

The Inaugural Grace-CERN Lecture CERN Medicis

The daunting complexity of cancer:
Understanding the battlefield is a
step toward winning the war

Douglas Hanahan
ISREC, EPFL

October 15, 2014

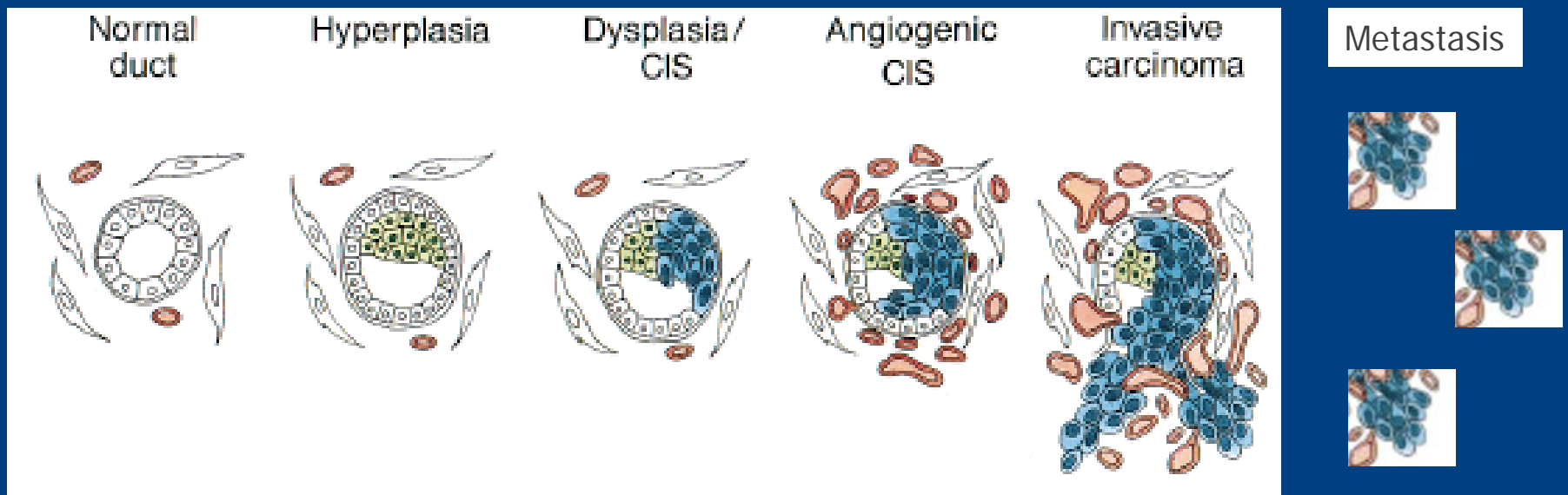


What is Cancer?

Fundamentally, a disease of uncontrolled cell growth, of excessive and chronic expansion of previously well-behaved cells in our bodies

What is Cancer?

Fundamentally, a disease of uncontrolled cell growth, of excessive and chronic expansion of previously well-behaved cells in our bodies



What is Cancer?

Cancer originates from alterations to the DNA of the chromosomes - mutations in genes

'Cancer cells' or 'tumor cells' have altered programs that cause them to stop performing their duties as members of societies of cells in the organs of our bodies

Instead they become outlaw cells re-programmed for proliferative expansion

What is Cancer?

Arises in dozens of organs and cell types in the body

Multiple subtypes of organ-specific cancers

Hundreds of different genetic aberrations can drive tumor growth

Dizzying genomic disarray and histological variety

What is Cancer?

Remarkably diverse severity and pathogenic consequences for an affected individual

Disconcertingly transitory therapeutic benefits for many forms of human cancer

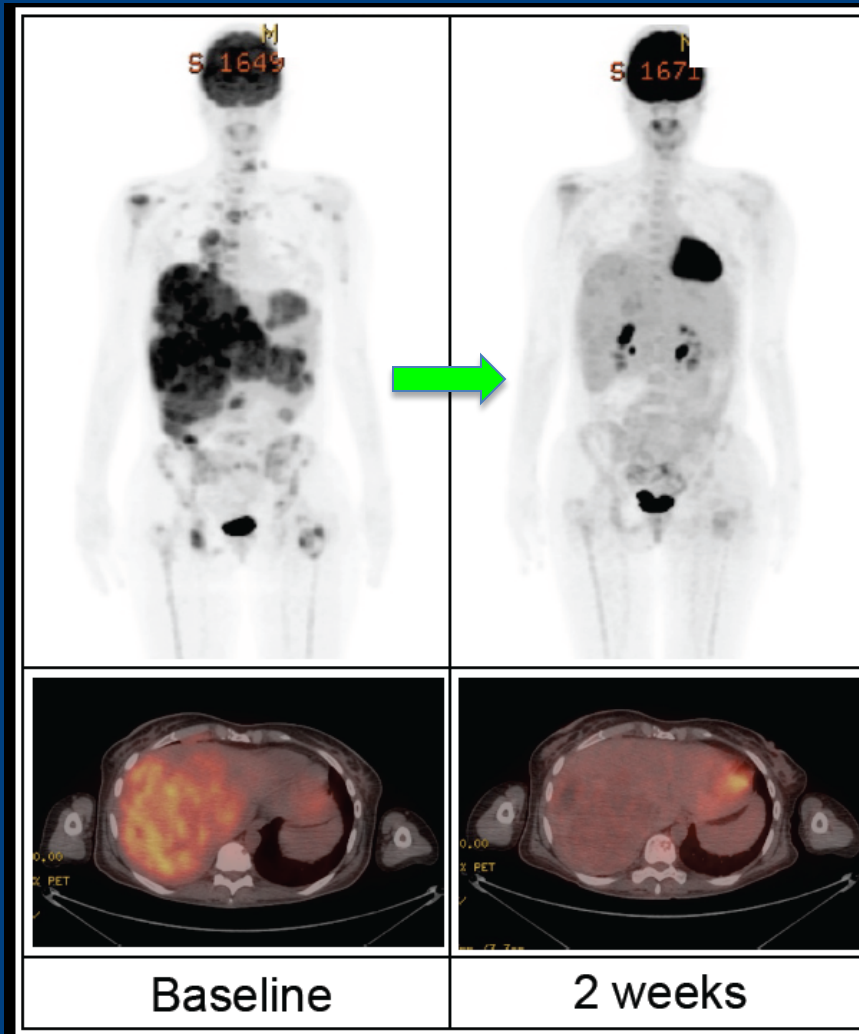
For example:
Melanoma, an often deadly
form of skin cancer



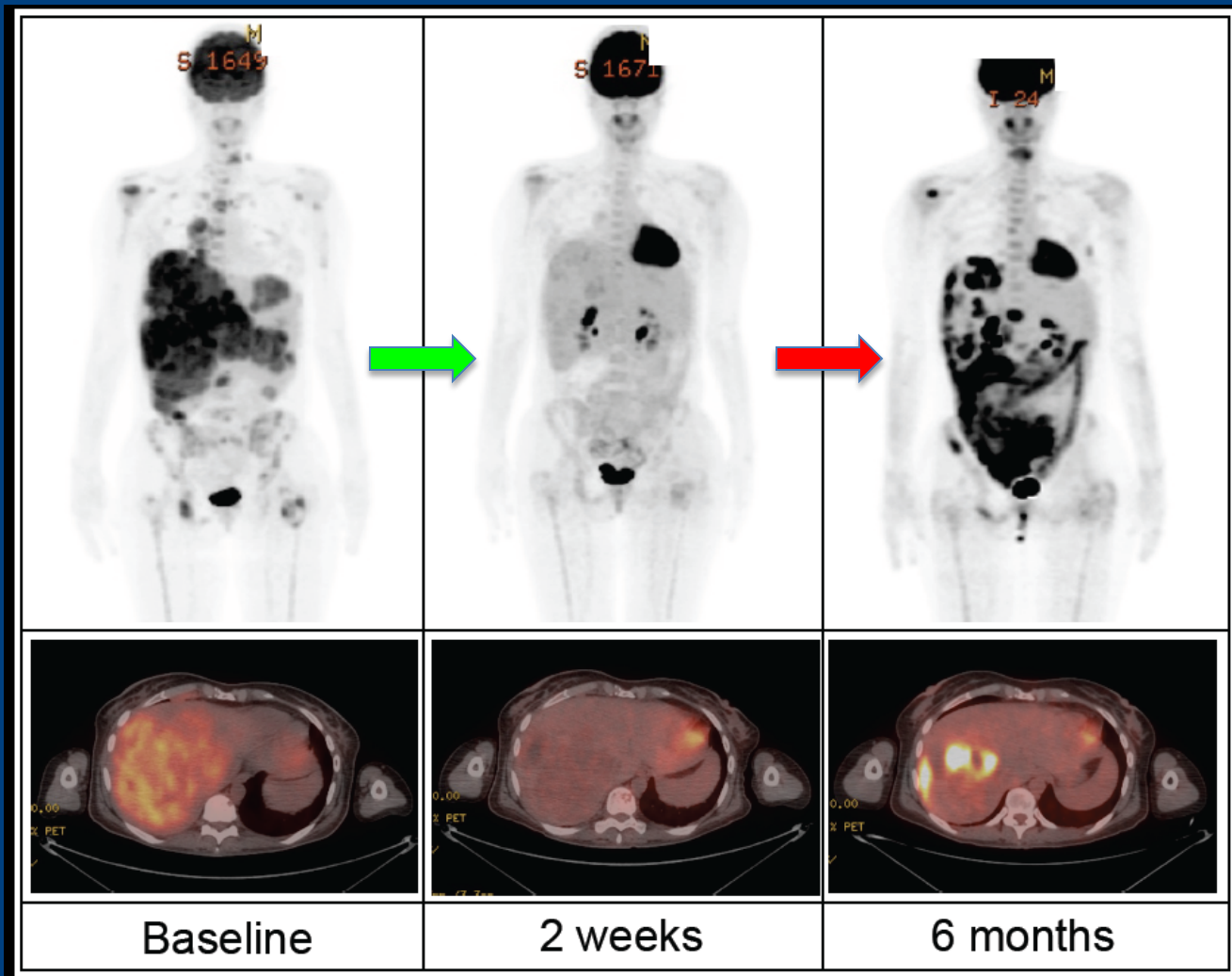
Melanoma becomes deadly when it metastasizes throughout the body



A new drug, a targeted (smart) therapy, melts the tumors away!



The amazing cure is transitory:
in 6 months, the tumors are back, with a vengeance



What is Cancer?

Cancers develop and become increasingly aggressive in a form of Darwinian evolution, which selects for those cells that are fittest at 'illegal' expansion

Most cancers consist of mass assemblages of cancer cells (and other cells) called 'tumors'

What is Cancer?

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

What is Cancer?

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

How can we rationalize this complexity?

Are there common principles underlying this daunting diversity?

A hypothesis for rationalizing the complexity of cancer

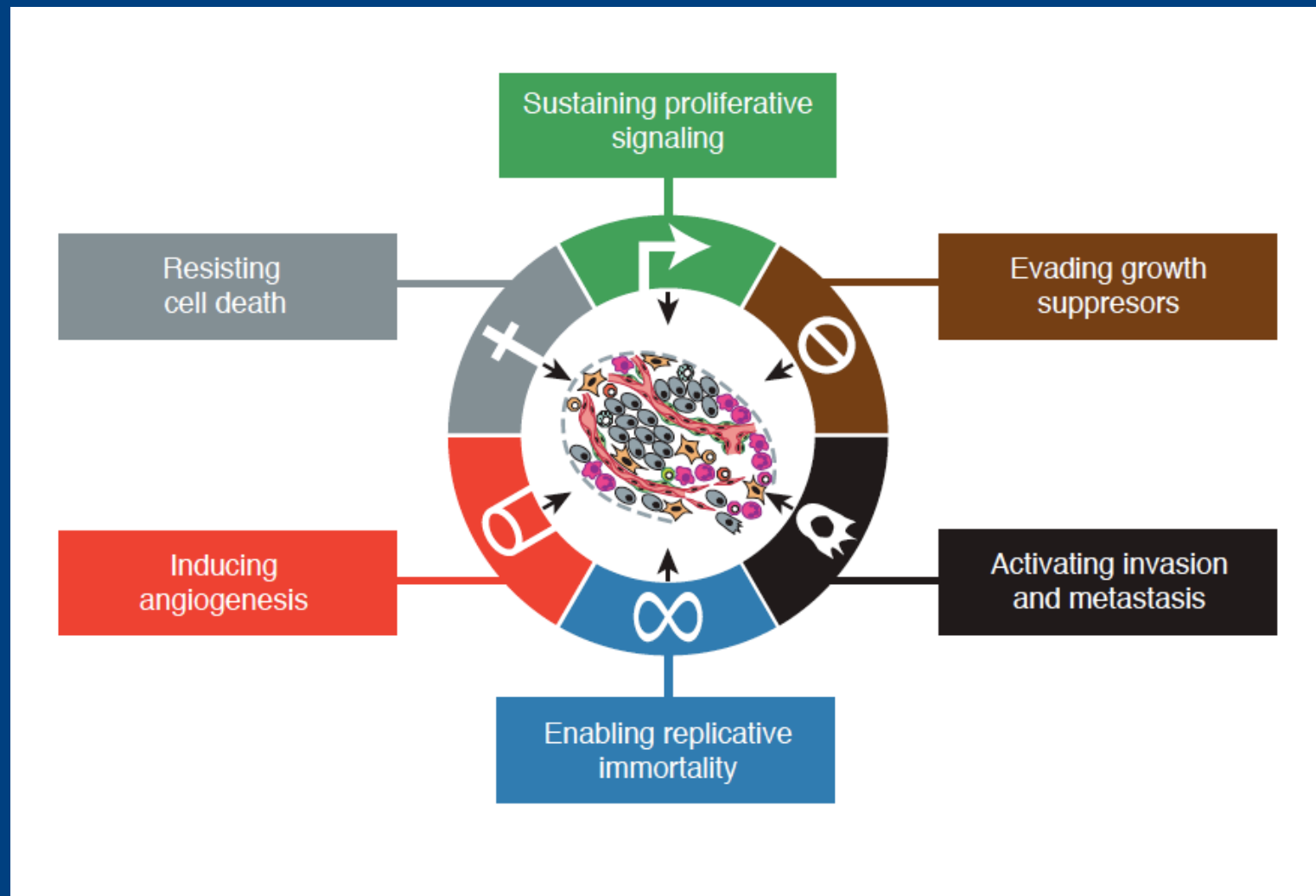
- Disparate cancers share fundamental qualities

