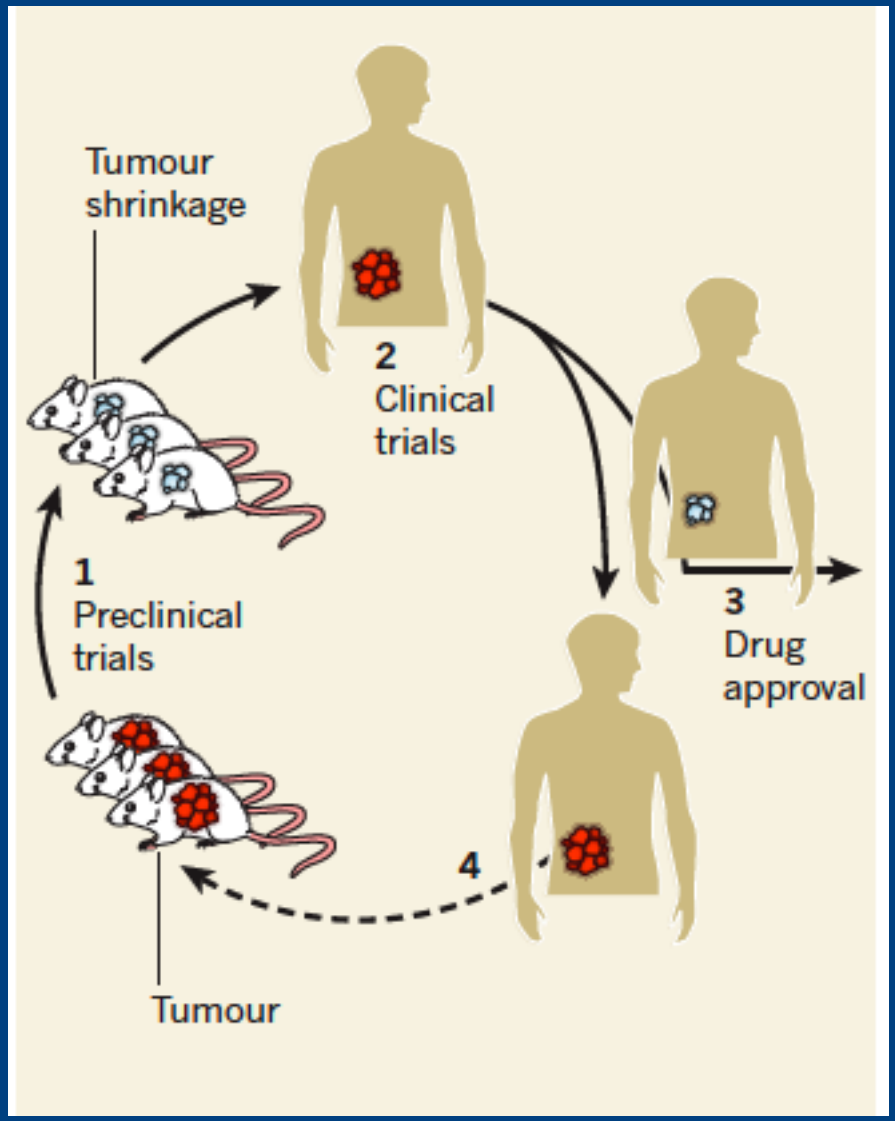
(1) **Pre/Co-clinical trials in mice modeling a human cancer**



