Epistemology of the Origin of Cancer

A graphical overview of the Cancer Paradigm Series, presenting a stepwise integrative framework from pathogenic (biological or chemical) stimulus, chronic inflammation, fibrosis, and its remodeling to the formation of the precancerous niche (PCN), cell transition plasticity, heterogeneity, pre-metastatic niches (PMNs) and metastatic niches (MNs). This Paradigm offers the identification of new targets to treat cancers and to block or reverse metastases which are the bases for most cancer mortality.

Background

Most cancers (~80%) are epithelial and are not due to genetic causes, yet this assumption persists in textbooks and publications, and is widely promoted by editors and cancer organizations. The continued belief that the somatic mutation theory can explain carcinogenesis in most cancers is erroneous, because mutations causally account for approximately 5% of cancers.

No single gene; epigenetic event; protein; or set of genes, epigenetic events, or proteins has been found to cause human epithelial cancers. Furthermore, genetics does not predict diseases, because no genetic basis for disease, mortality, or disease progression exists except for inborn errors of metabolism. Biomarkers are not always reliable, and mismatch repair gene defects have clinical relevance in approximately 10%–15% of epithelial cancers, not 90%.

Overview

The Cancer Paradigm Series synthesizes a new approach to the origin of cancer and of its metastases by explaining how the disruption of homeostasis impacts tumor biology, fibrosis, extracellular matrix remodeling, cancer-associated fibroblasts, cell transition plasticity, immune modulation, and leads to the formation of the pre-cancerous niche (PCN), pre-metastatic niches (PMNs) and metastatic niches (MNs) in most epithelial cancers.

The conception of 'Epistemology of the Origin of Cancer' was finalized in 2012, and realized in a stepwise fashion until 2026. It set out to challenge established thinking on cancer and metastasis, and present a new cancer paradigm providing compelling evidence on how carcinogenesis and metastasis occurs in the vast majority of cancers, epithelial cancers, with their vast heterogeneity.

This page is designed as a visual entry point. It does not replace the full peer-reviewed papers, but helps readers follow the conceptual development across the published works.

EDITORIAL NOTE: THE SERIES IS PRESENTED AS AN INTEGRATIVE, HYPOTHESIS-GENERATING FRAMEWORK INTENDED TO SUPPORT SCIENTIFIC DISCUSSION AND FURTHER CAUSE-BASED RESEARCH.

KEY WORDS

Chronic inflammation Fibrosis PCN CSES MET / EMT CAFs / MAFs Metastasis PMNs MNs

DEVELOPMENT OF THE SERIES

2014

PART I – CANCER PARADIGM I

The initial model describes a six-step sequence from (1) pathogenic stimulus (biological or chemical), (2) chronic inflammation to (3) fibrosis, (4) extracellular matrix remodeling, to a pre-cancerous niche (PCN), which triggers (5) a chronic stress escape strategy (CSES) (principle in nature to maintain homeostasis), and when this fails, (6) results in the transition of a normal cell to cancer cell (NCCCT).

Development of the Series

2016

AD Part I – SMT, Genomics, miRNA, Proteomics and Cancer

Various aspects necessary for the understanding of carcinogenesis and metastasis such as the Somatic Mutation Theory (SMT), Genomics, miRNA, Epigenetics, and Proteomics, were scrutinized and re-analyzed from a cause-based approach.

2019

AD Part I – Updated signaling and crosstalk

Further development of the signaling framework and cellular crosstalk including eicosanoids, microbiome, morbid obesity, metformin, Nf-κB, SCD1, FADS2, and YAP, linked to the original paradigm were provided 5 years after the Cancer Paradigm was published. Additionally, the cancer burden in regard to homeostasis with all of the necessary cancer research and prevention strategies were elucidated.

Development of the Series

2022

AD Part I – Physics and Carcinogenesis

An understanding of the essentials of physics helps to explain the interconnections between physics and the biology of cancer. This allows for a much-needed reconciliation of past errors and leads to a deeper understanding of carcinogenesis.

2023

Part II – First Cancer Cell

The framework expands to the chronic stress escape strategy, EMT/MET, and a proposed role for cancer-associated fibroblasts in the origin of the first cancer cell.

2025

Part III – Pre-Metastatic Niches

The series extends from the pre-cancerous niche (PCN) to the pre-metastatic niches (PMN-1, PMN-2, and PMN-3), including their motility, immune modulation, extracellular matrix gradients, and cancer satellites.

Development of the Series

2025

AD Part I-to-III – Integrity in Science and Healthcare

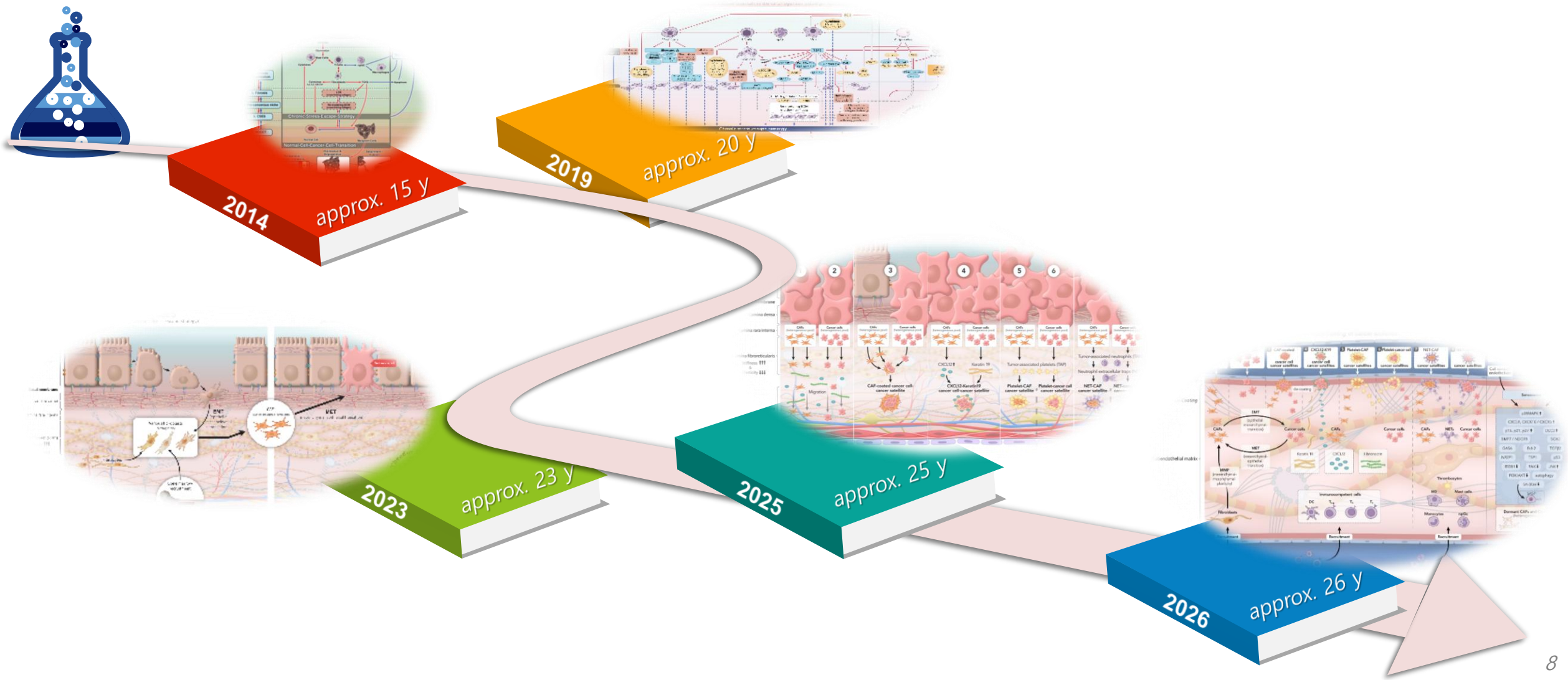
Integrity of healthcare and science directly influence quality in cancer science. Due to the complexity in-depth contemplation was needed to address many variables, followed by psychological and sociological aspects which influence our views on how cancer and healthcare are perceived.

2026

Part IV – Metastatic Niches

The series extend from the pre-metastatic niche 3 (PMN-3) that leads to the formation of metastastic niches (MNs) as requisite conditions for metastases, which *occurs concurrently with carcinogenesis*. A vast heterogeneity of CAFs, MAFs, dormant and awakened cancer cells progress to metastatic cancer satellites, and these fulfill the conditions that predispose to metastases.