A hypothesis for rationalizing the complexity of cancer

- Disparate cancers share fundamental qualities
- This daunting complexity merely reflects different solutions to the same challenge:

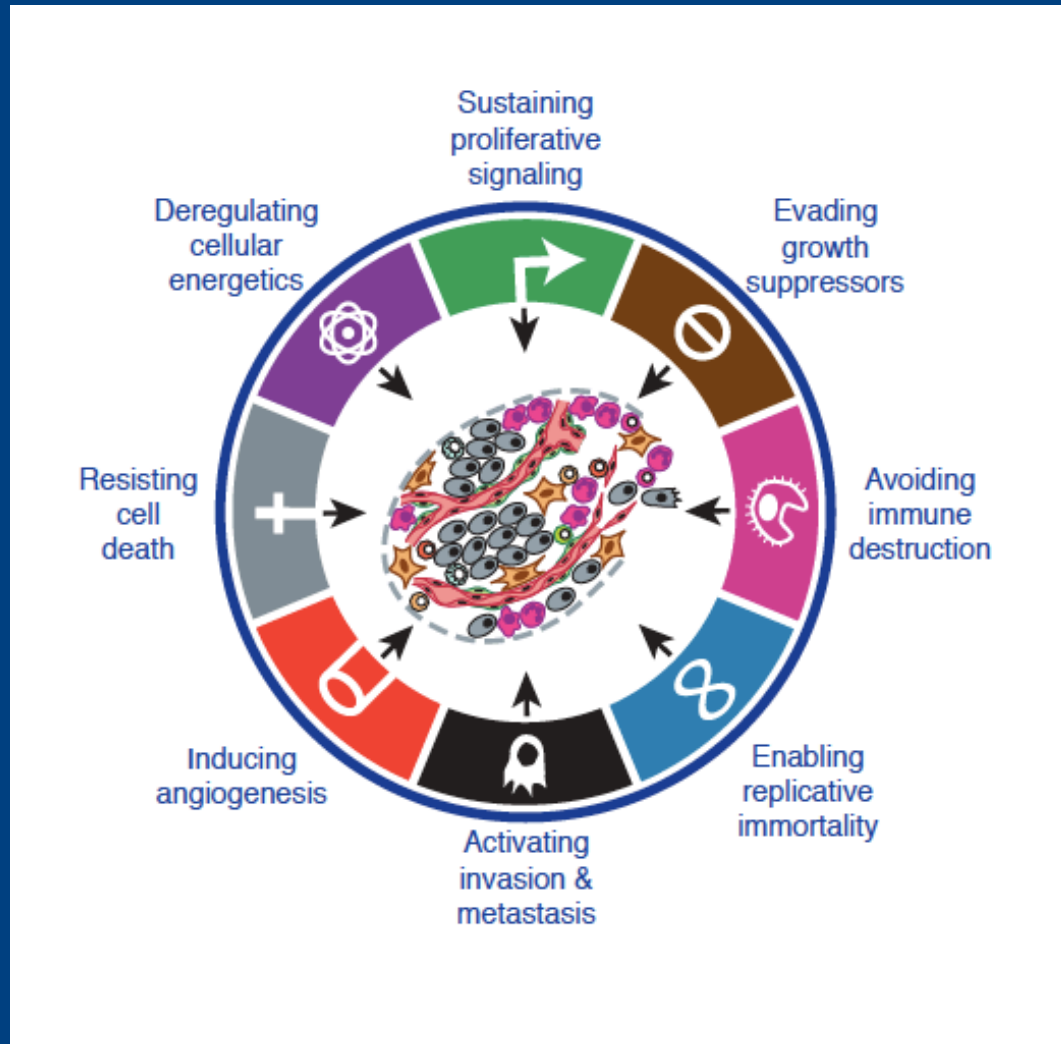
cancer cells must surmount multiple barriers and roadblocks used by the organism to prevent expansive cell proliferation, some of which differ from organ to organ

A hypothesis for rationalizing the complexity of cancer



Posed by Douglas Hanahan and Robert Weinberg in 2000

The Hallmarks of Cancer



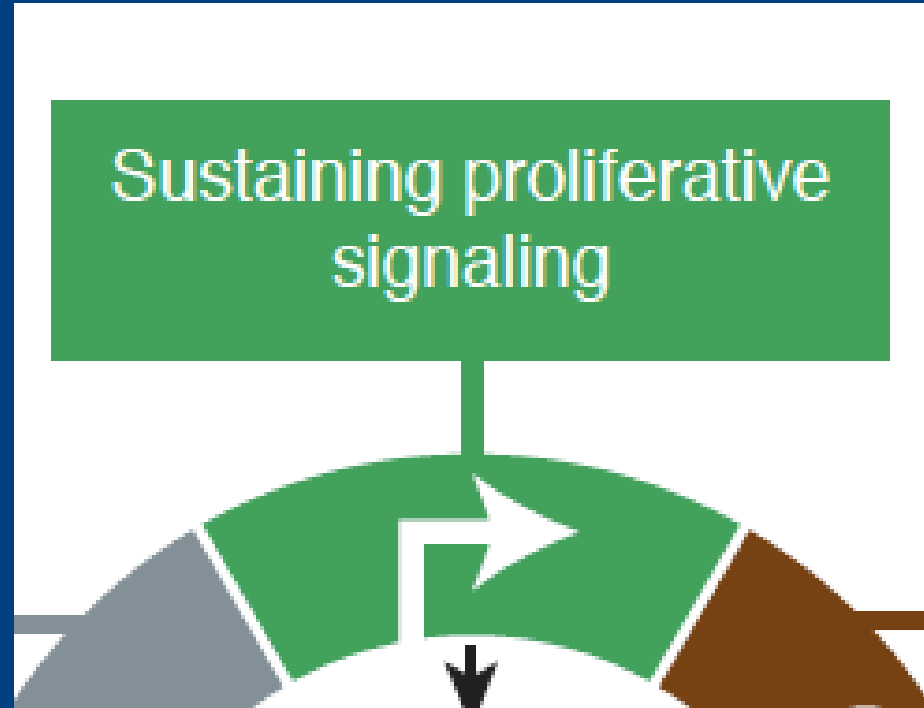
As refined by Douglas Hanahan and Robert Weinberg in 2000

What are hallmarks of cancer?

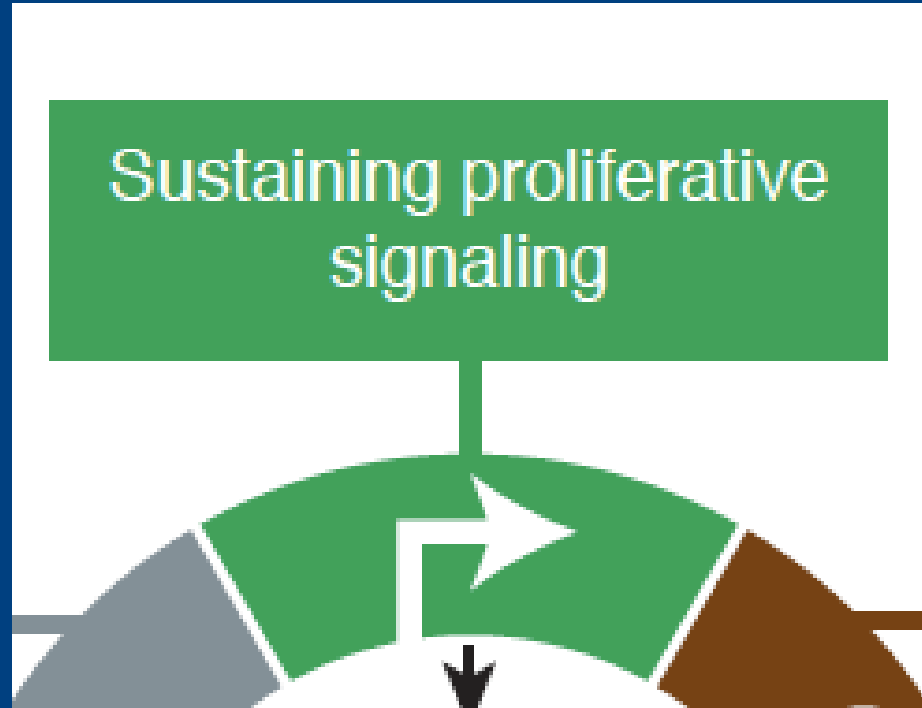
The hallmarks are **8** acquired functional capabilities, that allow tumors to

- *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

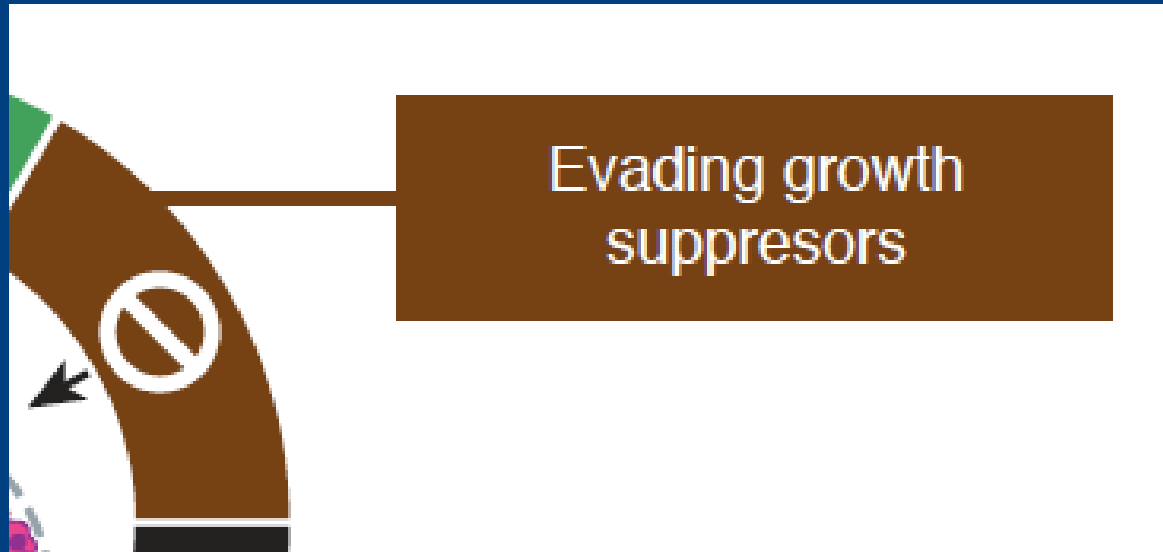


The first hallmark

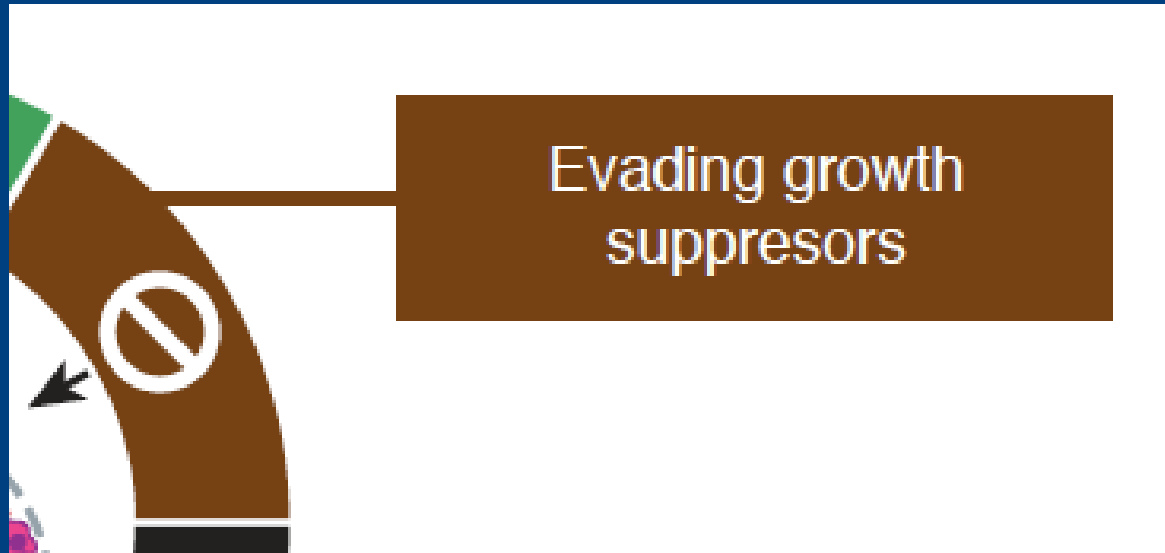


The accelerator => full speed ahead;
signals instruct cells to grow and divide chronically