Tuveson & Hanahan 2011

(2) Efficacy in mouse model motivates clinical trials

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



Tuveson & Hanahan 2011

Interspecies Translational Therapeutic Oncology

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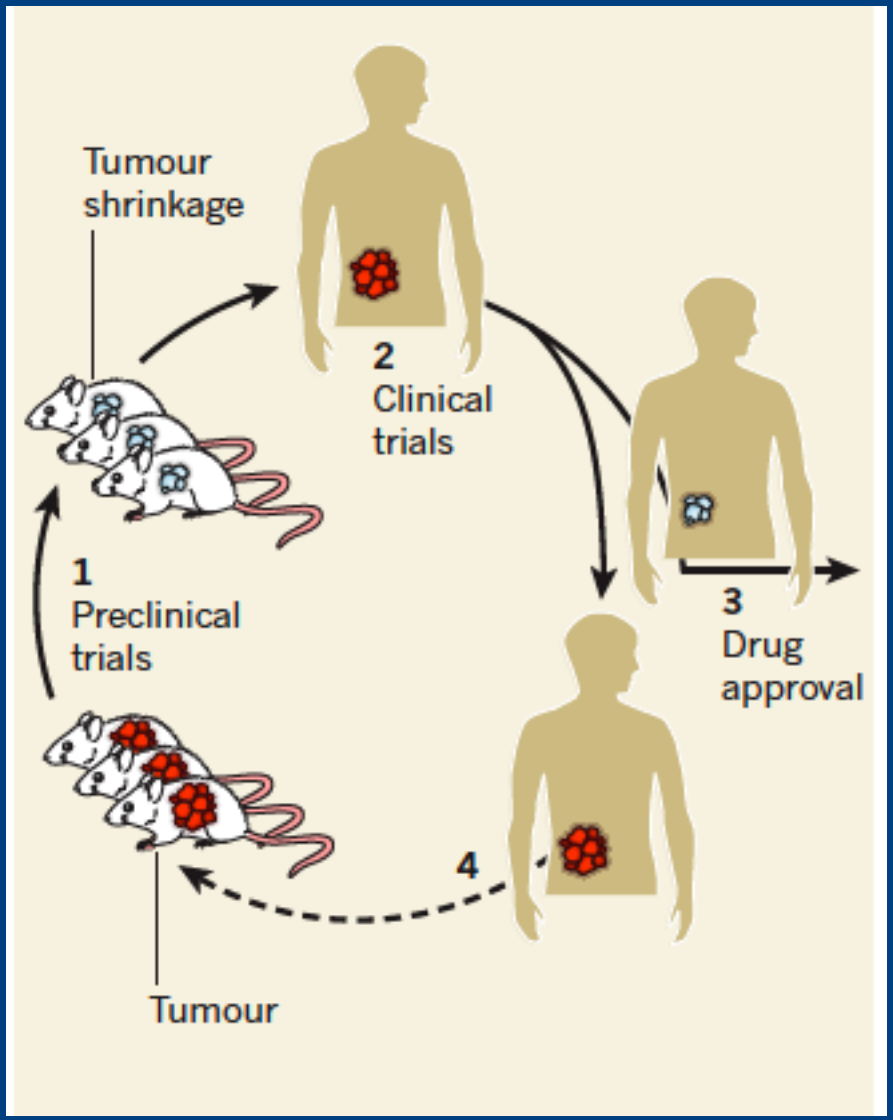
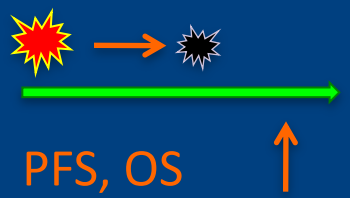