Graphical Highlights



Epistemology of the Origin of Cancer – Highlights

1. Part I – Cancer Paradigm I (2014)

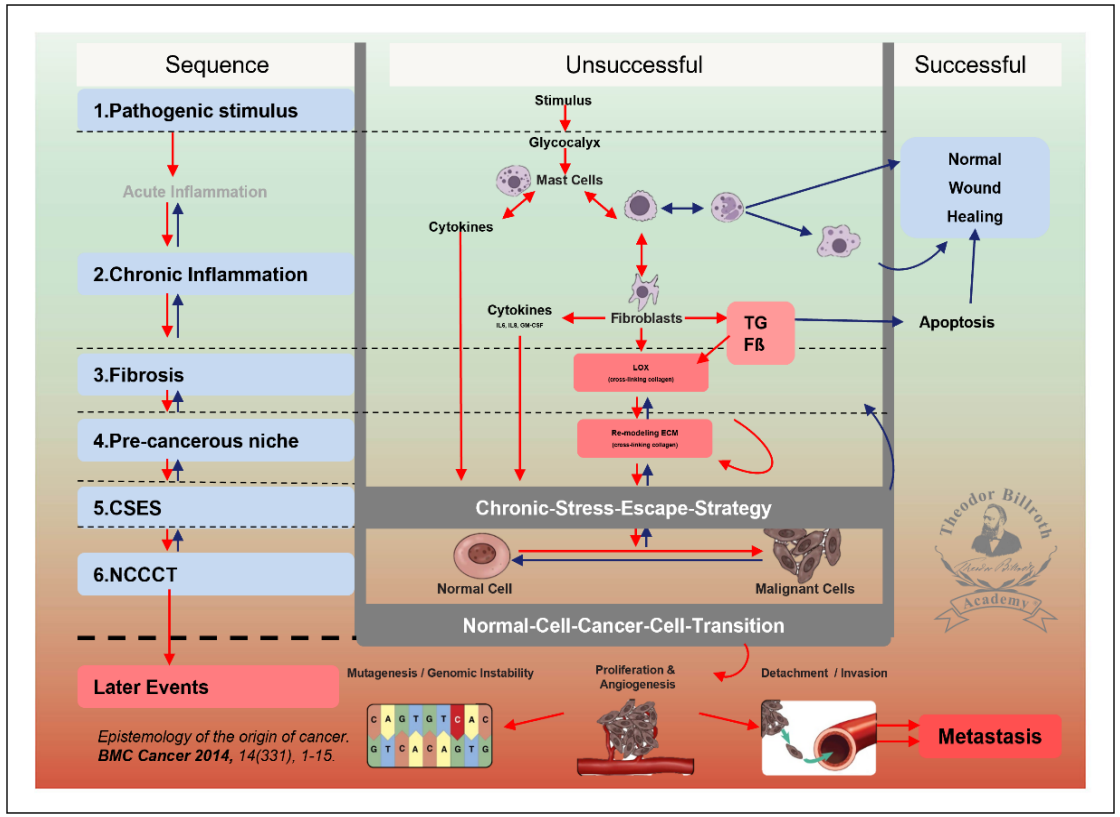
The majority of EPITHELIAL CANCER develop in response to:

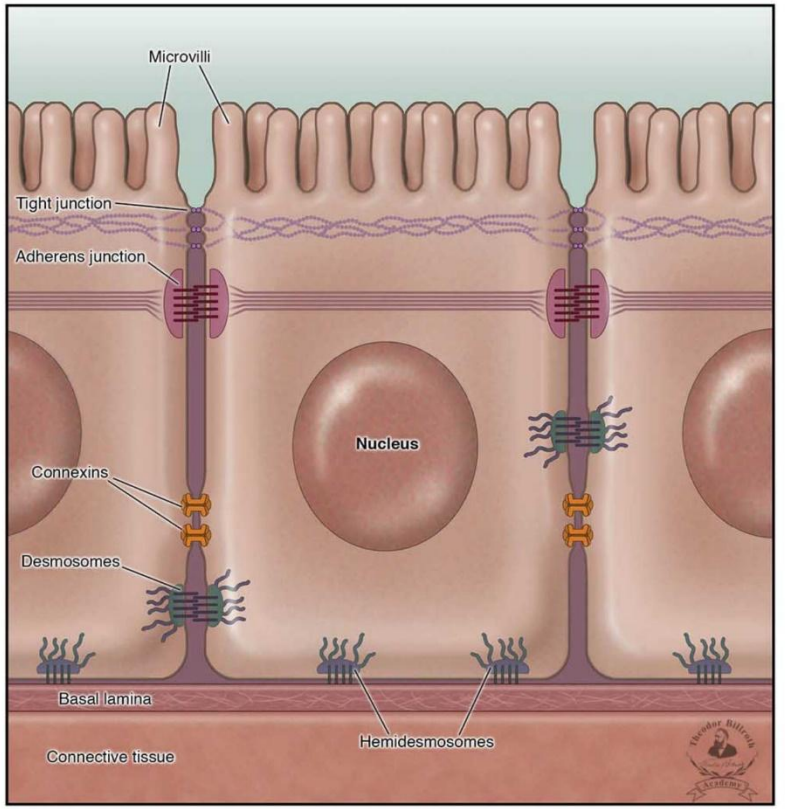
(1) pathogenic stimulus inducing
(2) chronic inflammation,
(3) fibrosis with remodeling from which a
(4) pre-cancerous niche (PCN) develops.

This is followed by a
(5) Chronic stress escape strategy (CSES) – see below Part II from 2023 –, and
(6) a transition from normal cell to cancer cell (NCCCT).

Modified figure from
Cell Physiol Biochem 2014
https://doi.org/10.1159/000362978

BMC 2014
https://doi.org/10.1186/1471-2407-14-331





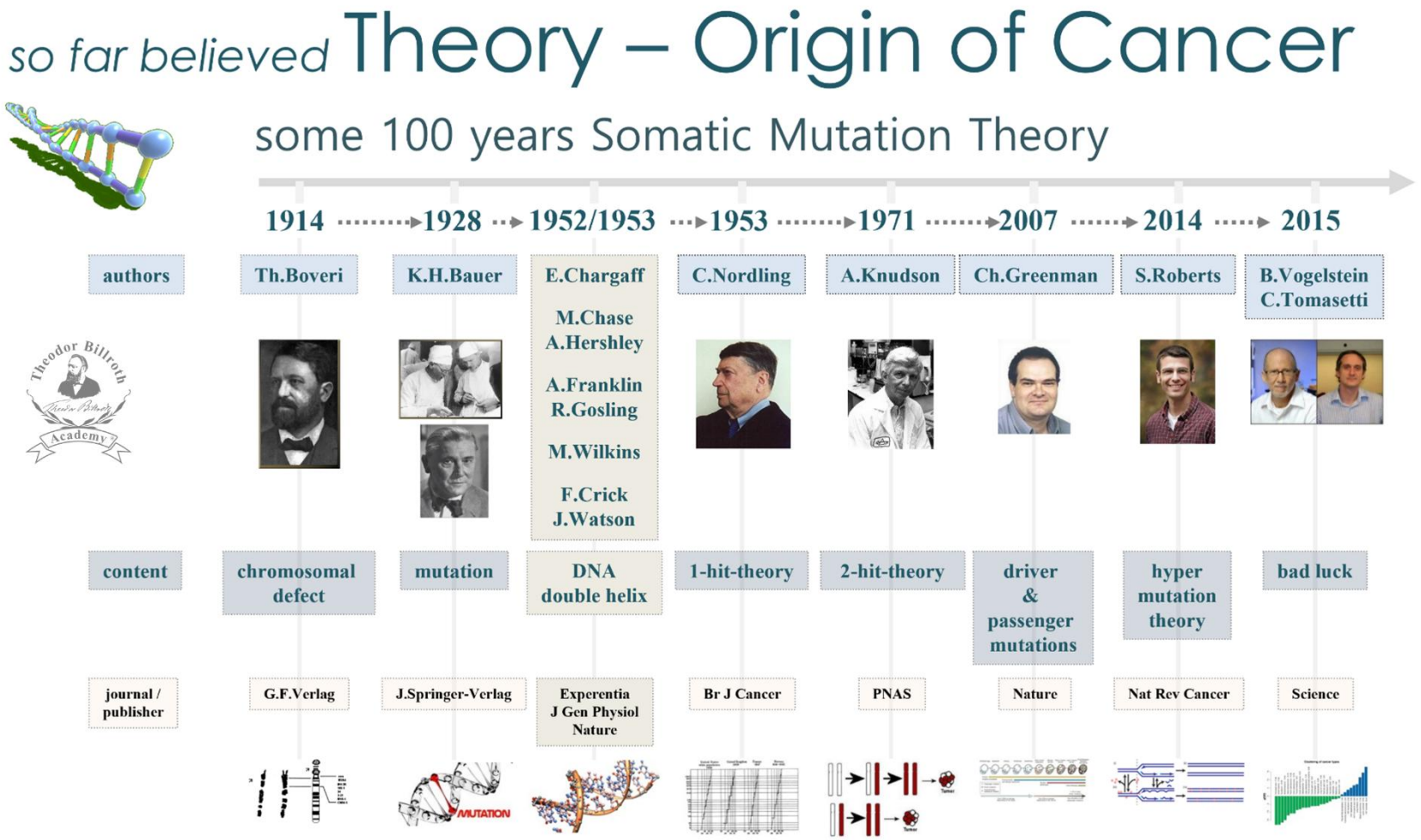
Epistemology of the Origin of Cancer – Highlights

ad Part I – Somatic Mutation Theory (2016)

Somatic Mutation Theory is de facto still believed to be causative, although proven

- to be causative for only for 5% of cancers.