The second hallmark



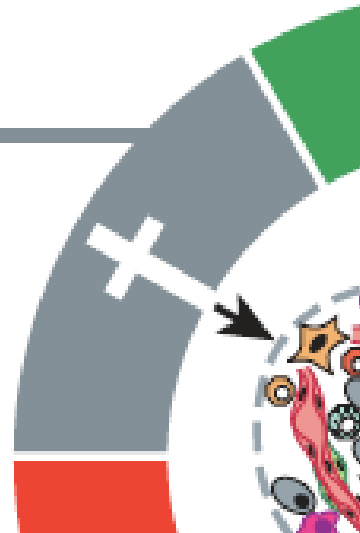
The second hallmark



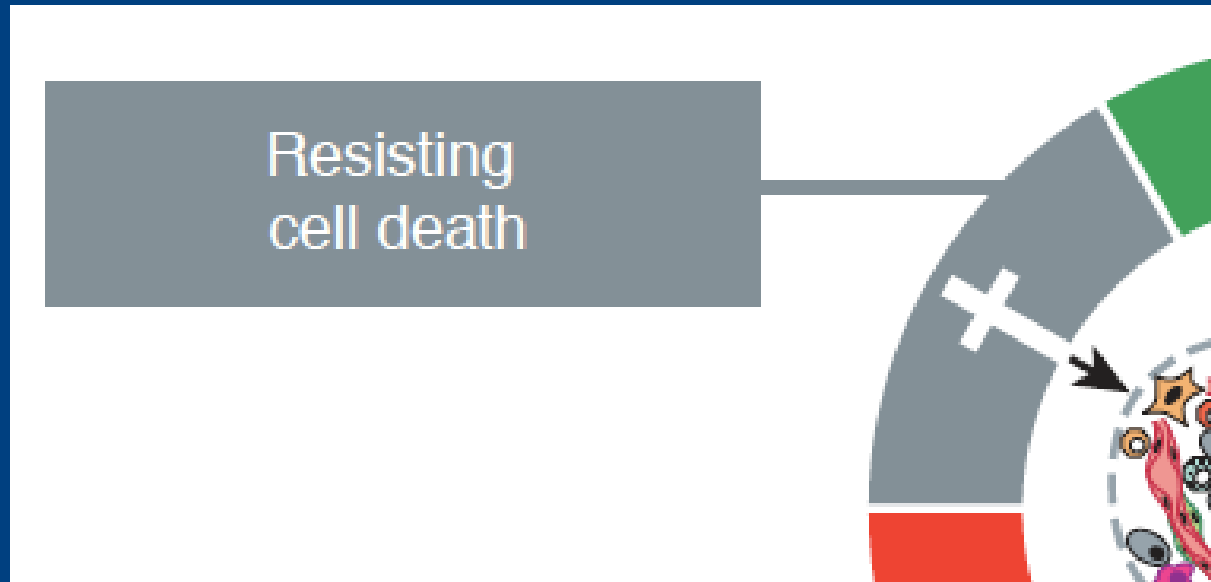
The brakes have failed; signals to STOP are disabled

The third hallmark

Resisting
cell death

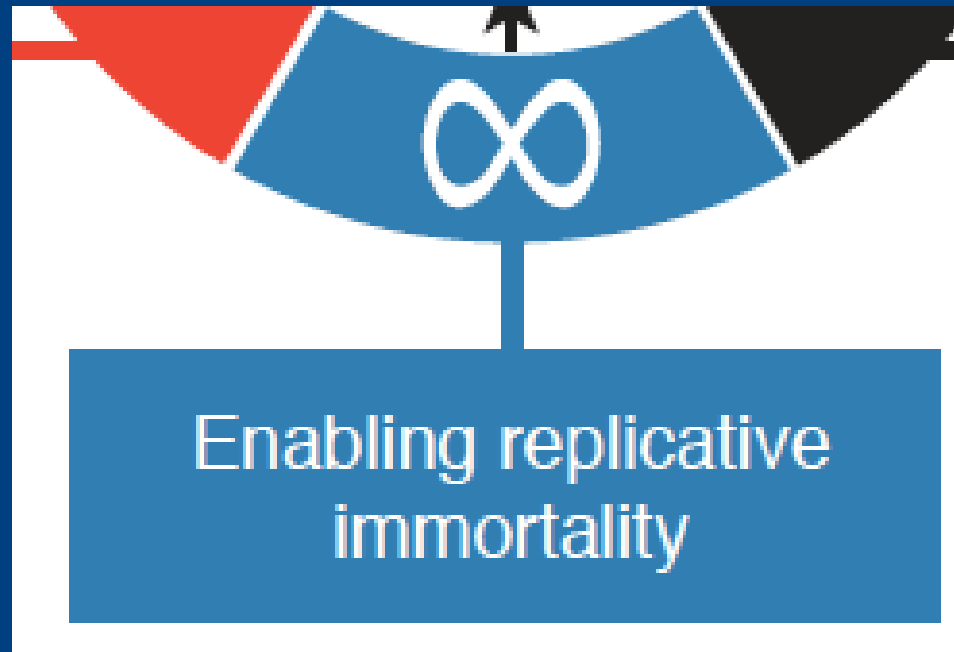


The third hallmark



Avoiding assisted suicide of outlaw cells;
abrogation of the inborn willingness of cells to die
for the benefit of the organism

The fourth hallmark



The fourth hallmark



Circumventing a counting mechanism that disrupts continuing cell division when a set limit is reached

The fifth hallmark

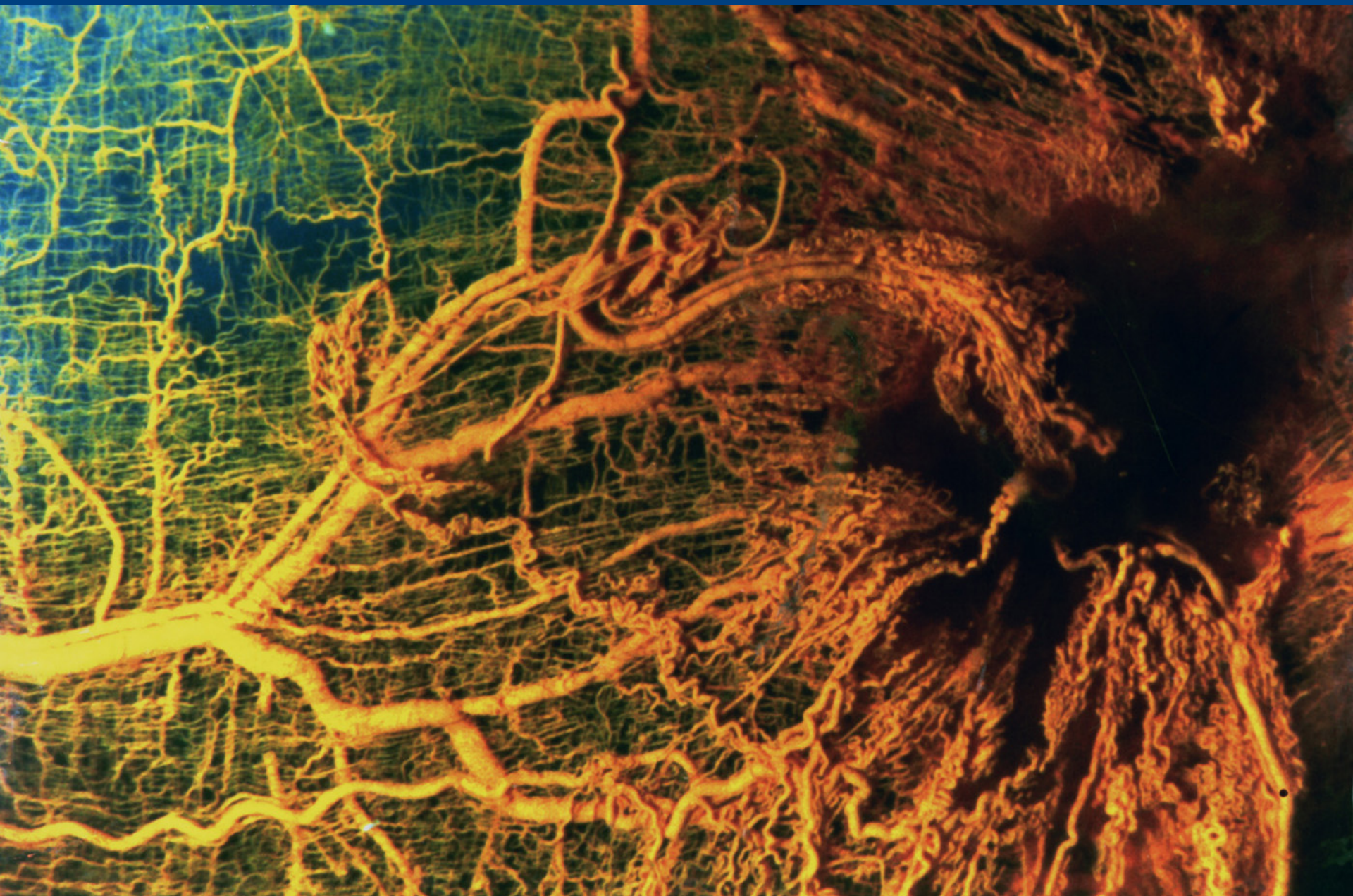
Inducing
angiogenesis



The fifth hallmark



Turning on new blood vessel growth, to feed and nurture the growing mass of cancer cells



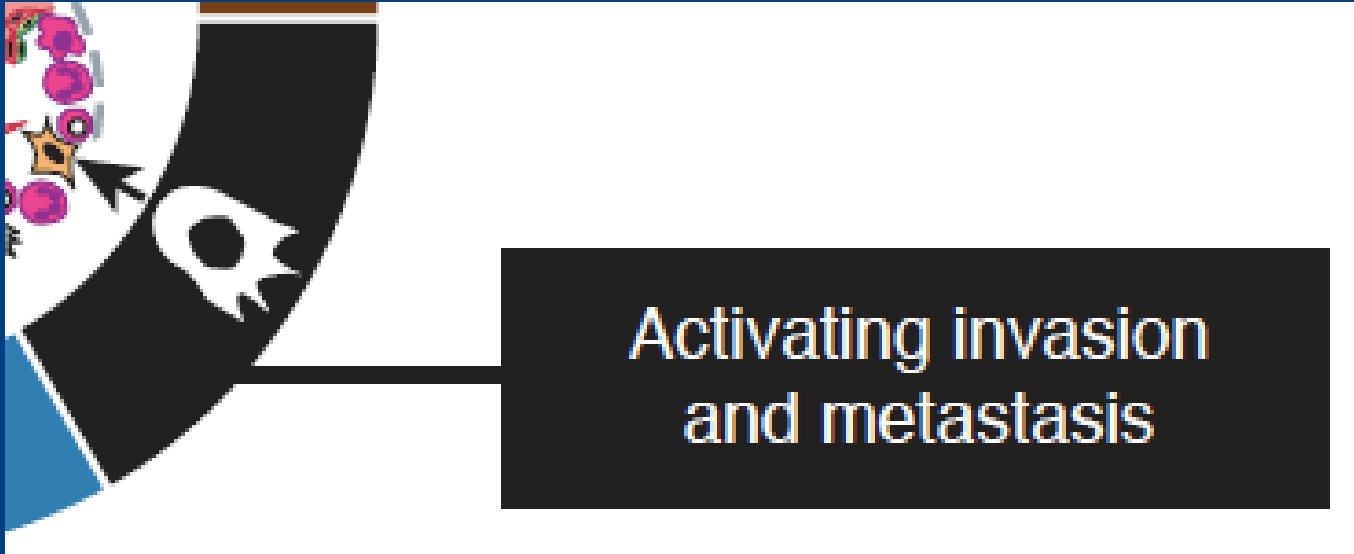
*Louis Heiser and Robert Ackland
University of Louisville School of Medicine*

The sixth hallmark



Activating invasion
and metastasis

The sixth hallmark



Guerilla cells that growing by migrating and invading into normal organs, locally and throughout the body, 'living off the fertile land'

The seventh hallmark

Deregulating cellular energetics



In 2011, an emerging hallmark

Deregulating cellular energetics

A diagram showing a pie chart with several segments. One segment is highlighted in purple and contains a white atomic symbol. A black arrow points from this segment to a callout box on the left. The callout box is purple with white text that reads "Deregulating cellular energetics".

Alternative energy sources - hybrid engines - tapped to provide fuel for cell growth; engines that also produce ample supplies of the cellular building blocks needed to generate new cancer cells

The eighth hallmark



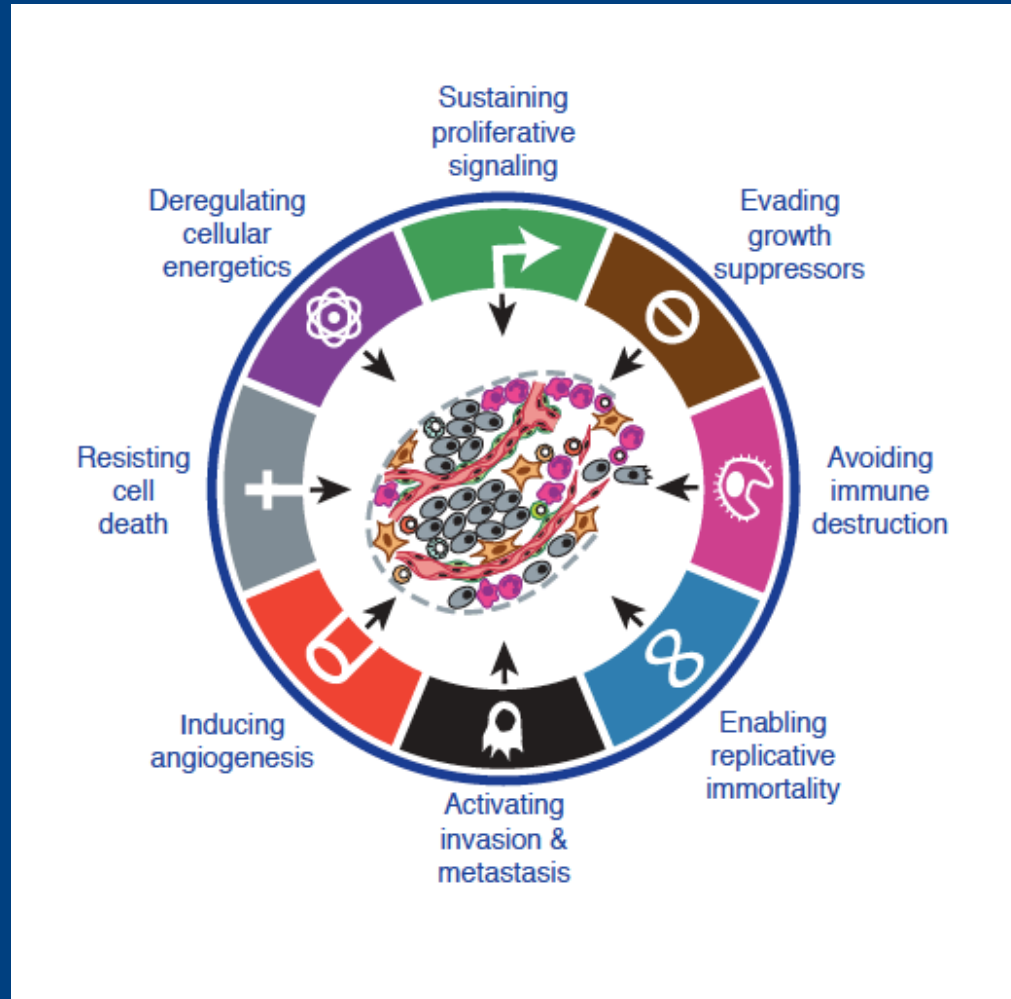
The eighth hallmark



In some cases, the immune system detects a problem and tries to kill cancer cells, an attack which lethal tumors learn to circumvent

The hypothesis:

These 8 hallmarks are sufficient to generate a lethal cancer



How are these hallmark capabilities acquired?