(3) Positive clinical results support drug approval,



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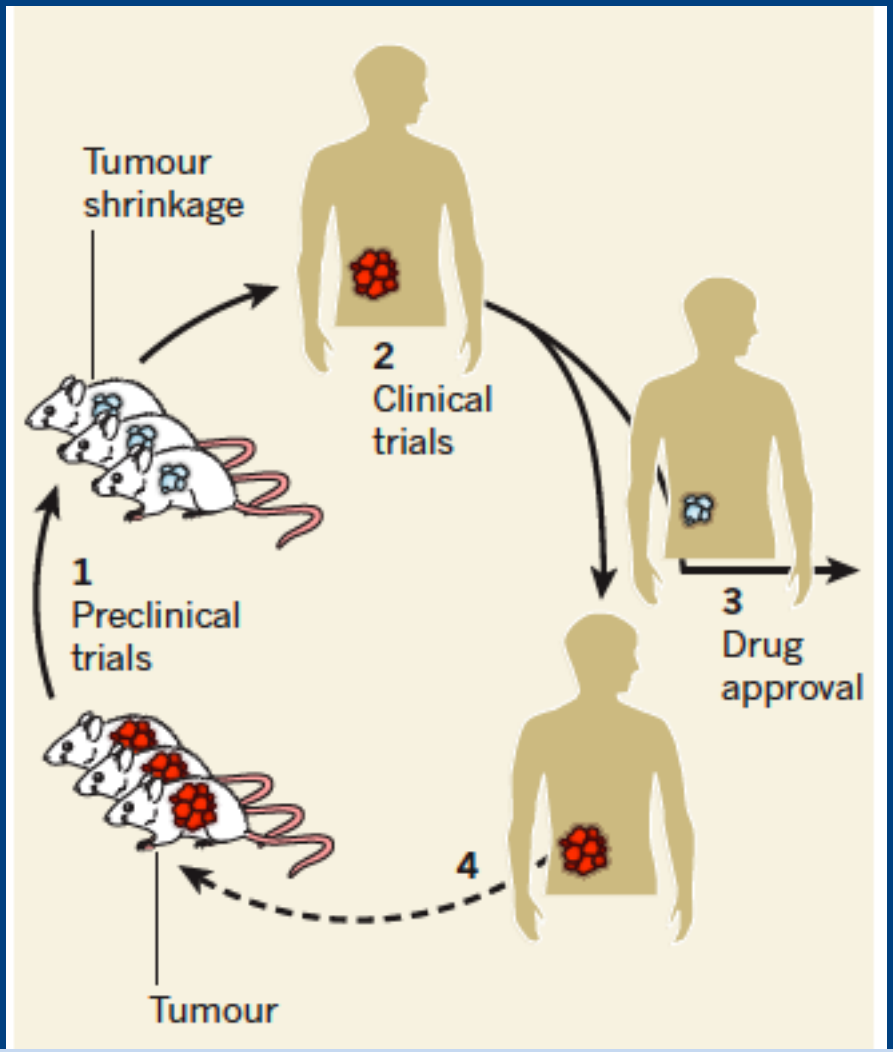

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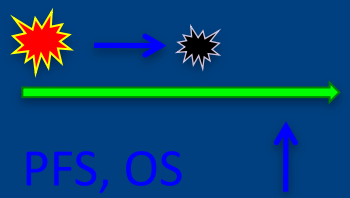