Modified figure from
Cell Physiol Biochem 2016
https://doi.org/10.1159/000443106



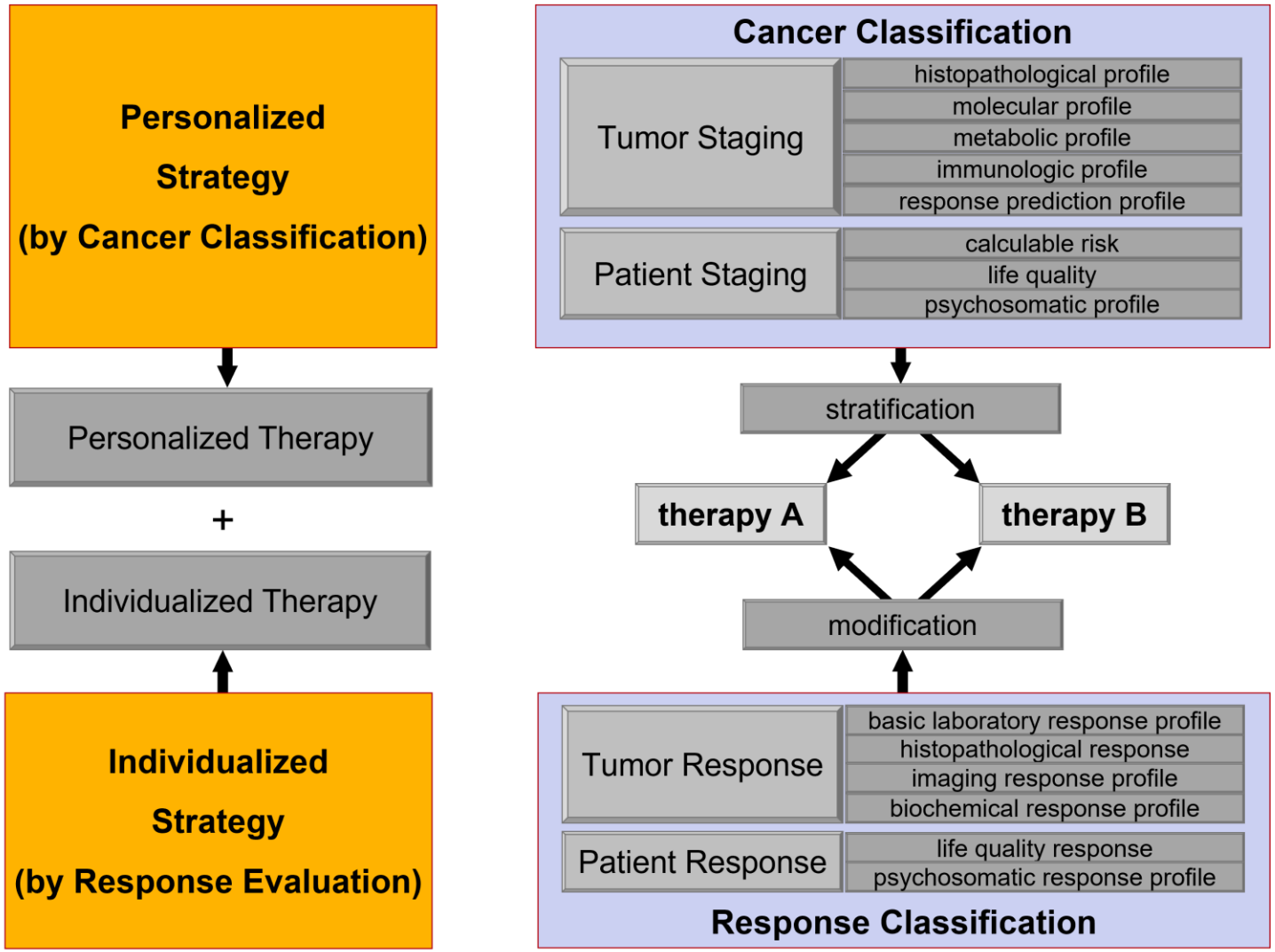
Epistemology of the Origin of Cancer – Highlights

ad Part I – Imagine A World Without Cancer (2014)

Introduction of an interdisciplinary anticancer Strategy

Modified figure from
BMC Cancer 2014
https://doi.org/10.1186/1471-2407-14-186

- named *Imagine a World Without Cancer.*



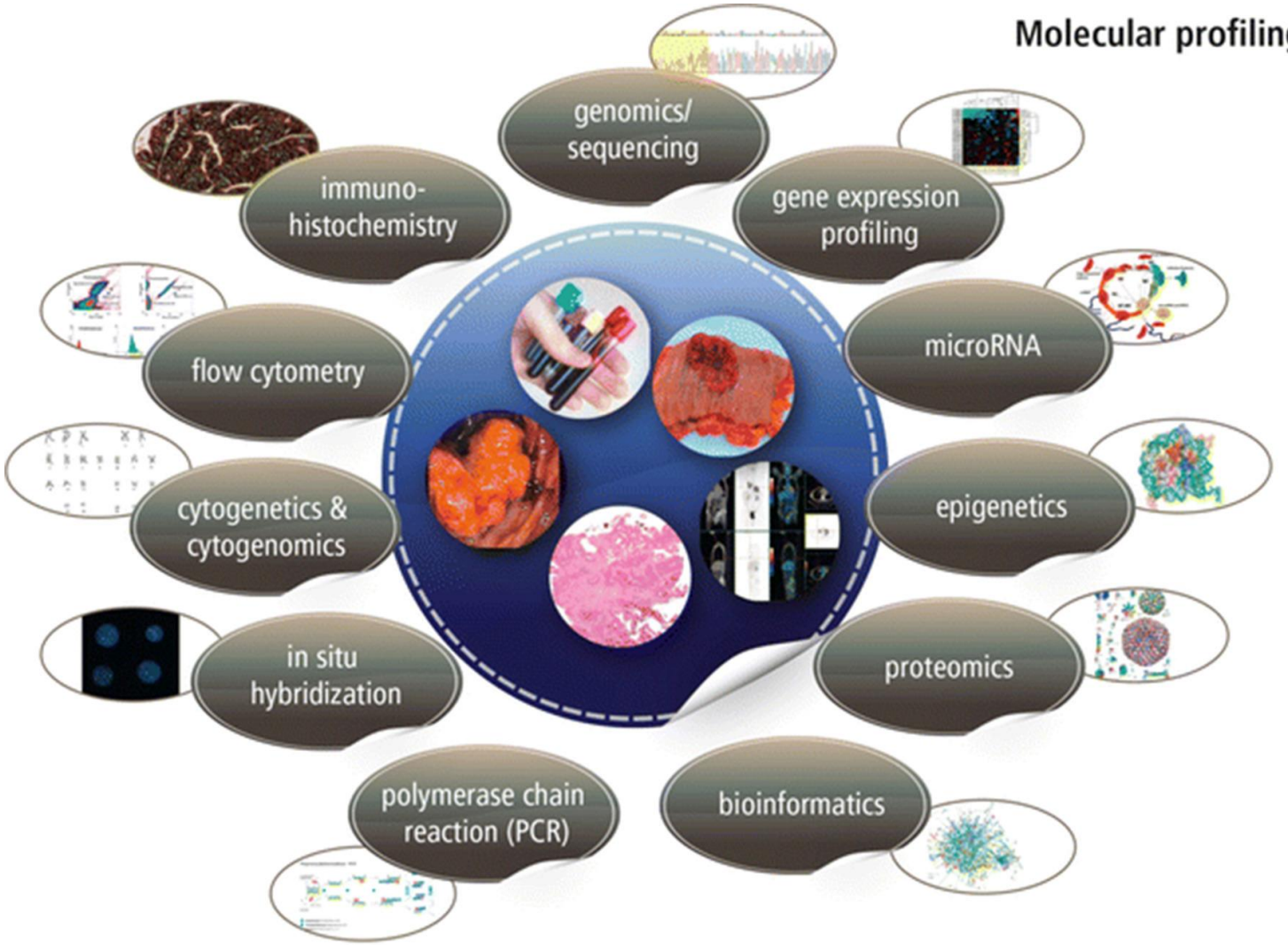
Epistemology of the Origin of Cancer – Highlights

ad Part I – Genomics, miRNA, Epigenetics, Proteomics (2016)

Translational data in Genomic, miRNA, Epigenetics, and Proteomics

Modified figure from
Clin Transl Med 2016
https://doi.org/10.1186/s40169-016-0093-6

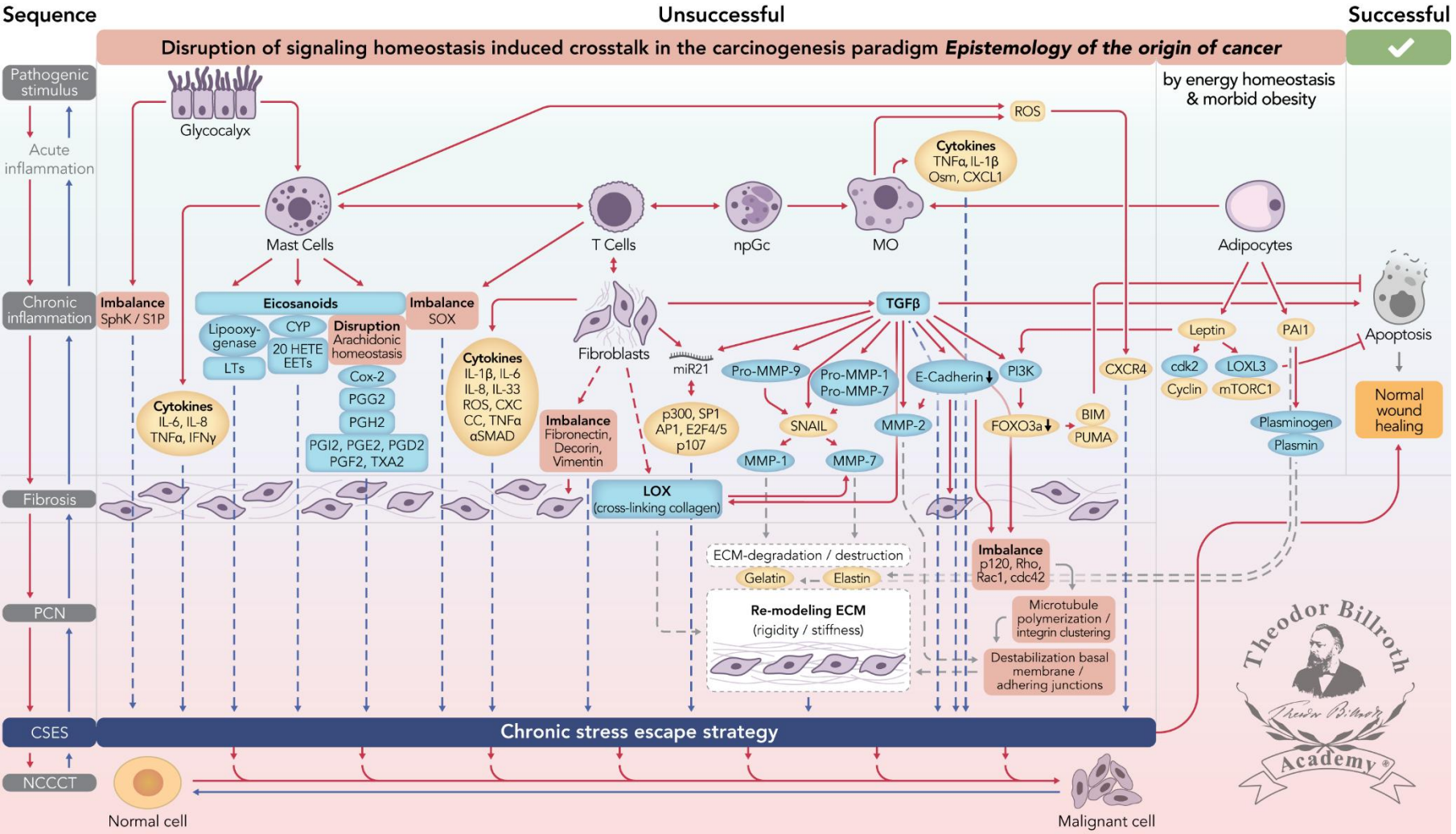
- for monitoring responses, and, where available, with an emphasis of GI carcinomas.



Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Paradigm I (2019)

Updated signaling and crosstalk of Cancer Paradigm.



Modified figure from
Cell Physiol Biochem 2014
https://doi.org/10.1159/000362978

BMC 2014
https://doi.org/10.1186/1471-2407-14-331

Updated signaling / crosstalk in 2019
4OPEN 2019
https://www.4open-sciences.org/component/toc/?task=topic&id=1080

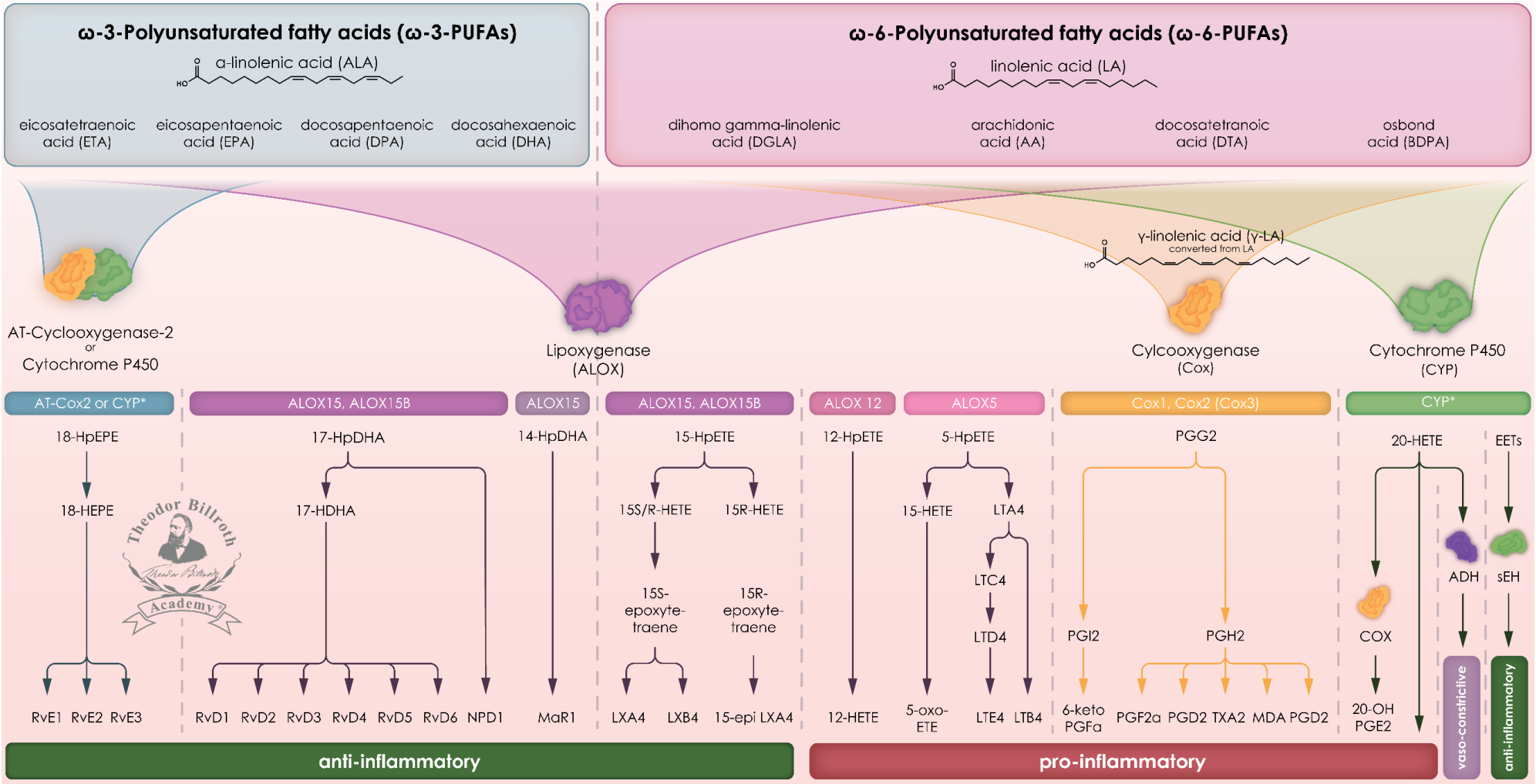
Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Paradigm I (2019)

Cancer Paradigm is consistent with

- pro- and anti-inflammatory Eicosanoid metabolism.

Modified figure from
4OPEN 2019
https://doi.org/10.1051/fopen/2018808



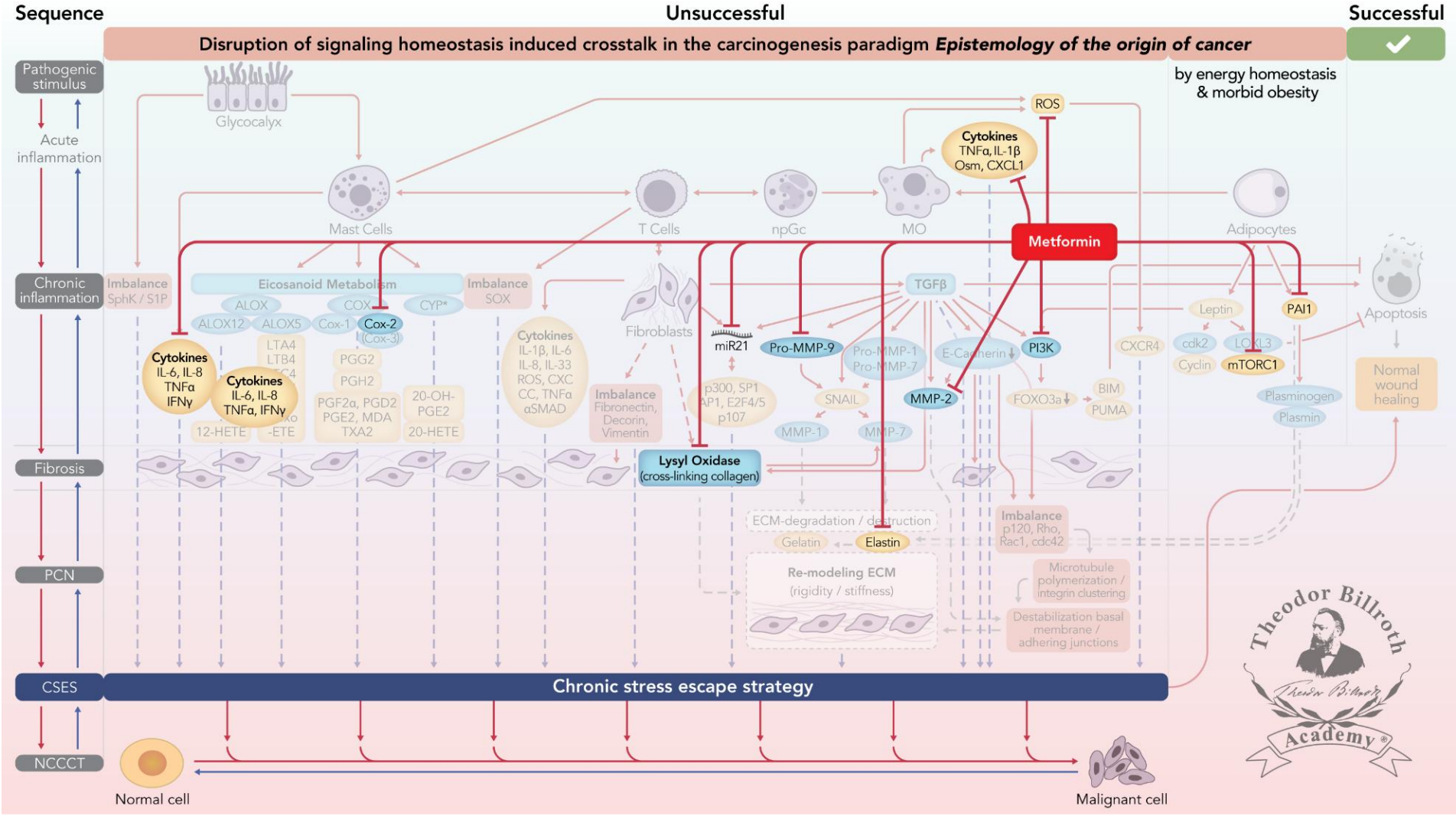
Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Paradigm I (2019)

Cancer Paradigm is consistent with altered signaling induced crosstalk by

- Metformin.

Modified figure from
4OPEN 2019
https://doi.org/10.1051/fopen/2019006



Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Paradigm I (2019)

Cancer Paradigm is consistent with altered signaling induced crosstalk by

- Nf-κB.