How are these hallmark capabilities acquired?

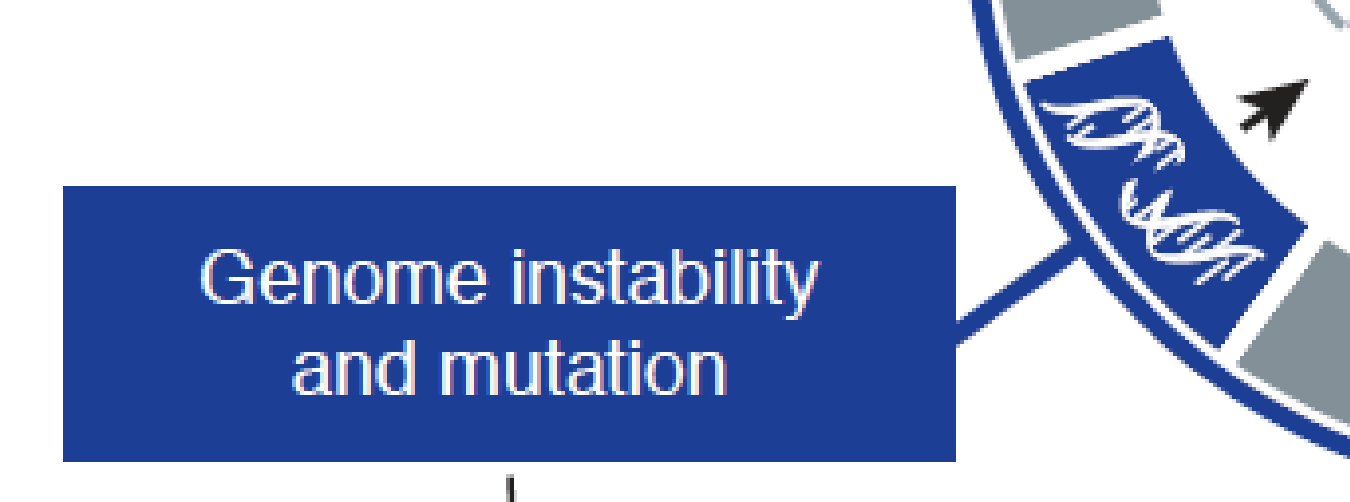
Via Enabling Characteristics

The key enabling characteristic for acquiring hallmarks

Genome instability
and mutation



The key enabling characteristic for acquiring hallmarks



Genome instability
and mutation

Failure of crucial teams of proteins that protect the DNA of the genome from being corrupted, rearranged, damaged;
the result is mutations that convey on cancer cells hallmark capabilities

A 2nd enabling characteristics for acquiring hallmarks



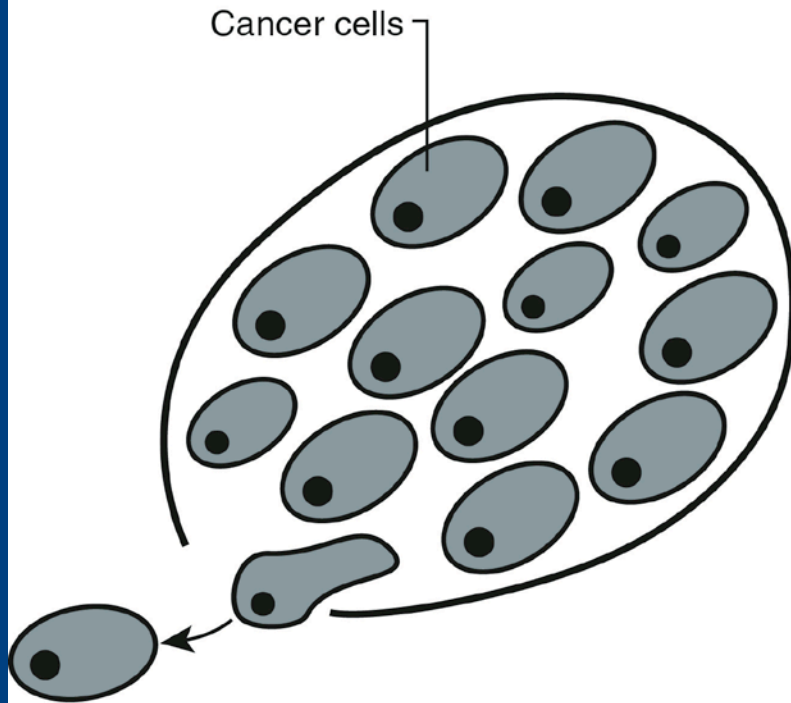
A 2nd enabling characteristics for acquiring hallmarks



Tumors are “wounds that don’t heal”;
Immune cells that normally participate in wound healing inadvertently help cancer cells acquire hallmark capabilities & become more aggressive

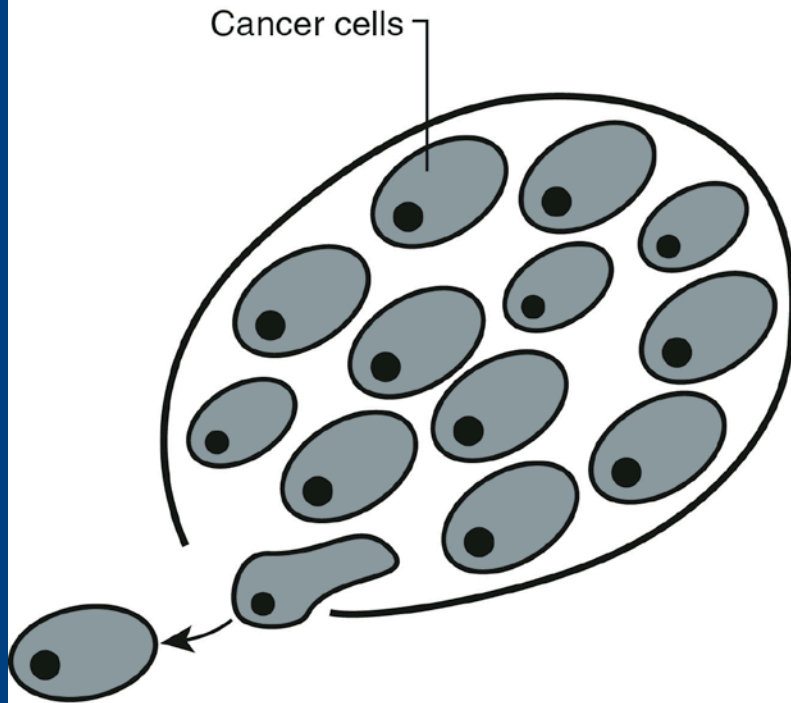
Another key concept: tumors are not bags of cancer cells!

The Reductionist View

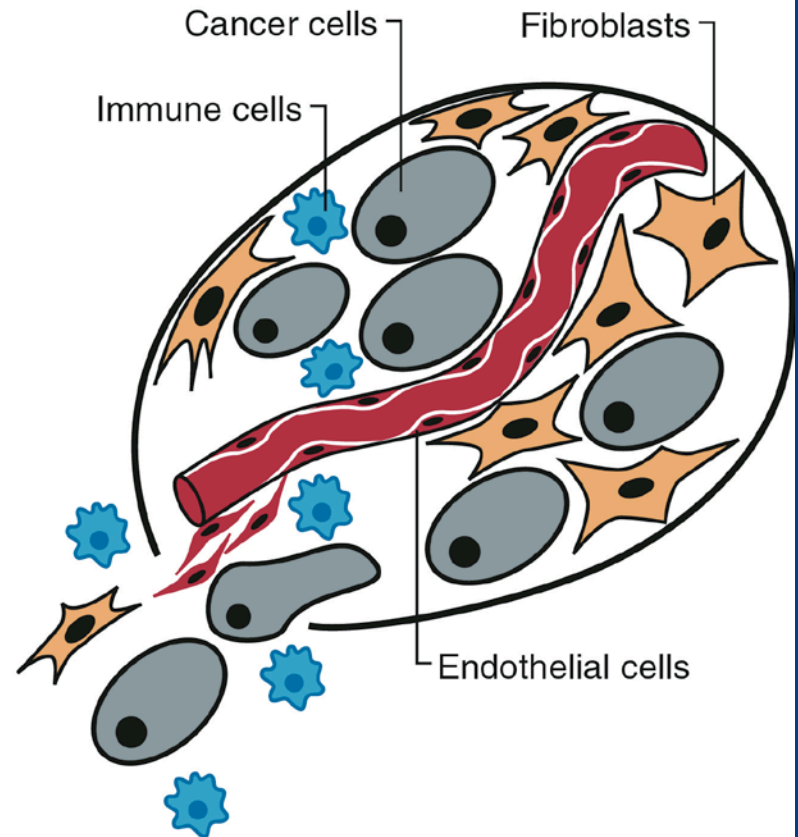


Another key concept: tumors are not bags of cancer cells!