e.g. in PNET:
- everoimous
- sunitinib

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

Tuveson & Hanahan 2011

A case study in PNET

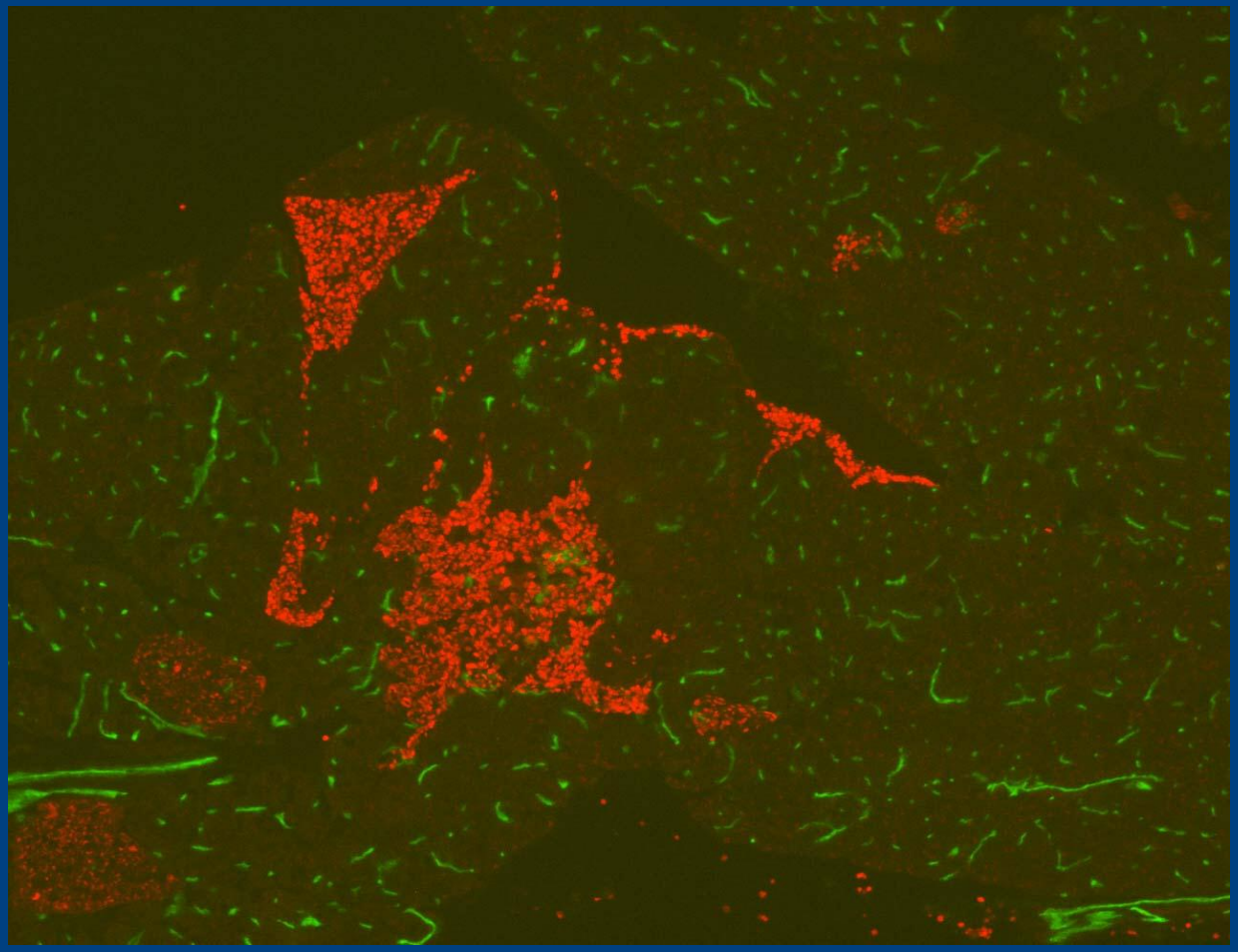
- Preclinical trials in a mouse model of human PNET predicted clinical benefit of sunitinib and rapalogs, and have motivated clinical trials in this tumor type

- Sunitinib and everolimus are the first new drugs approved by the FDA and European regulatory agencies for treating human PNET in 25 years

- *But, in both mouse and human PNET, the responses are limited in duration*

Adaptive – Evasive Resistance

Tumors in sunitinib-treated PNET mice become more invasive, growing diffusely by co-opting normal tissue vessels