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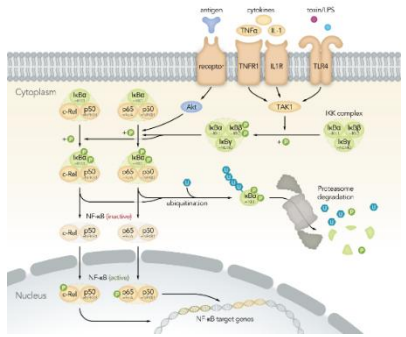
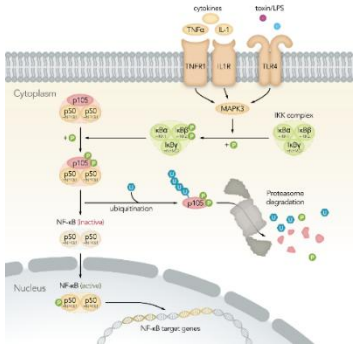
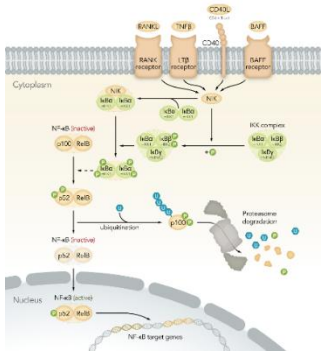
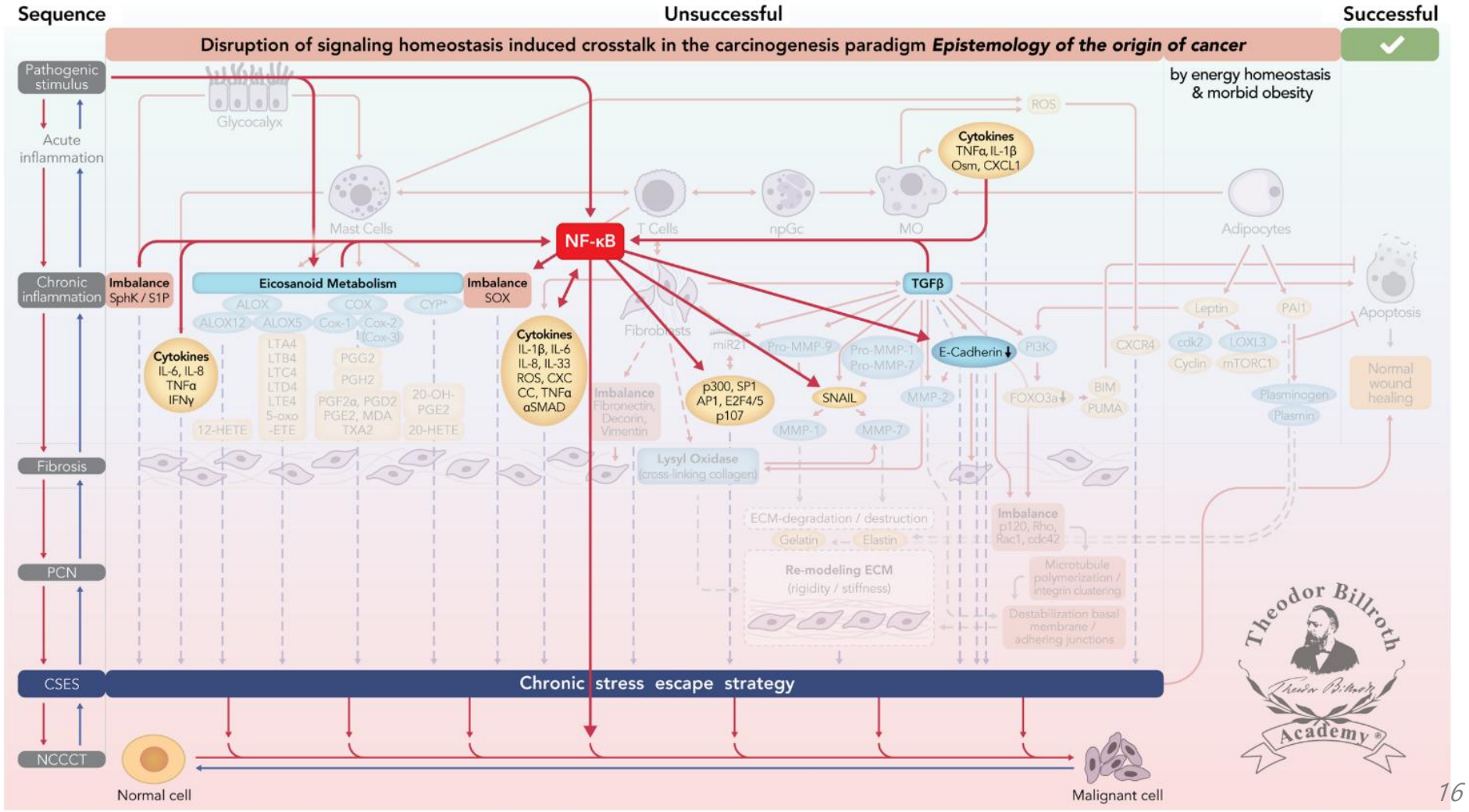
4OPEN 2019
https://doi.org/10.1051/fopen/2019010









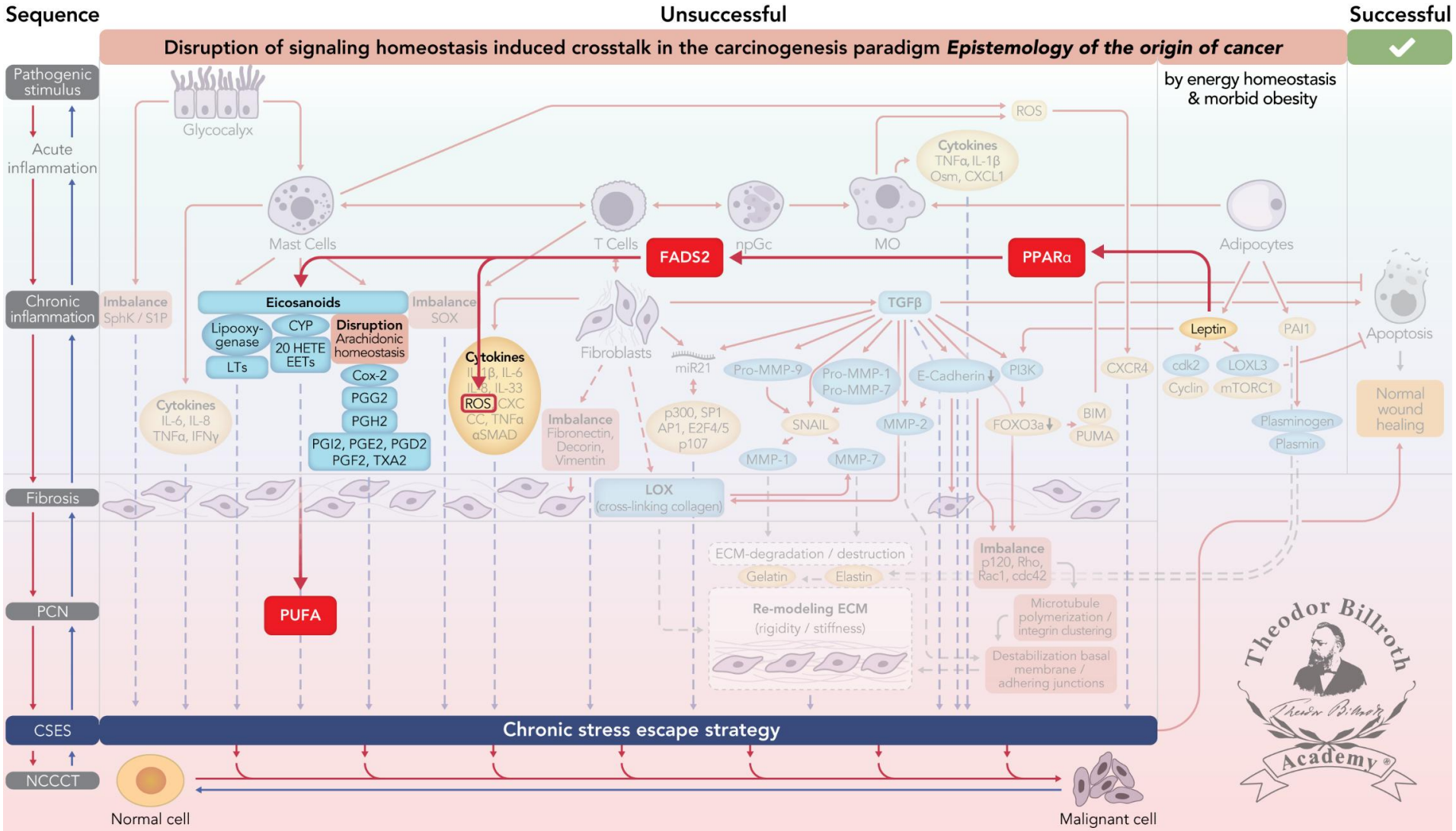
Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Paradigm I (2019)

Cancer Paradigm is consistent with altered signaling induced crosstalk by

Modified figure from
4OPEN 2019
https://doi.org/10.1051/fopen/2019023

- sapienate and fatty acid desaturase 2 (FADS2) = Δ-6-desaturase (D6D).