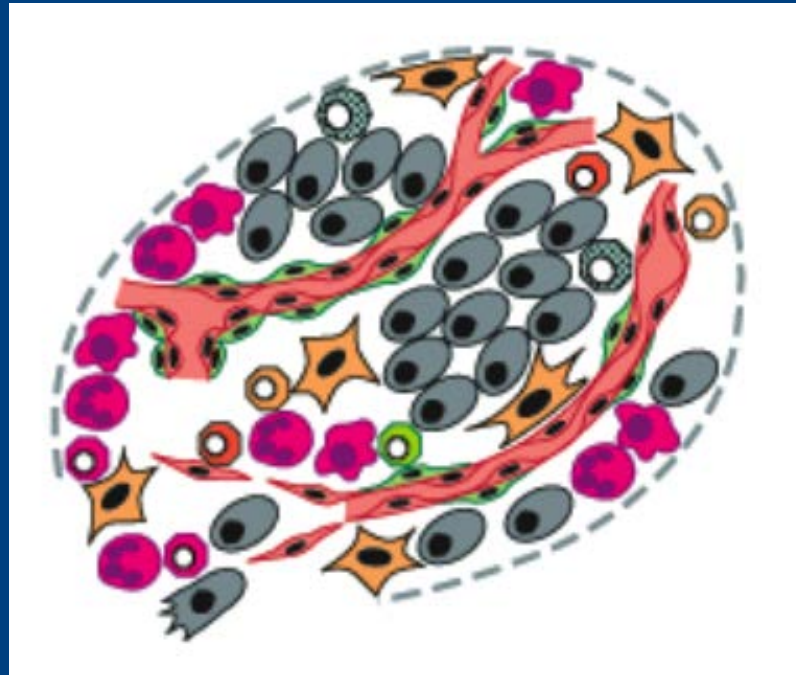
The Reductionist View



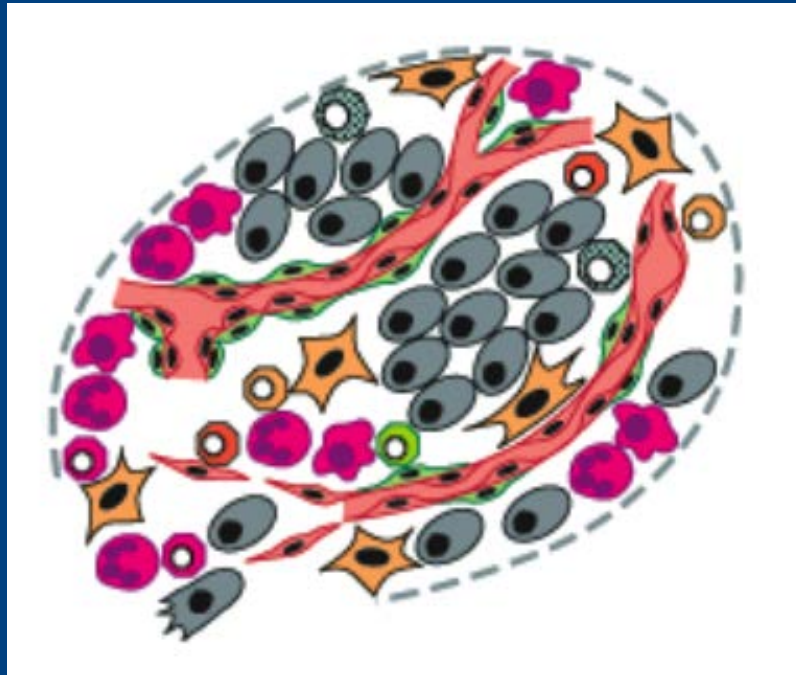
A Heterotypic Cell Biology



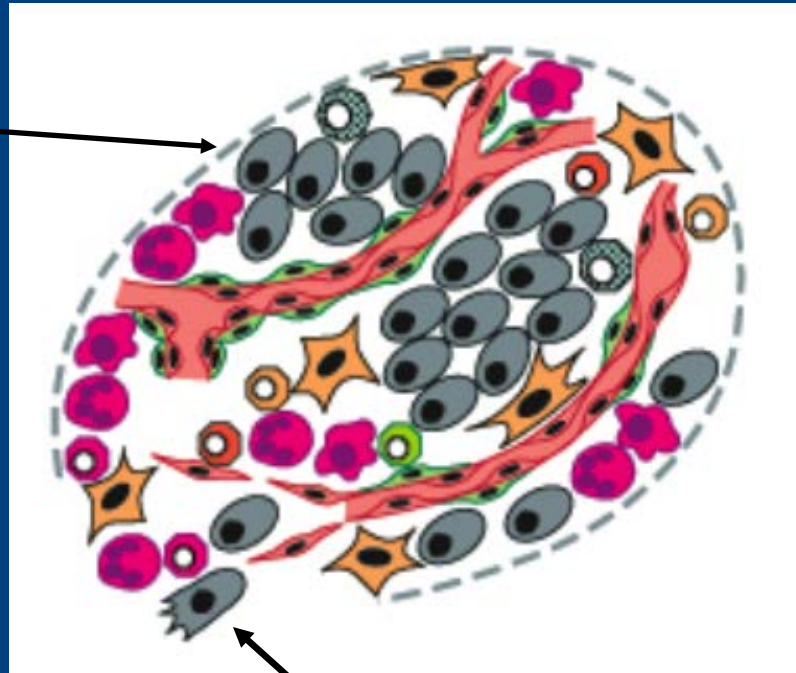
Tumors are not bags of cancer cells but rather
outlaw organs



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



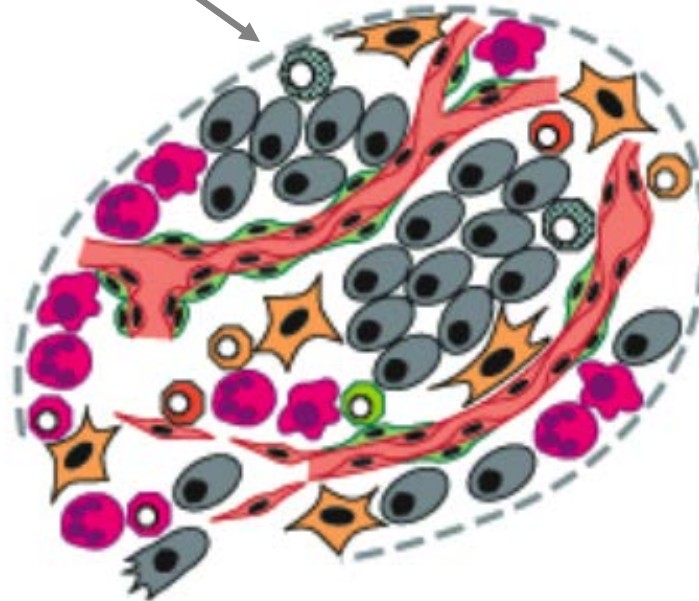
Cancer Cell
(CC)



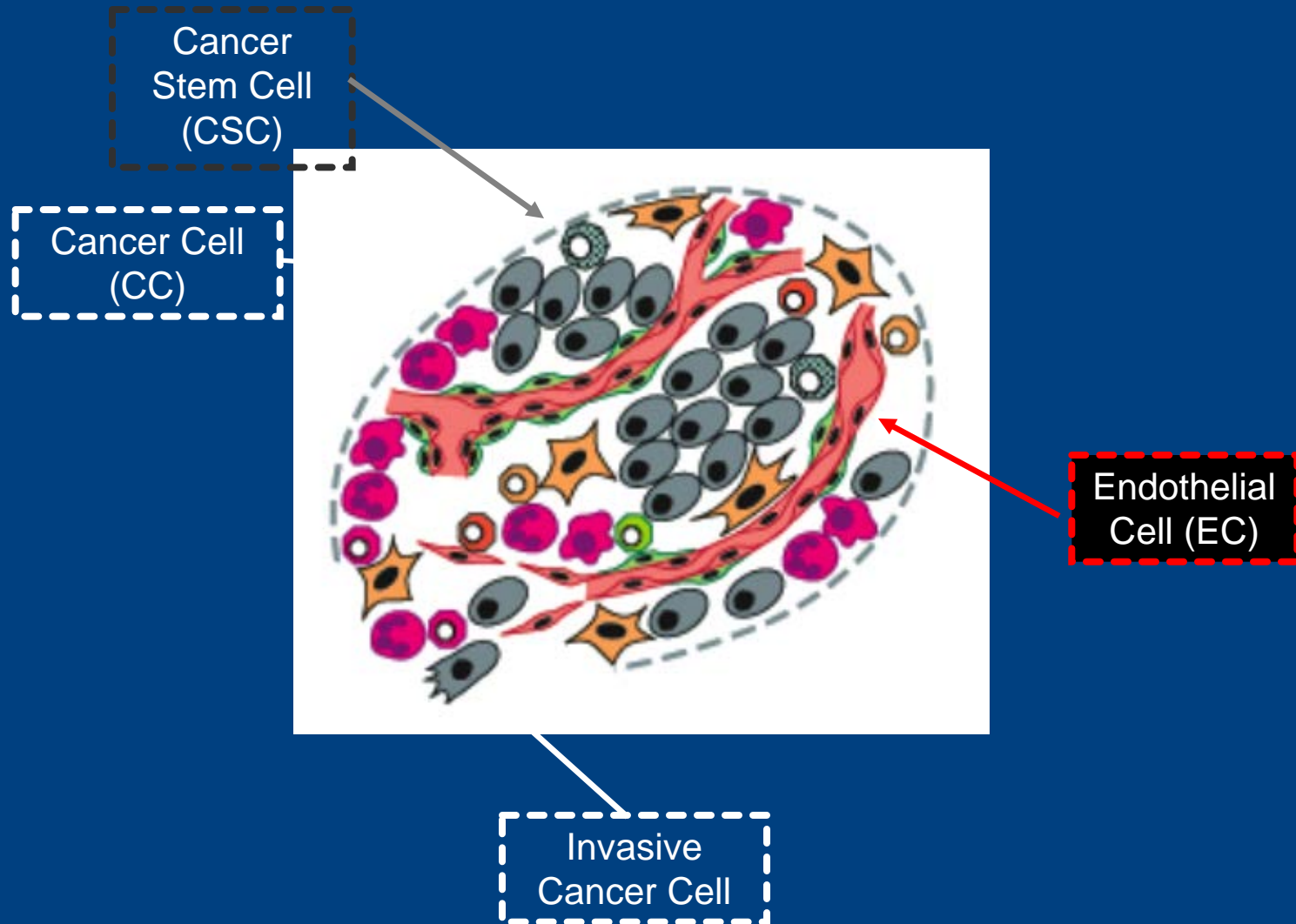
Invasive
Cancer Cell

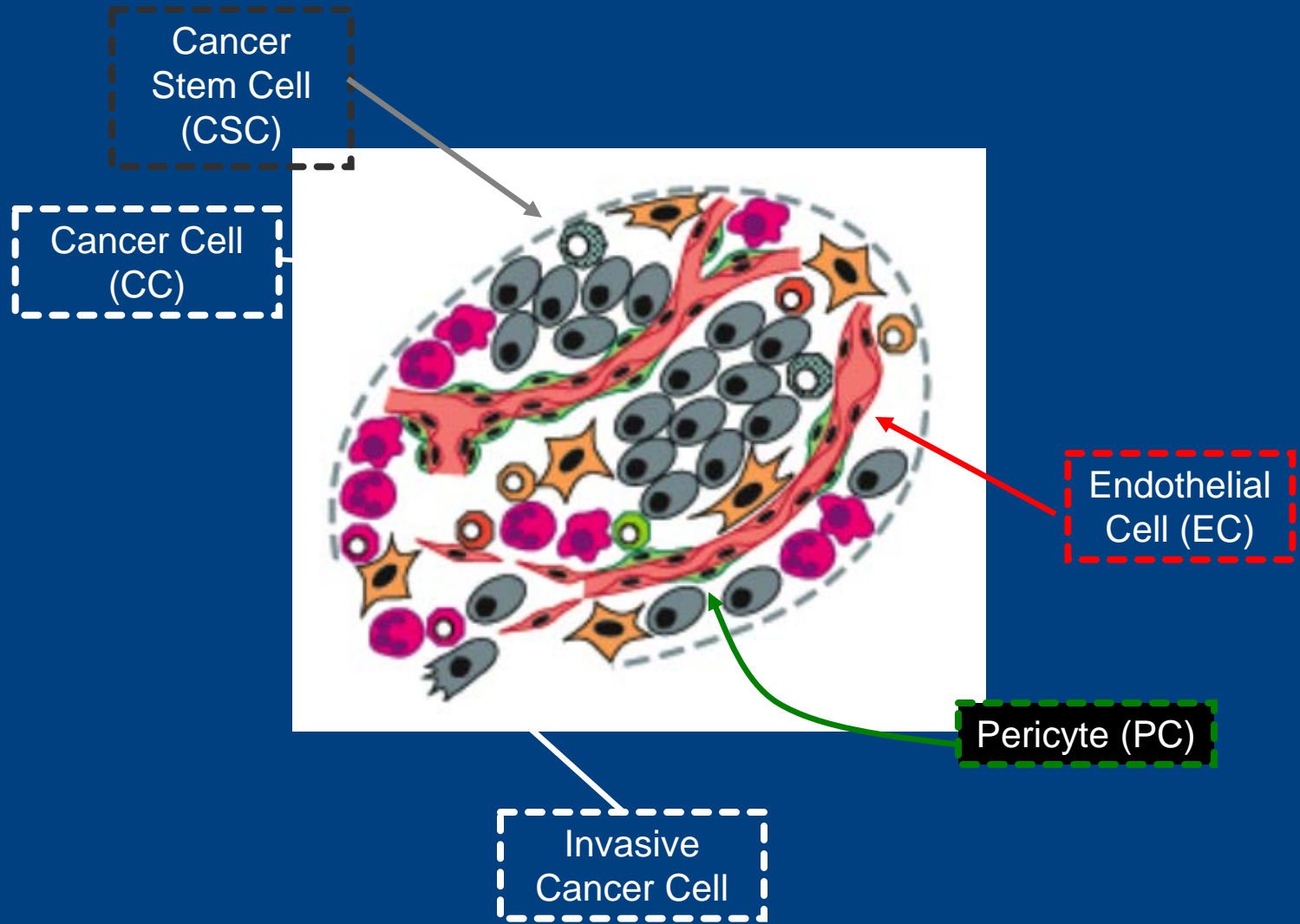
Cancer
Stem Cell
(CSC)

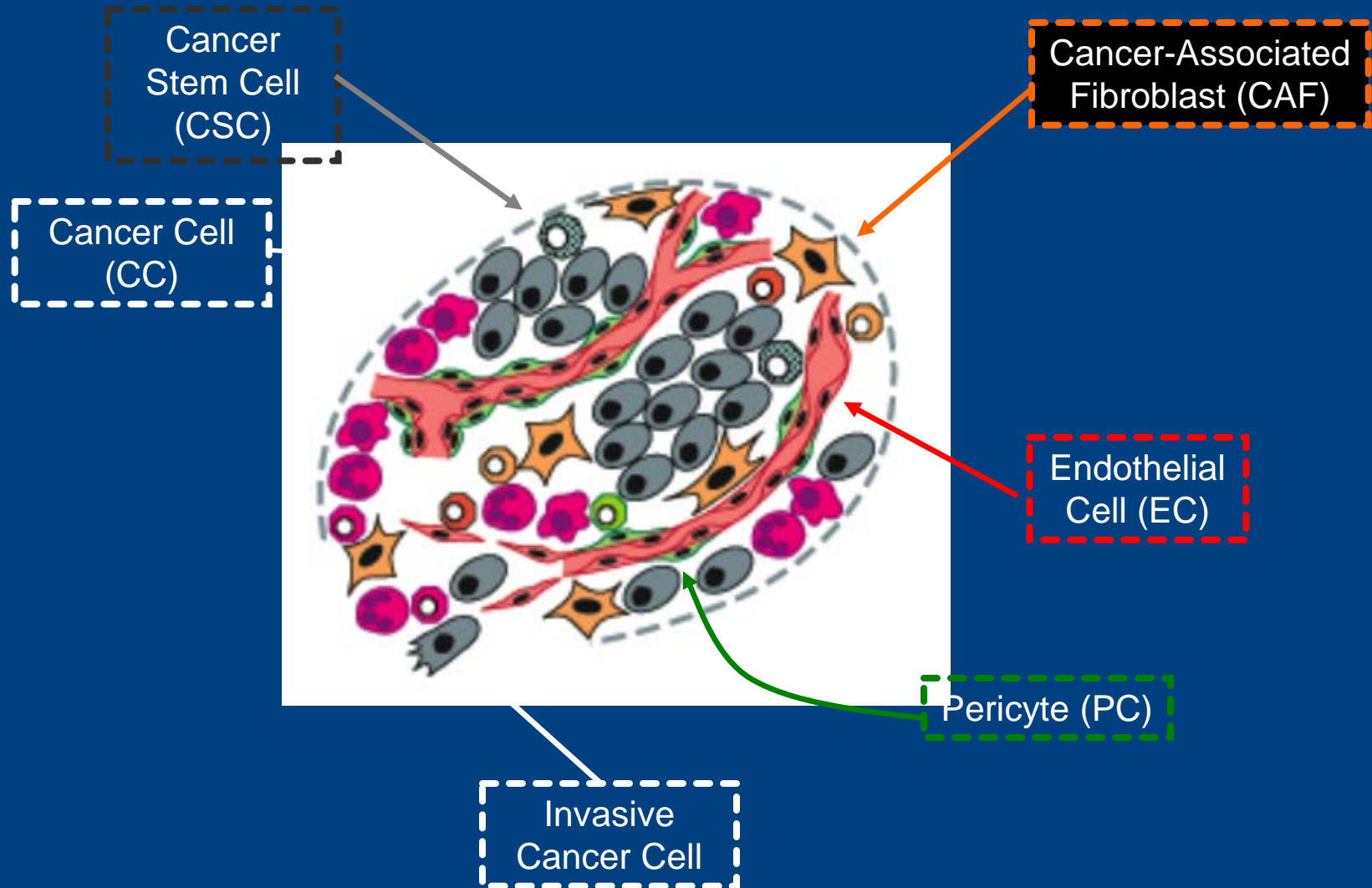
Cancer Cell
(CC)