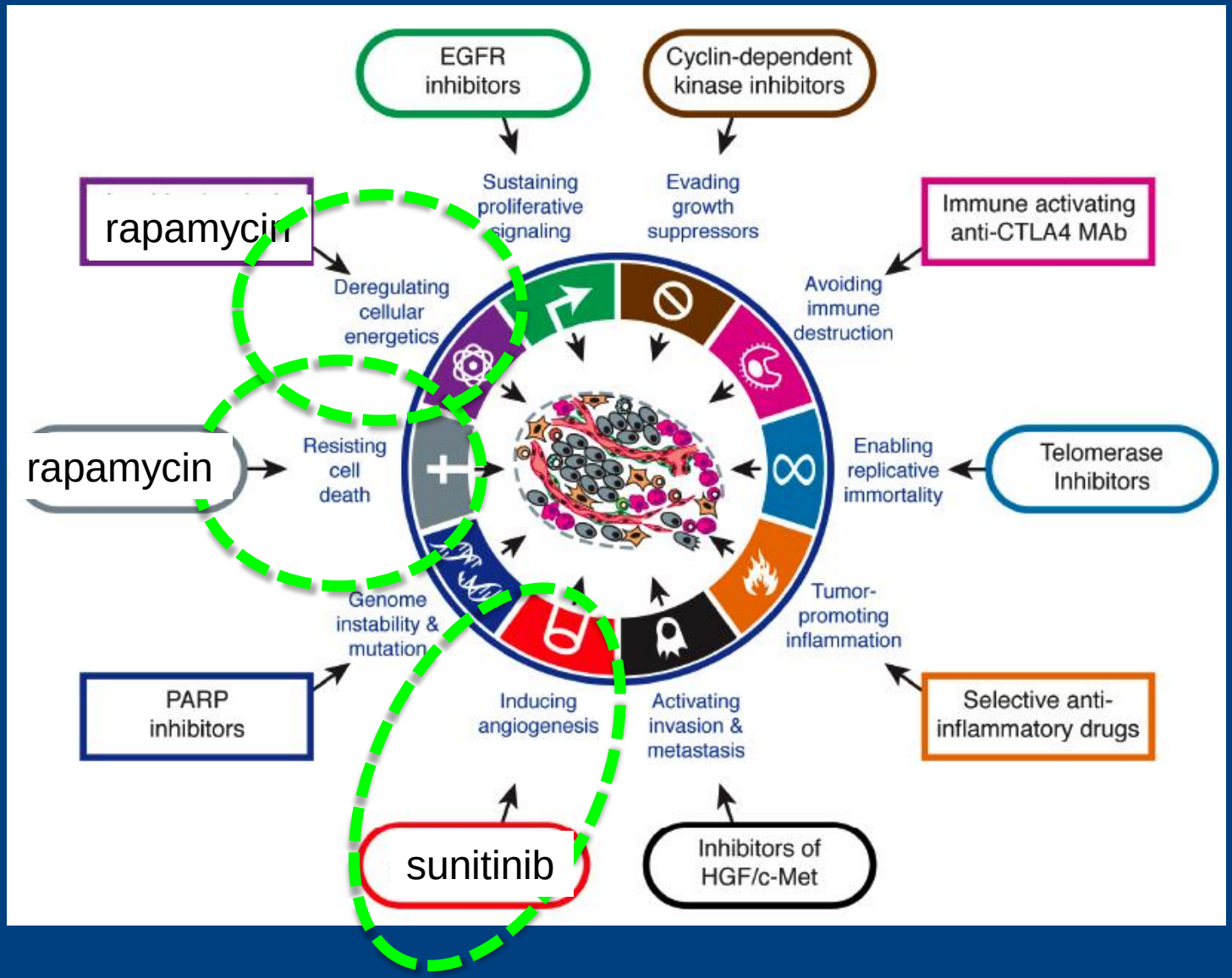
Red – Tag Oncoprotein Green – FITC-Lectin

Initial efficacy, followed by development of adaptive/evasive resistance to anti-angiogenic therapy

Angiogenesis inhibitors evoke adaptive resistance mechanisms, including

- revascularization mediated by other proangiogenic growth factors
- perivascular accumulation of proangiogenic myeloid cells
- heightened invasion and metastasis (hallmark switching)

An e.g. from the Hanahan lab: co-targeting angiogenesis and resistance to apoptosis (& metabolism?)