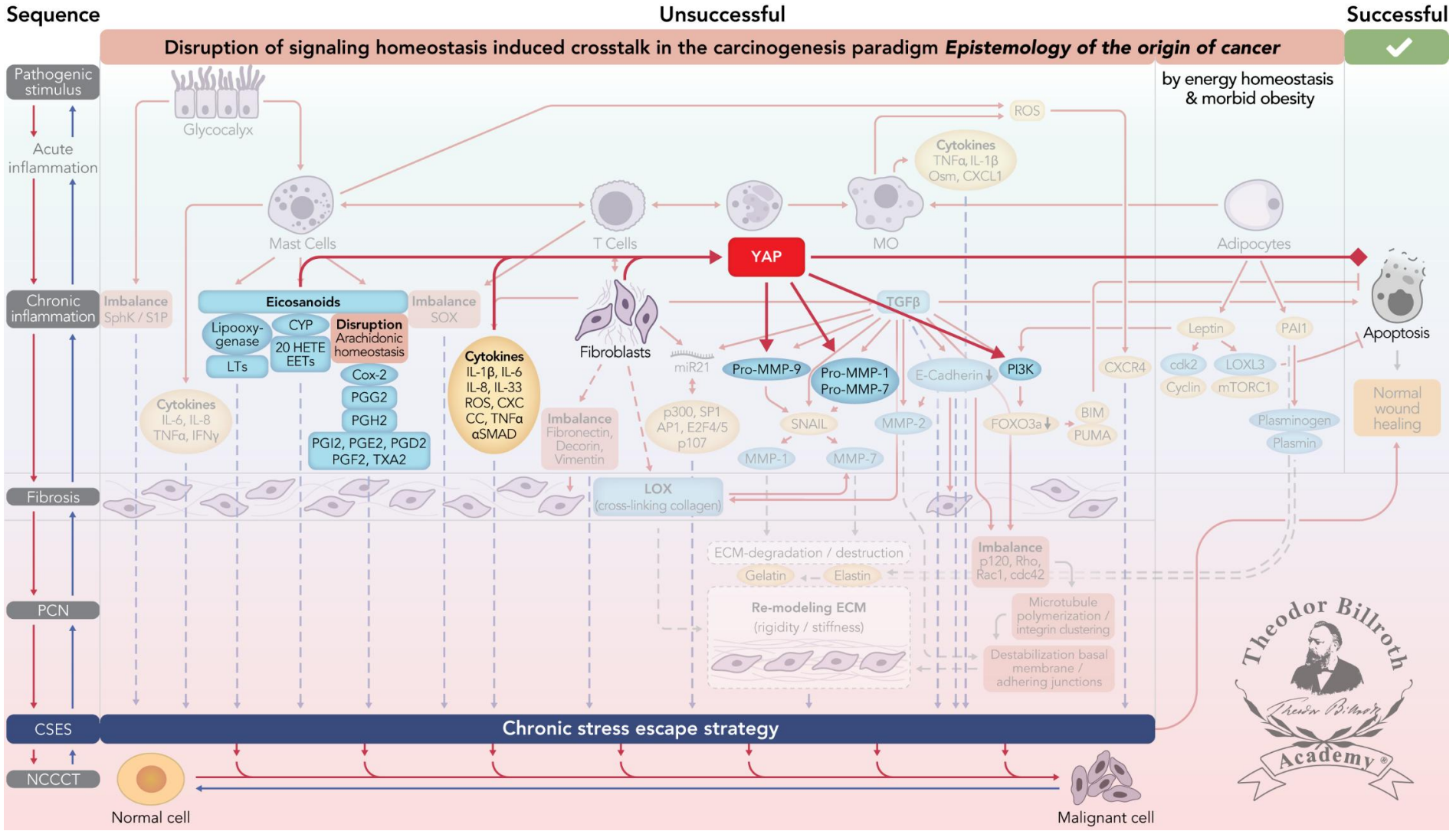
Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Paradigm I (2019)

Cancer Paradigm is consistent with altered signaling induced crosstalk by

Modified figure from
4OPEN 2019
https://doi.org/10.1051/fopen/2019023

- transcriptional coactivator yes-associated protein (YAP).



Epistemology of the Origin of Cancer – Highlights

ad Part I – Cancer Burden I (2019)

Cancer Burden in the disruption of signaling and crosstalk in the

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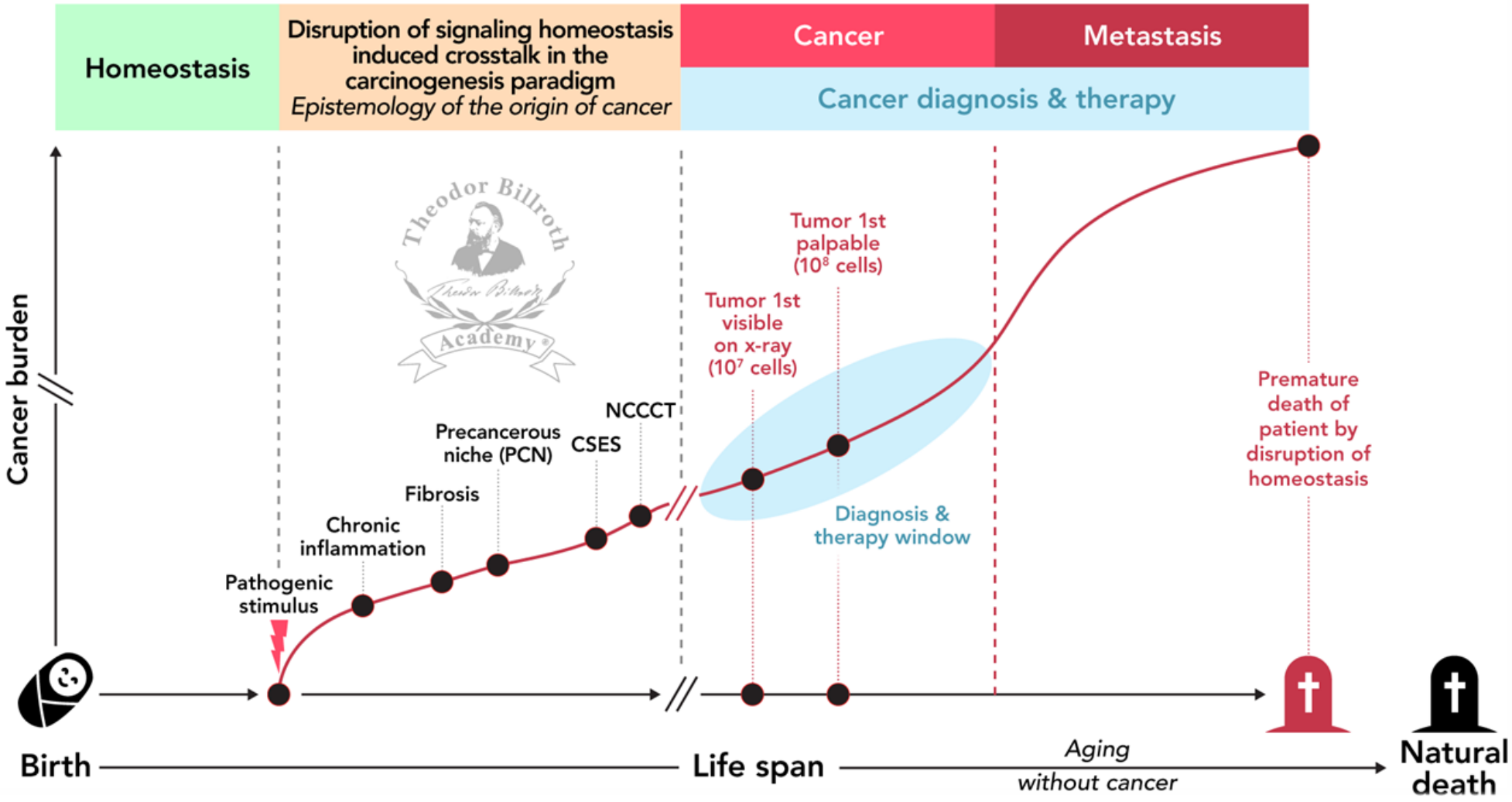
4OPEN 2019
https://doi.org/10.1051/fopen/2019023

- Cancer Paradigm 'Epistemology of the Origin of Cancer'.



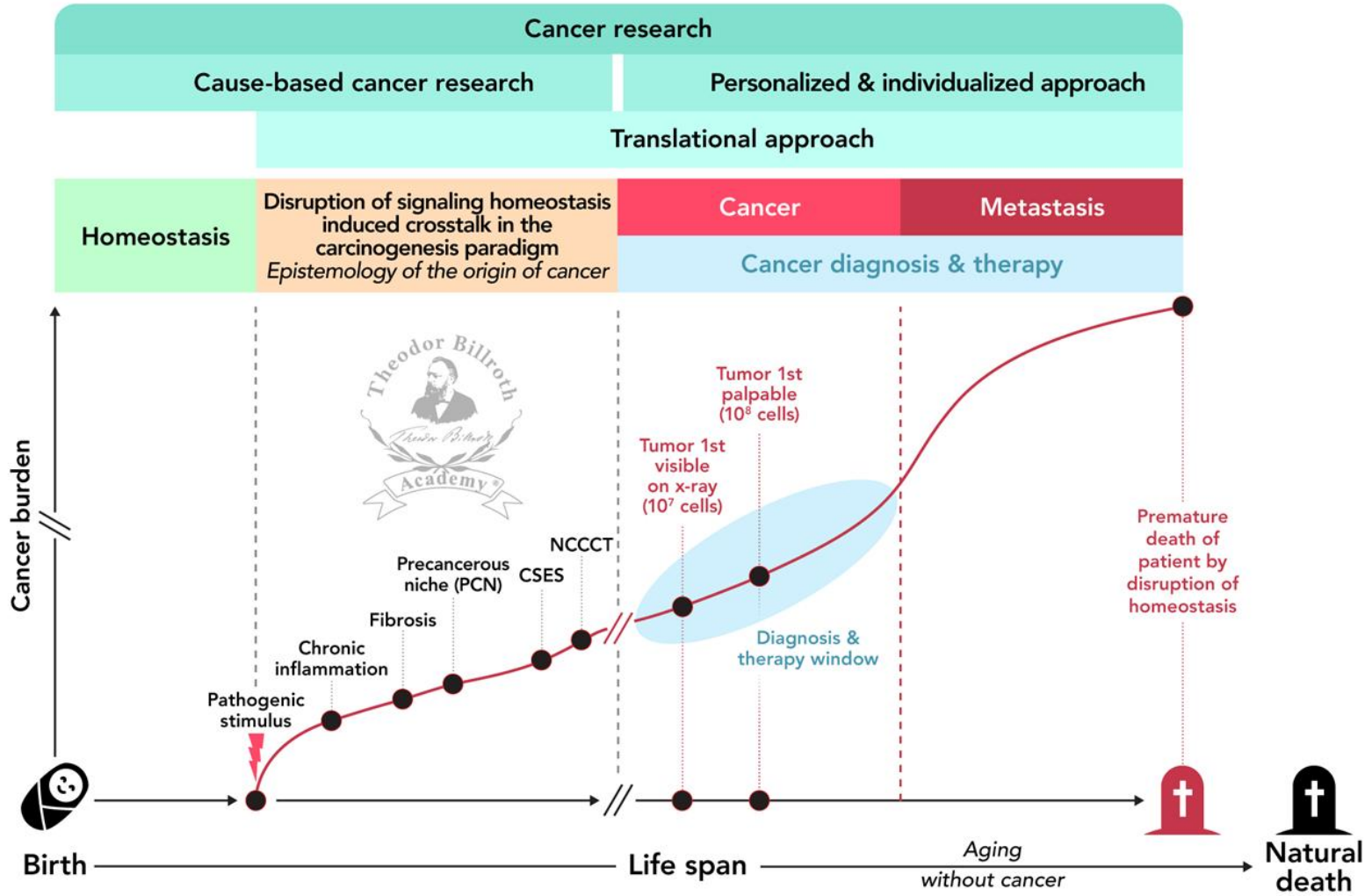
Epistemology of the Origin of Cancer – Highlights

ad Part I – Necessary Cancer Research Strategies (2019)

Necessary Cancer Research Strategies

Modified figure from
4OPEN 2019
https://doi.org/10.1051/fopen/2019023

- together with Cancer Burden in the Cancer Paradigm 'Epistemology of the Origin of Cancer'.