Invasive
Cancer Cell







Cancer
Stem Cell
(CSC)

Cancer Cell
(CC)

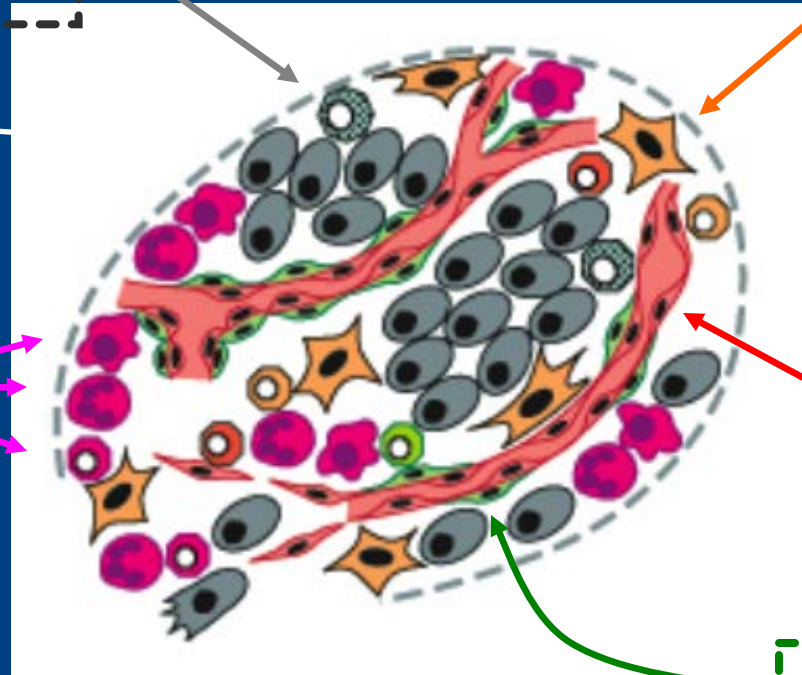
Tumor-Promoting
Inflammatory
Cells (TPIC)

Cancer-Associated
Fibroblast (CAF)

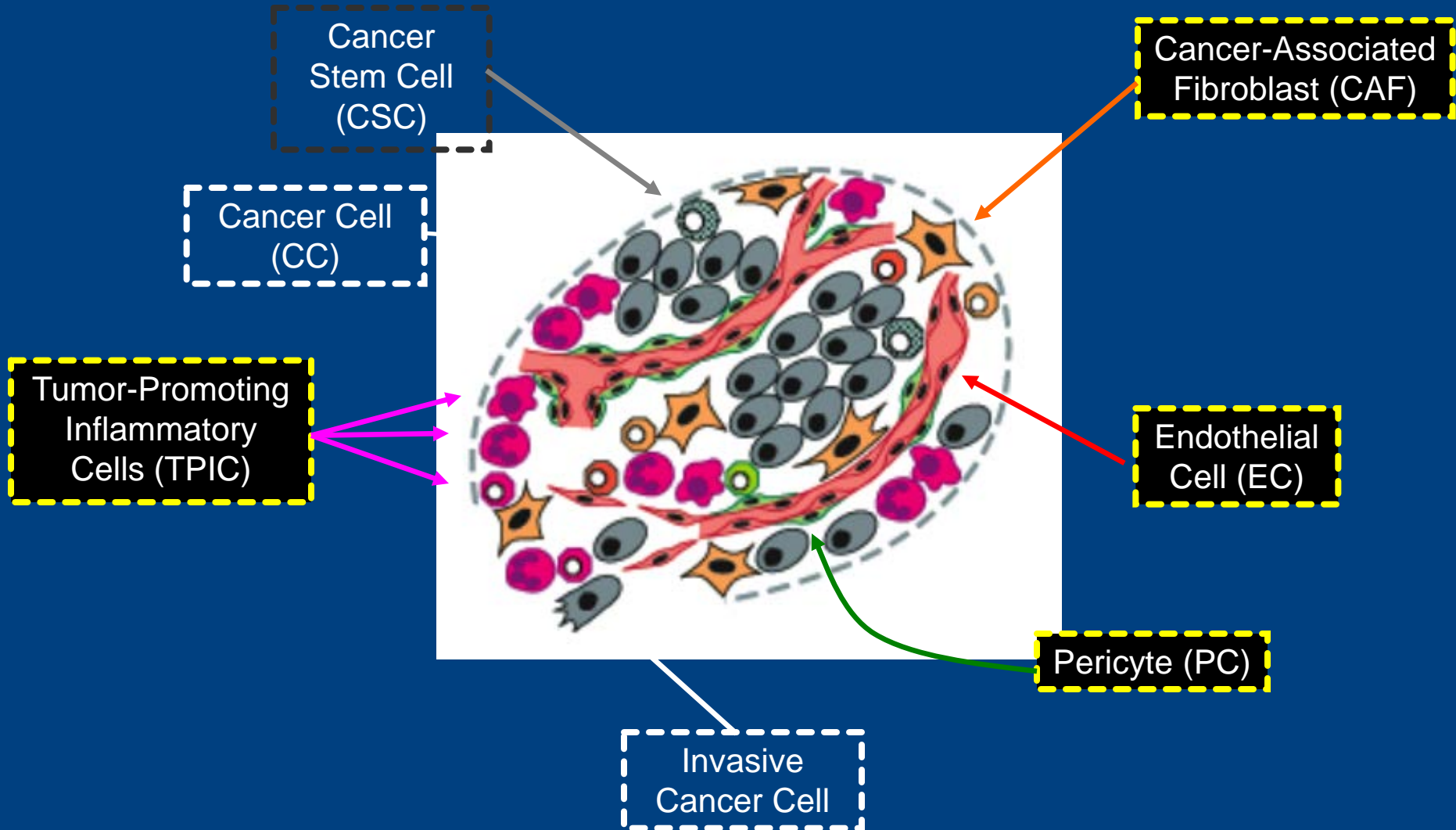
Endothelial
Cell (EC)

Pericyte (PC)

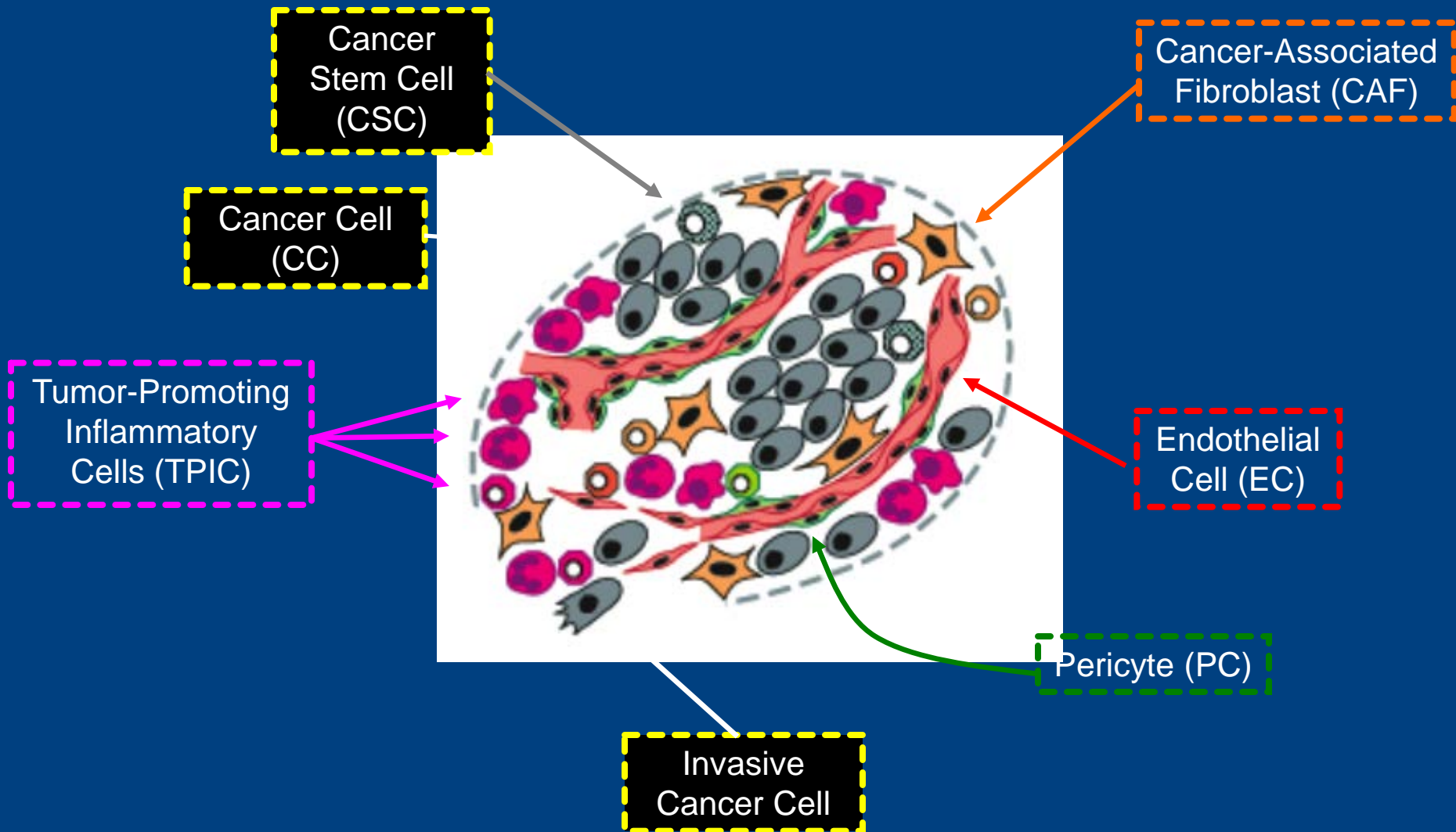
Invasive
Cancer Cell



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

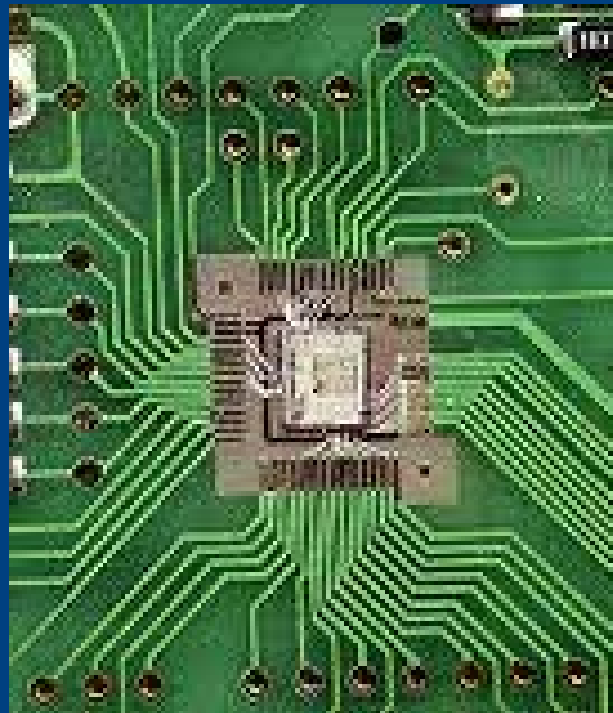


The foundation of all cancers remains the cancer cells, now including variable numbers of cancer stem cells