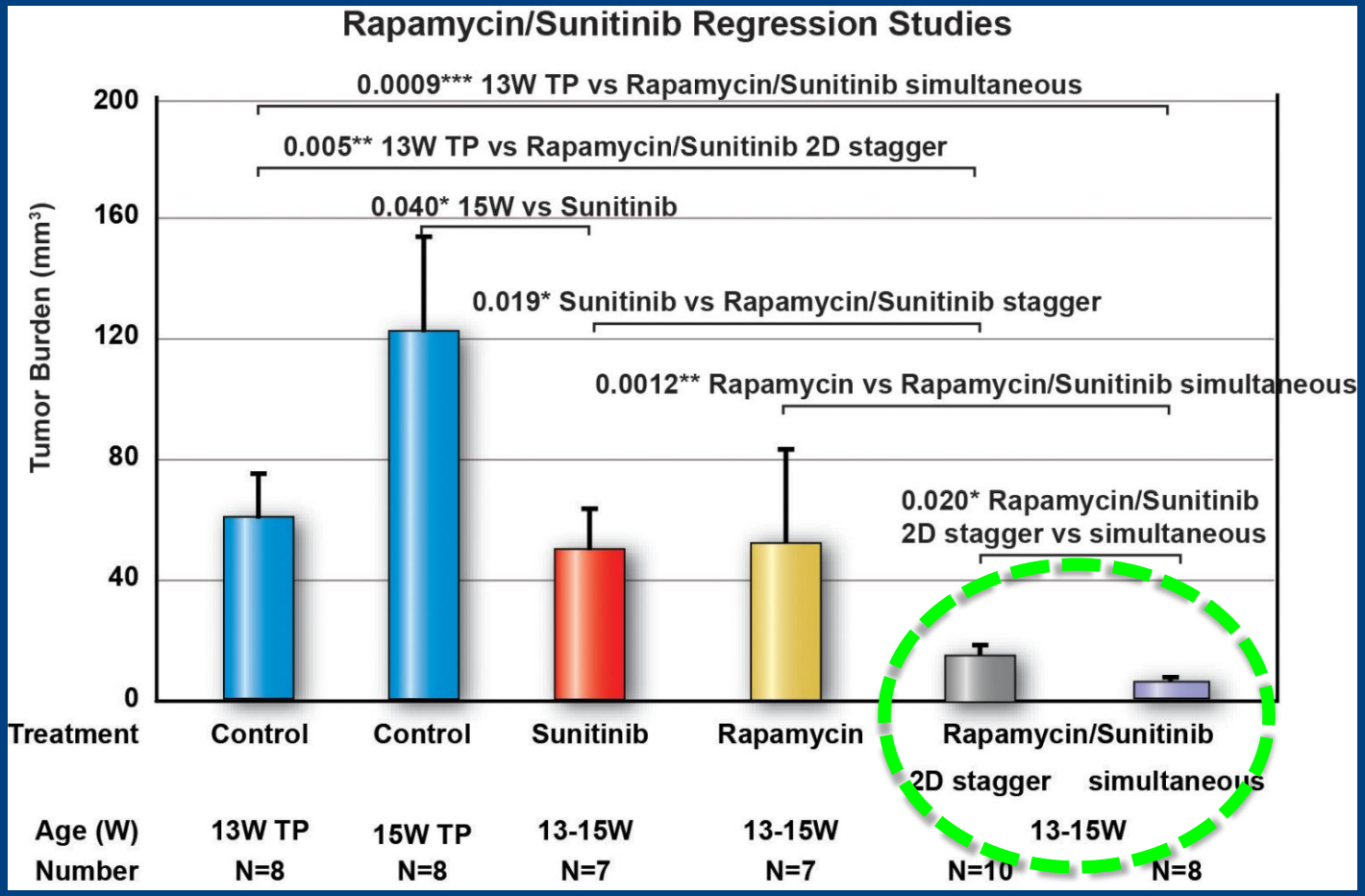


Rationale for a hallmark co-targeting strategy

- Sunitinib targets the angiogenic hallmark
- The mTOR inhibitor rapamycin targets the cancer cells in this tumor type (PNET), increasing apoptosis (and possibly impairing metabolic reprogramming)

Preclinical trials to assess the combination

Defined-endpoint Regression Trial



Status and implications of the preclinical trials

- In a defined endpoint ("Regression") trial, the combination has added benefit with no short term toxicity issues

- Survival trials are showing modest benefit – perhaps limited by longer-term sunitinib toxicity –> switch to a second generation VEGFRi such as axitinib or tivozanib?