Epistemology of the Origin of Cancer – Highlights

ad Part I – Necessary Cancer Strategies (2019)

Necessary Prevention Strategies

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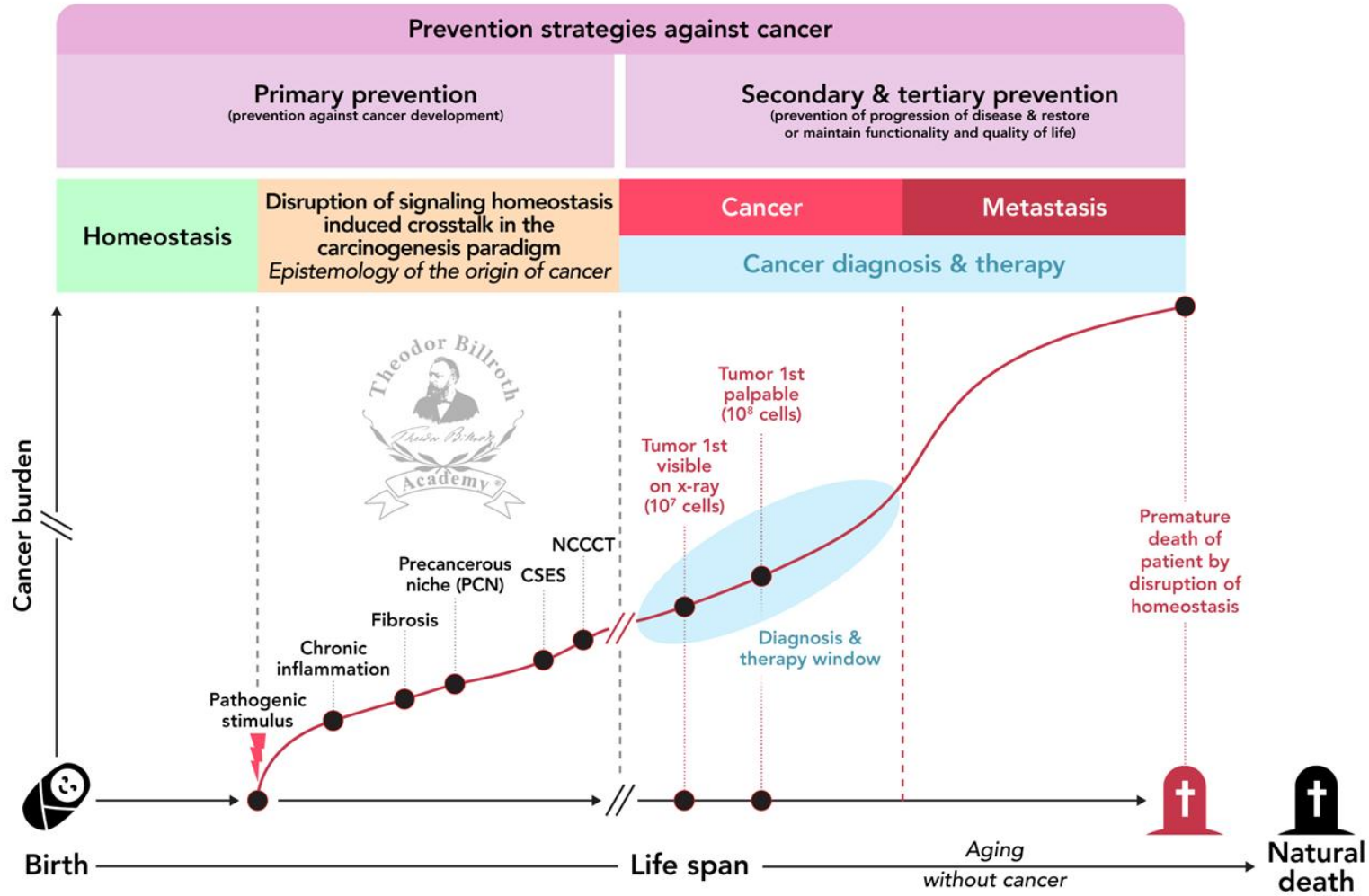
4OPEN 2019
https://doi.org/10.1051/fopen/2019023

- together with Cancer Burden in the Cancer Paradigm 'Epistemology of the Origin of Cancer'.



Epistemology of the Origin of Cancer – Highlights

ad Part I – Physics and Carcinogenesis (2022)

Physics Essentials Enable Deeper Understanding in Signaling and Crosstalk

Modified figure from
Cell Physiol Biochem 2022
https://doi.org/10.33594/000000575

SUPPLEMENT
Cell Physiol Biochem 2022
https://www.cellphysiolbiochem.com/Articles/000575/SM/SM_1033594000000575.pdf

- in the Cancer Paradigm 'Epistemology of the Origin of Cancer'.

Table 1. Units of dose (modified from [34])

	Unit	Symbol	Conversion factor
Quantifying radioactive decay	Becquerel (SI)	Bq	1 disintegration/s = 2.7×10^{-11} Ci
	Curie	Ci	3.7×10^{10} disintegrations/ s = 3.7×10^{10} Bq
	activity of substances are expressed as activity per weight or volume e.g., Bq/g or Ci/L)		
Quantifying exposure and dose	Gray (SI)	Gy	1 J/kg = 100 rad
	Rad	rad	0.01 Gy = 100 erg/s
	Sievert (SI)	Sv	1 J/kg = 100 rem

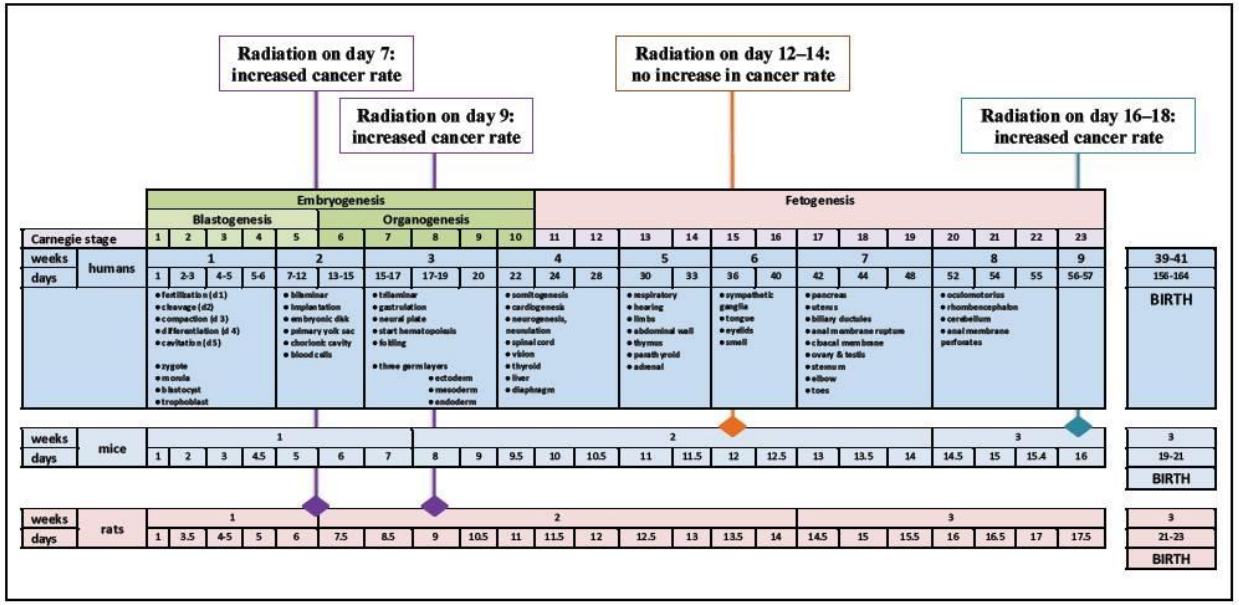
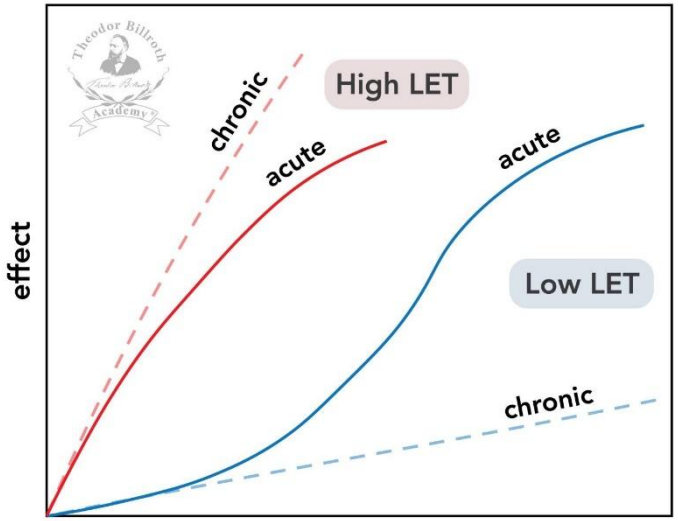


Fig. 3. Radiation effects and cancer response during development according to Carnegie stages in humans, mice, and rats. Approximate Carnegie stages delineated through the development of structures, modified according to [185-195]; also reviewed in [196]. Results are presented for various irradiation dates in rats [197-199] and mice [200, 201].