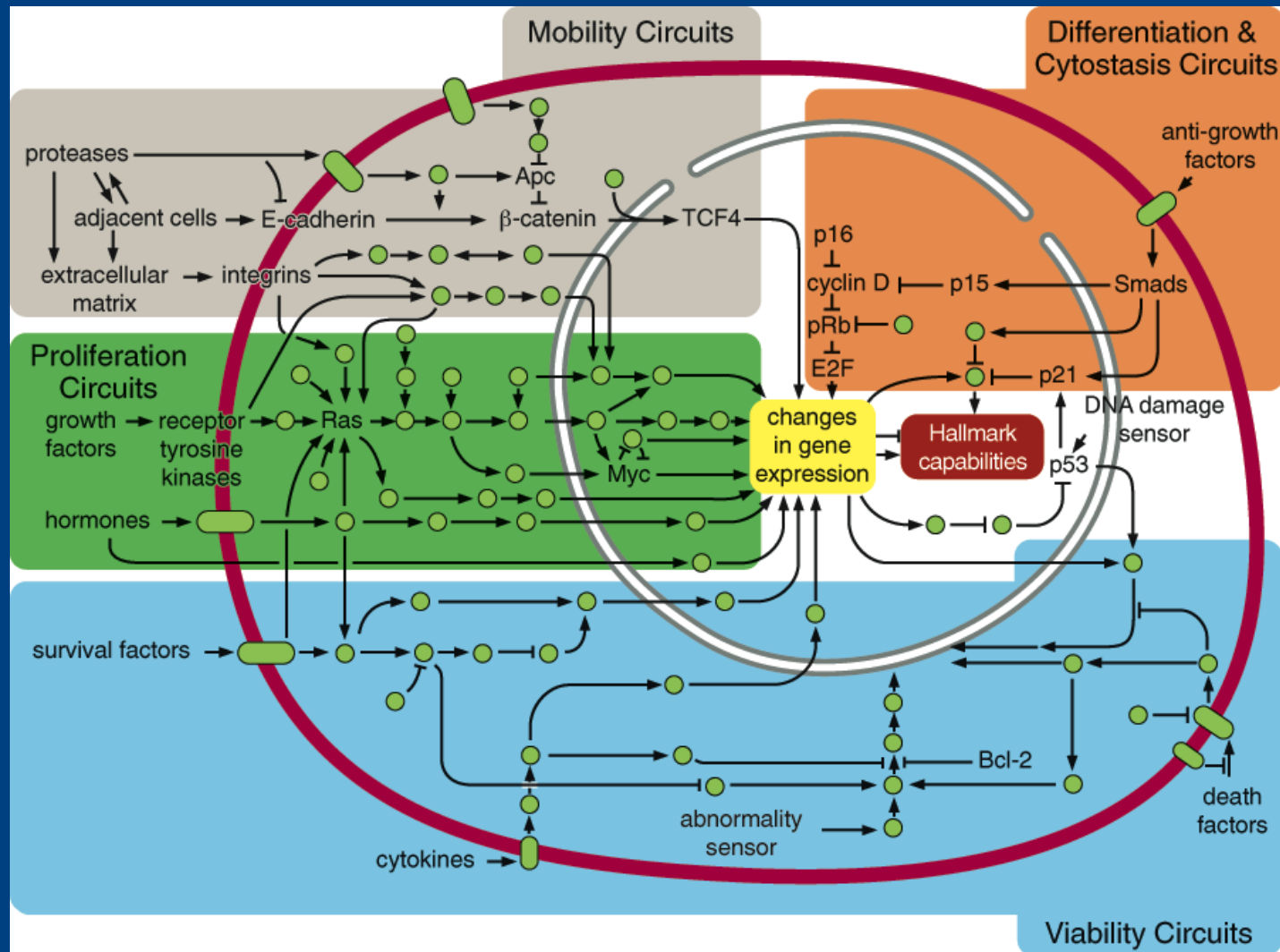


Cancer involves re-programming of an integrated signaling circuit in the cancer cell

Analogies to integrated circuits in electronics

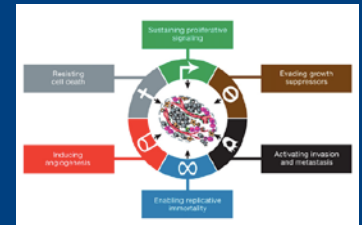


Cancer involves re-programming of an integrated signaling circuit in the cancer cell



An unanticipated success

- *The original Hallmarks of Cancer article, published in the millennium issue of the journal Cell, in January 2000:*
 - is the most highly cited article in the history of the journal (>12,000 references)
 - has several schematic figures that are now iconic, widely shown in lectures and reprinted
 - has been downloaded as a PDF over 200,000 times (by e-book standards, a best seller!)



Origins

- *How did this (free) 'best seller' come to be conceived, and written?*
- you might imagine two scientists at high tea, (or at the pub), or in their university offices?

Hallmarks of Cancer: Origins

- February 1998:
 - USA-Japan Cancer Symposium, Maui, Hawaii
 - Hnahan & Weinberg, **who had never collaborated before**, skipped out on some lectures, to take a long day trip to hike into the dormant volcano Haleakala;

Origins: Haleakala



Origins: Haleakala



Origins: Haleakala



Hallmarks of Cancer: Origins

- February 1998:
 - USA-Japan Cancer Symposium, Maui, Hawaii
 - Hnahan & Weinberg skipped out on some lectures, with a day trip to hike into the dormant volcano Haleakala;
 - During the long day, discussions about cancer
 - while driving from sea level to 3600 meters,
 - during a hike down into the crater,

Origins: Haleakala



Hallmarks of Cancer: Origins

- February 1998:
 - USA-Japan Cancer Symposium, Maui, Hawaii
 - Hnahan & Weinberg skipped out on some lectures, with a day trip to hike into the dormant volcano Haleakala;
 - During the long day, discussions about cancer
 - while driving from sea level to 3600 meters,
 - during a hike down into the crater,
 - and then driving down to the shore and back to the conference

Hallmarks of Cancer: Origins

- February 1998:

- USA-Japan Cancer Symposium, Maui, Hawaii
- Hnahan & Weinberg skipped out on some lectures, with a day trip to hike into the dormant volcano Haleakala;
- During the long day, discussions about cancer
 - while driving from sea level to 3600 meters,
 - during a hike down into the crater,
 - and then driving back

→ *the inception of the hallmarks concept*

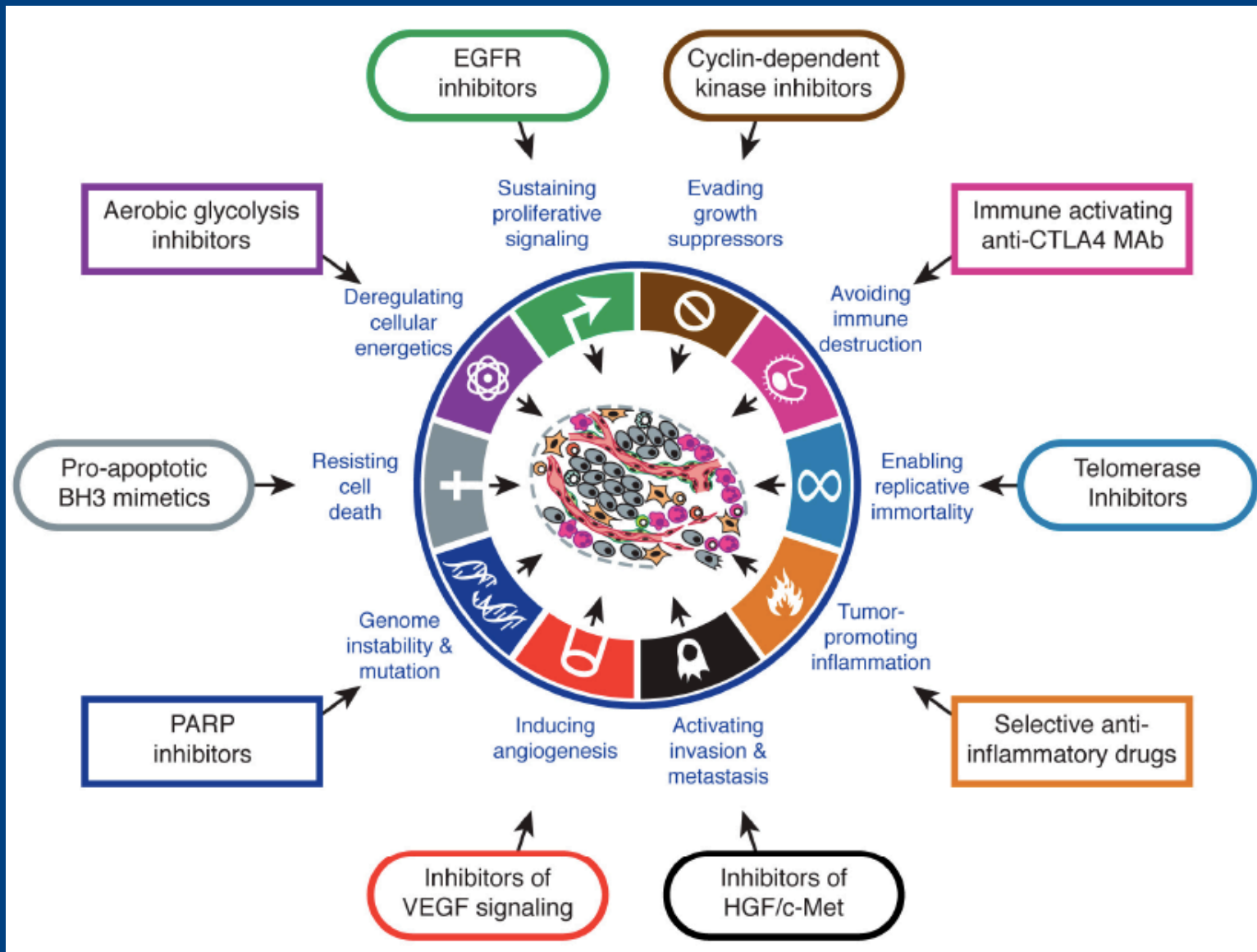
Hallmarks of Cancer: Origins

- Spring 1998 - Summer 1999: Continuing communications and brainstorming about the hallmarks concept, and beginning to outline it (*code named "The Haleakala Review"*)
- In addition to text, conceiving figures to crystallize the concepts (lessons from Jim Watson's groundbreaking textbook)
- January 2000: "The Hallmarks of Cancer" published in the millennium issue of Cell

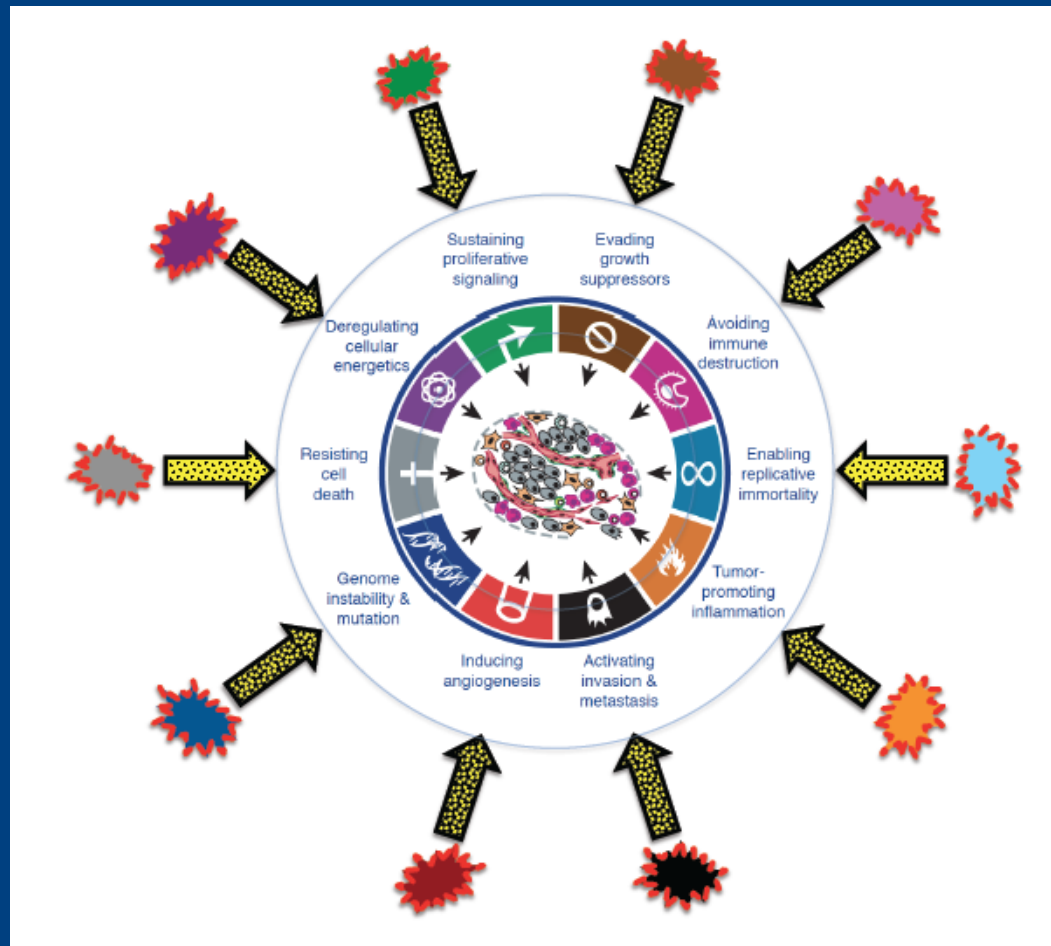
Hallmarks of Cancer: Applications to Cancer Medicine?

- 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?