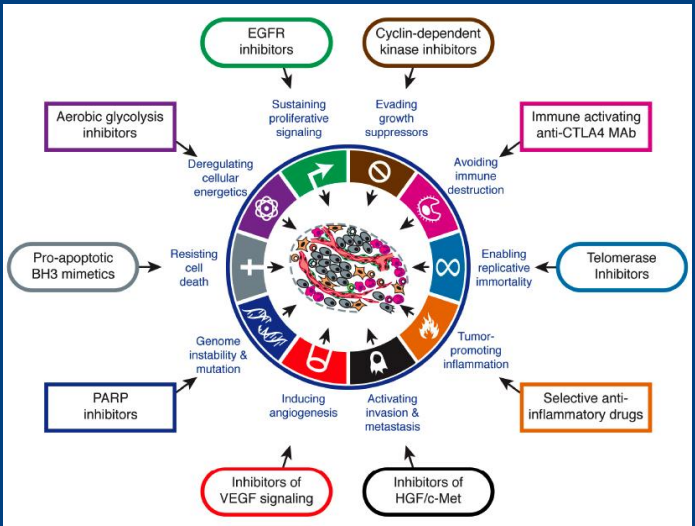
Acknowledgements – Unpublished Results

Liz Allen Hanahan Lab, ISREC@EPFL

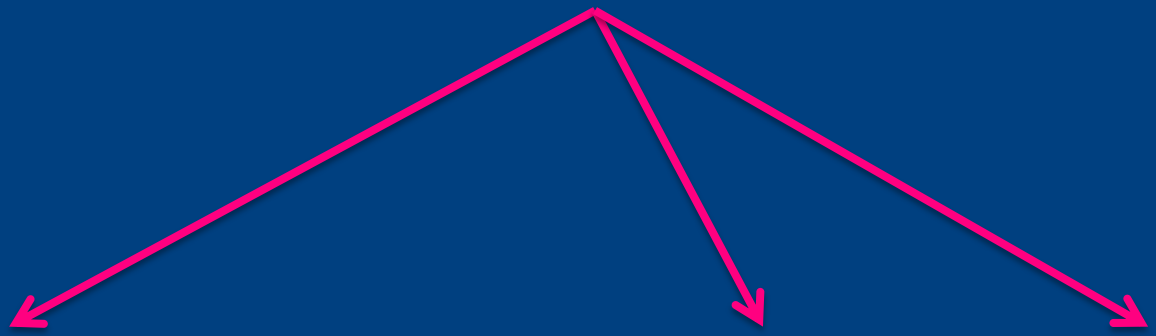
Hallmarks of Cancer:

Applications to Cancer Medicine?

- The hallmarks concept is helping to integrate ostensibly diverse mechanisms of cancer
- There may be value in applying the conceptual framework to treating human cancers