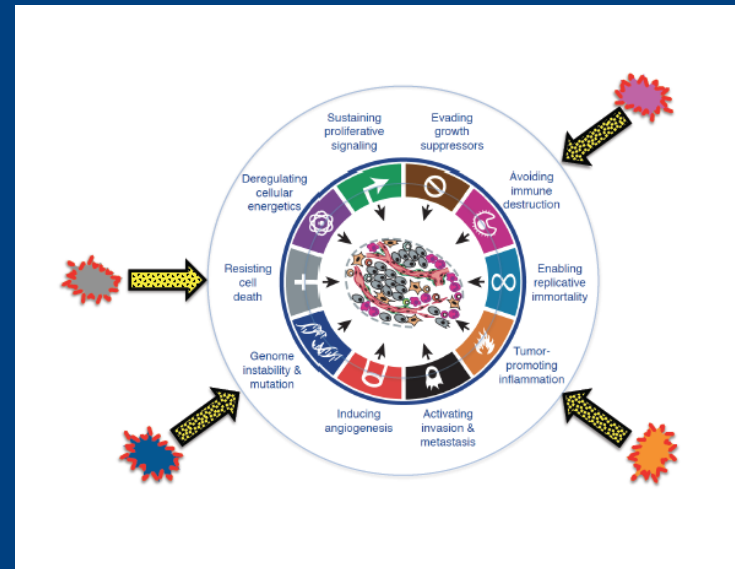
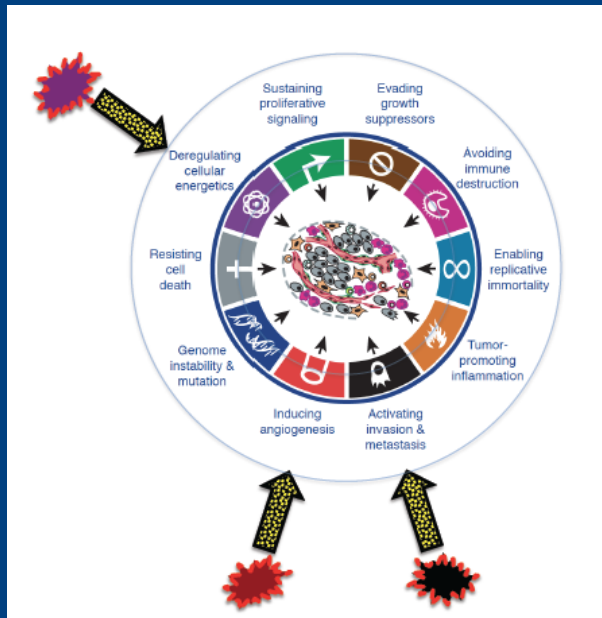
'smart bombs' can target each of the 8 hallmarks and their enablers



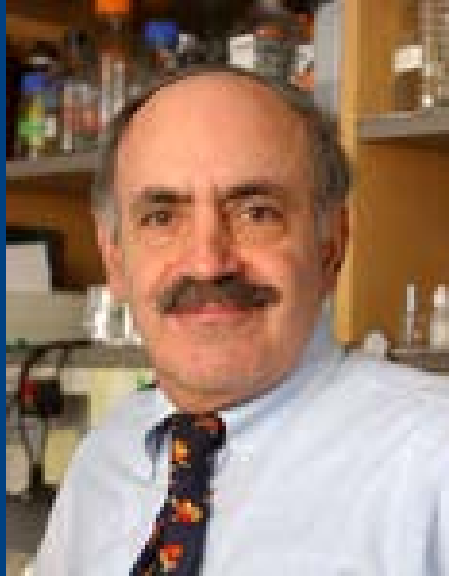
The dream scenario: Attacking of the hallmarks simultaneously, to stop tumors dead in their tracks



A more realistic future of cancer therapy: combinations, layers, sequences (a 'Hail Mary' attack likely has too many side effects)



Acknowledgements



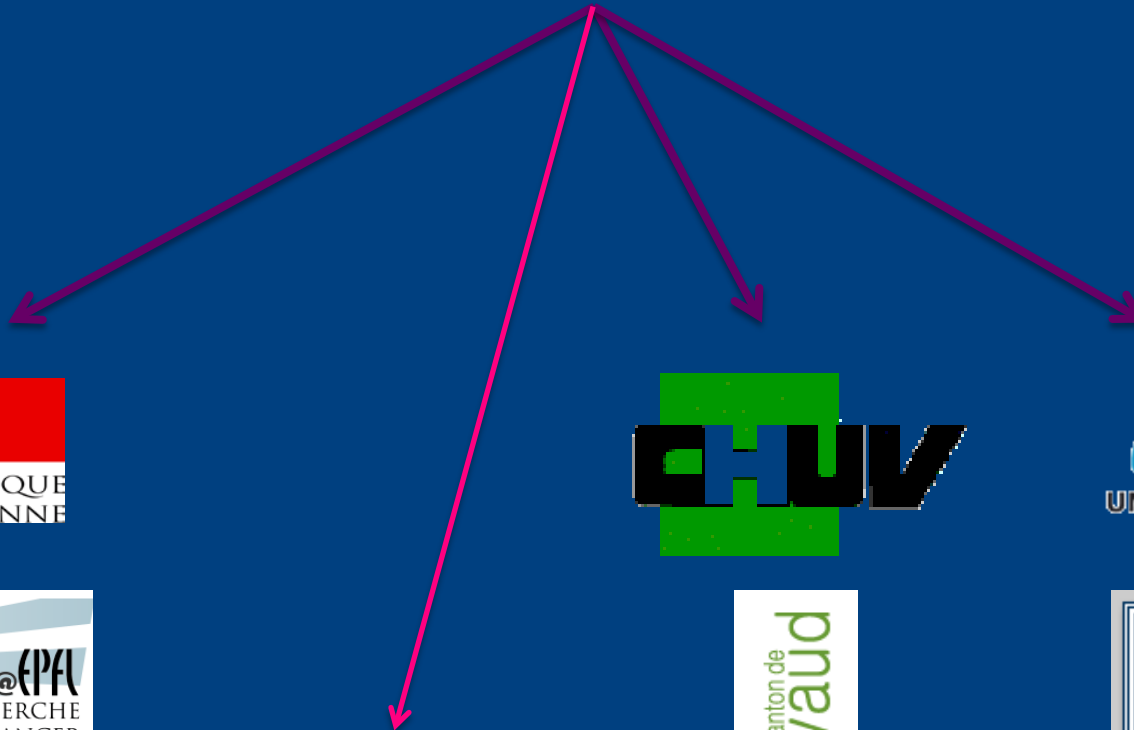
Bob Weinberg!!!

(Whitehead Institute & MIT,
Cambridge, USA)

Terry Schoop

OFC Graphics, Kensington, CA
(converting crude sketches into iconic figures)

A relevant new initiative in the region:
We are building a new multi-institutional
cancer center based in Lausanne



Complimentary Expertise Vested in the Three Major Stakeholders



- The University Hospital and Medical Research Campus; the new Dept of Oncology (Coukos)

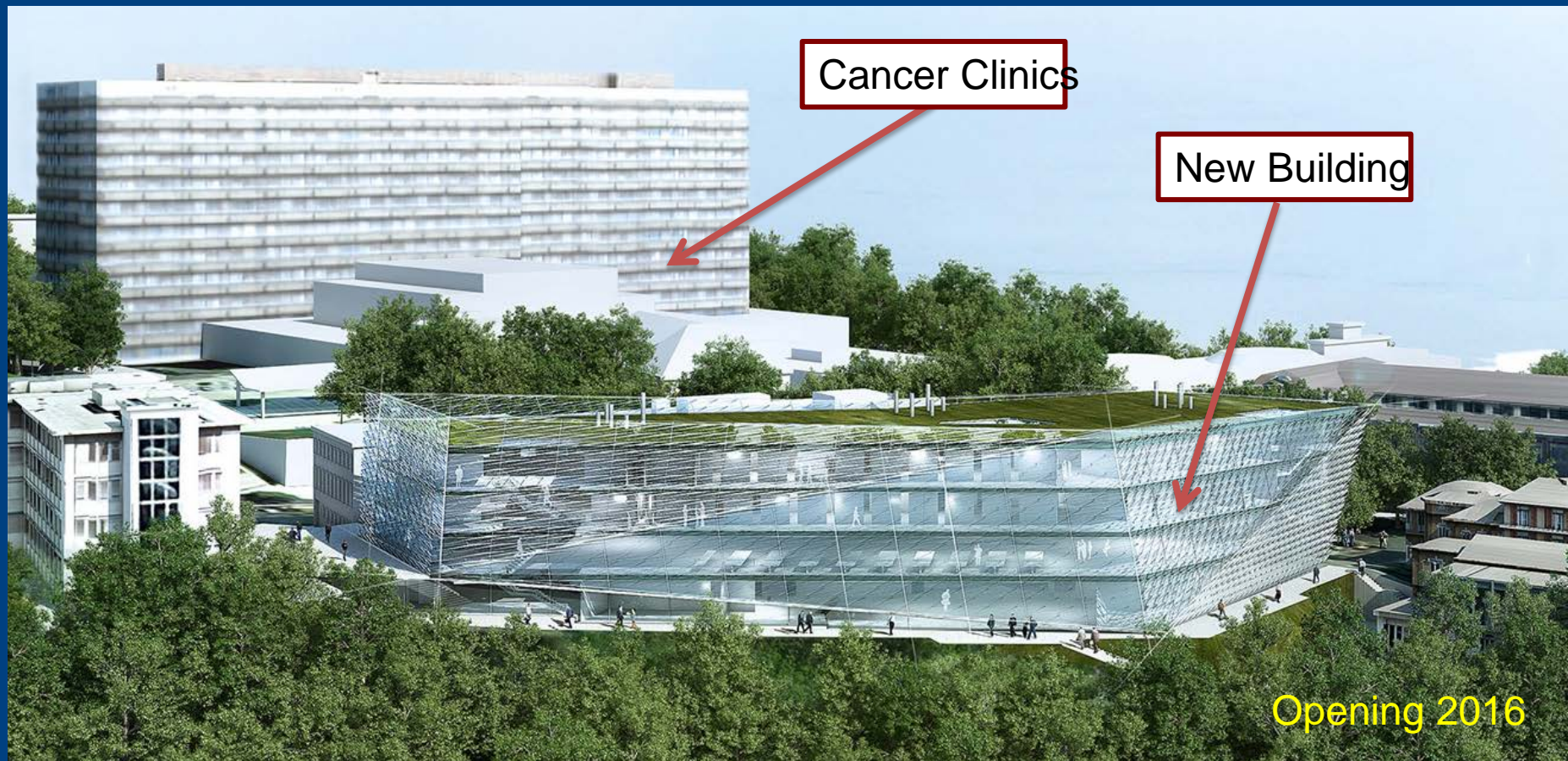


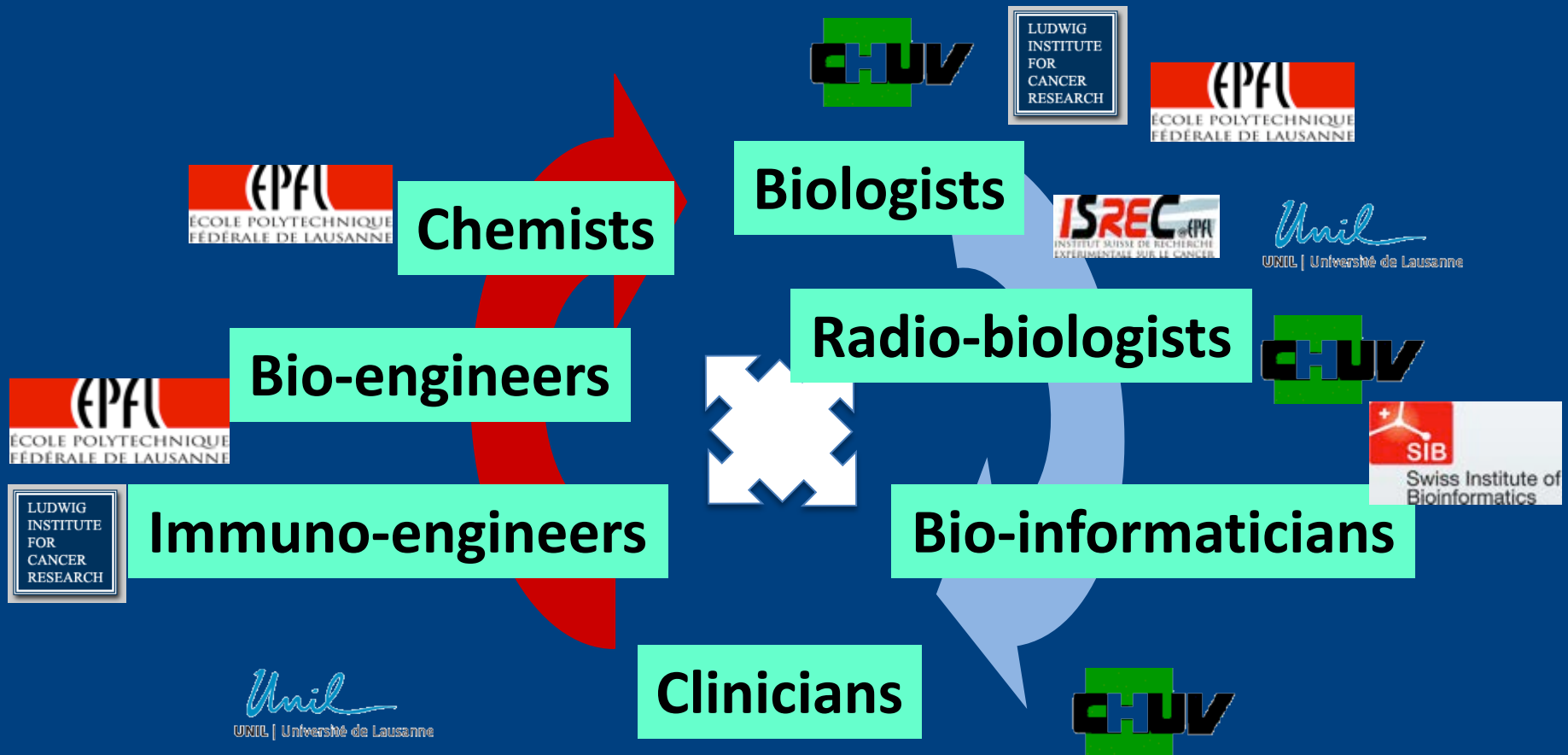
- The Epalinges/Biopole Bio-Medical Research Campus (Immuno-biology, Cancer, etc)
- The Ludwig Institute Center at UNIL (Coukos)
- Radiology, Radiation Oncology, Nuclear Medicine
- The Swiss Institute for Bioinformatics (SIB)



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

The nucleus of the Swiss Cancer Center Lausanne will be a new "Agora" Translational Cancer Research Building, coalescing basic and clinical cancer researchers, bio- and immuno-engineers, into thematic programs





Our new Cancer Center will engage colleagues throughout Switzerland and abroad, including **CERN, HUG, and UNIGE**



Questions?

Thank You