An aside: we are developing a new multi-institutional cancer center in Lausanne



ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

CHUV

UNIL | Université de Lausanne

ISREC @EPFL
INSTITUT SUISSE DE RECHERCHE EXPÉRIMENTALE SUR LE CANCER

canton de vaud

LUDWIG INSTITUTE FOR CANCER RESEARCH

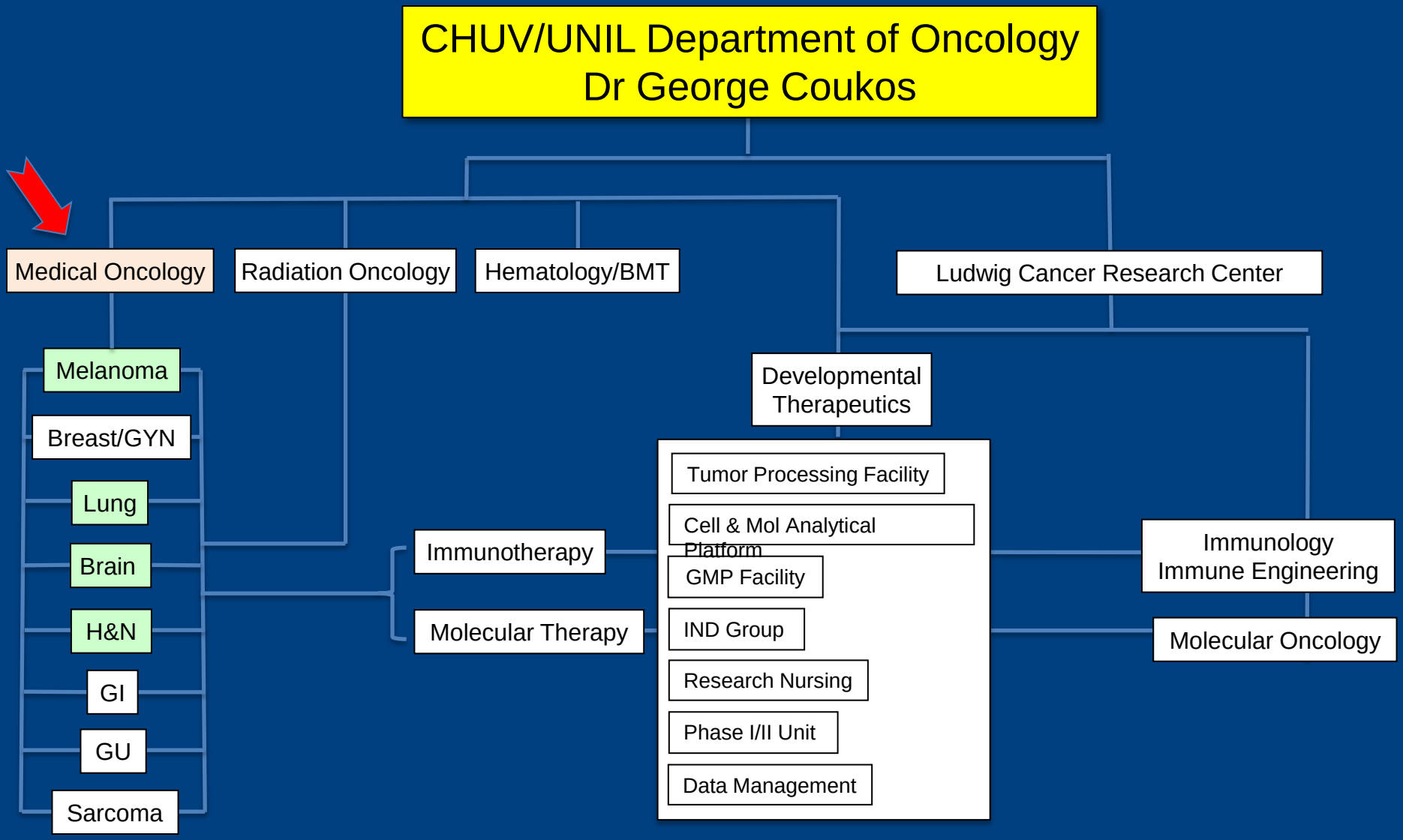
A partnership involving three institutions with complimentary skillsets

- The Cantonal/University Hospital and Medical Research Campus

- The Epalinges/Biopole Bio-Medical Research Campus (Immuno-biology, Cancer, etc)
- The Ludwig Institute Center at UNIL
- The Center of Integrative Genomics (CIG)
- The Swiss Institute for Bioinformatics

- ISREC
- Bioengineering
- Chemistry
- The Center for Biomedical Imaging (joint w/UNIL)

An open position: Division Chief of Medical Oncology



The End

Thank You