Table 2. Atomic bombs detonated at Hiroshima and Nagasaki [34, 55, 61, 63]

Variable	Hiroshima	Nagasaki
Date, time	6 Aug 1945, 08:15 AM	9 Aug 1945, 11:02 AM
Atomic bomb designation	L-11, Little Boy	F-31, Fat Man
Atomic bomb material	Uranium-235, 238	Plutonium-239
Isotope mass	64 kg	6.2 kg
Burst height	1.903 ft (600 m)	1.650 ft (503 m)
Wind	8 knots at 170 grad	1-knot head wind
Head wind spread	0	1
Yield (uncertainty)	15 kt (20%)	21 kt (10%)
Outside range	12–18 kt	18.9–23.1 kt



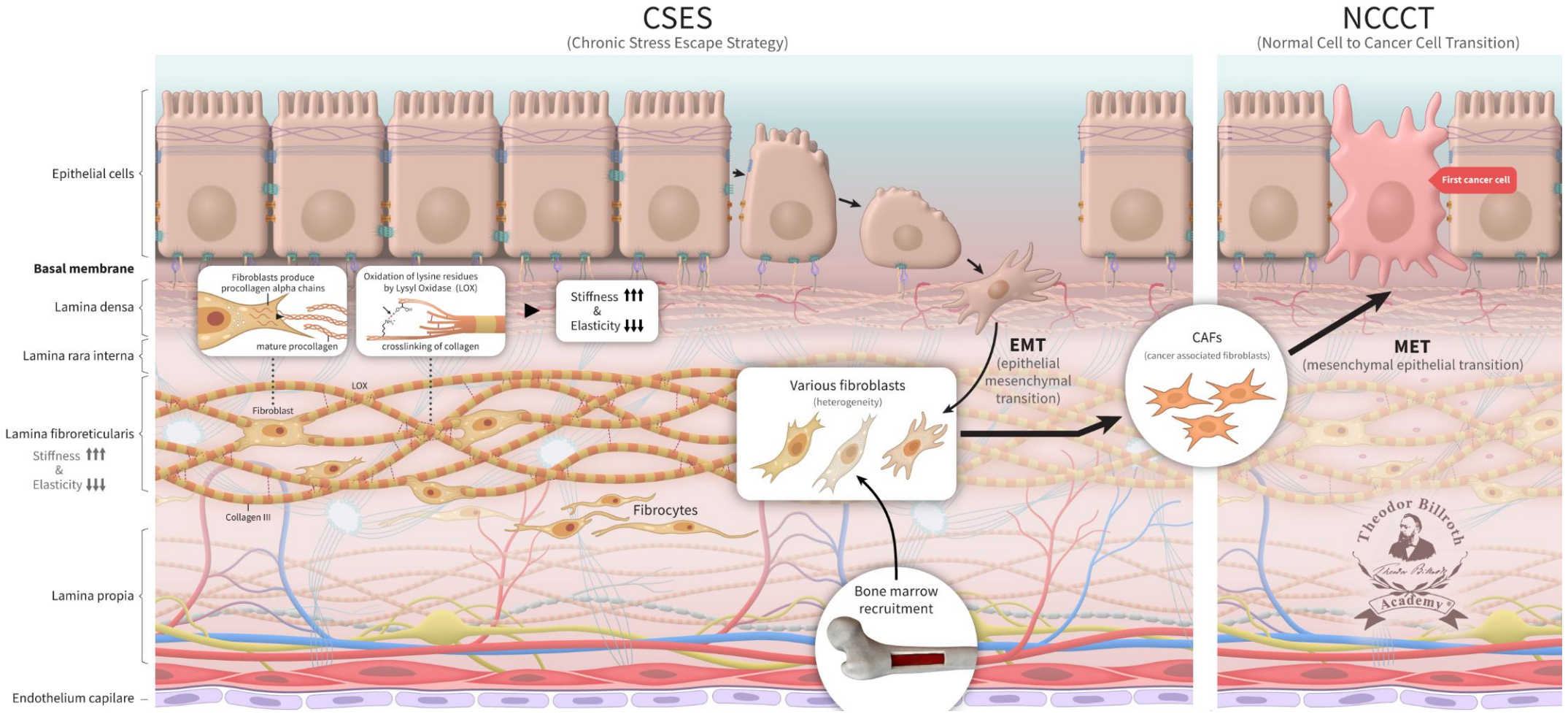
Epistemology of the Origin of Cancer – Highlights

2. Part II – First Cancer Cell (2023)

The 'First Cancer Cell: (5) Chronic stress escape strategy (CSES), including EMT from epithelial cells, lead to differentiation into cancer-associated fibroblasts (CAFs), expressing epithelial & mesenchymal markers. (6) Finally, CAFs undergo MET. Epithelial marker facilitates the integration into the epithelium. Fibroblasts are the initial precursors.

Modified figure from
Cell Physiol Biochem 2023
https://doi.org/10.33594/000000672

SUPPLEMENT
Cell Physiol Biochem 2023
https://www.cellphysiolbiochem.com/Articles/000672/SM/000672_SM.pdf



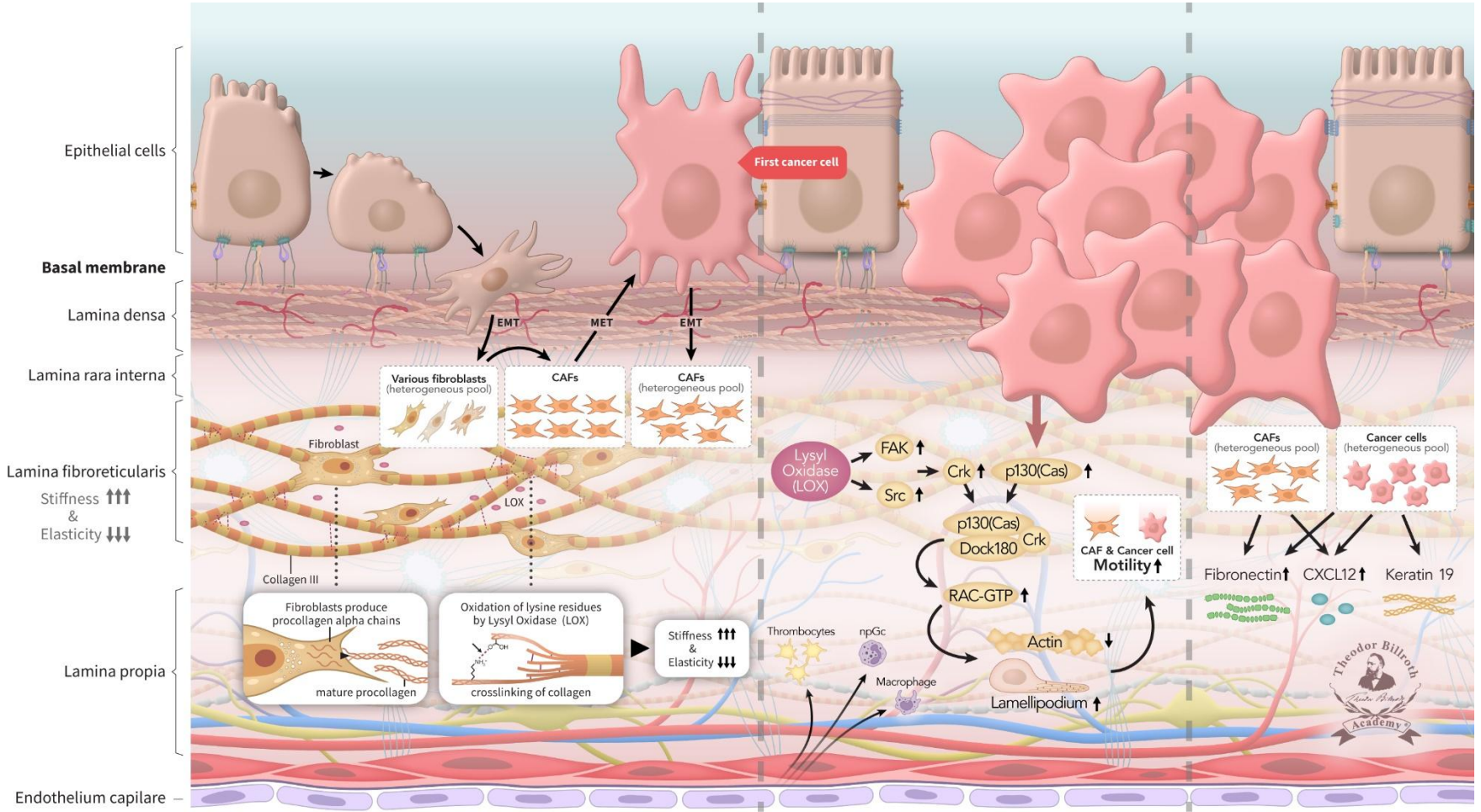
Epistemology of the Origin of Cancer – Highlights

3. Part III – Pre-Metastastic Niches (2025)

Pre-Cancerous Niche (PCN) transforms to Pre-Metastatic Niche 1 (PMN-1): Lysyl oxidase induced FAK with p130(cas)/crk/DOCK180 formation, lead to lamellipodia. CAFs and cancer cells secret fibronectin & CXCL12, each prerequisite for rising migration. Platelets, neutrophils, and macrophages are increasingly recruited.

Modified figure from
Cell Physiol Biochem 2025
https://doi.org/10.33594/000000826

SUPPLEMENT
Cell Physiol Biochem 2025
https://www.cellphysiolbiochem.com/Articles/000672/



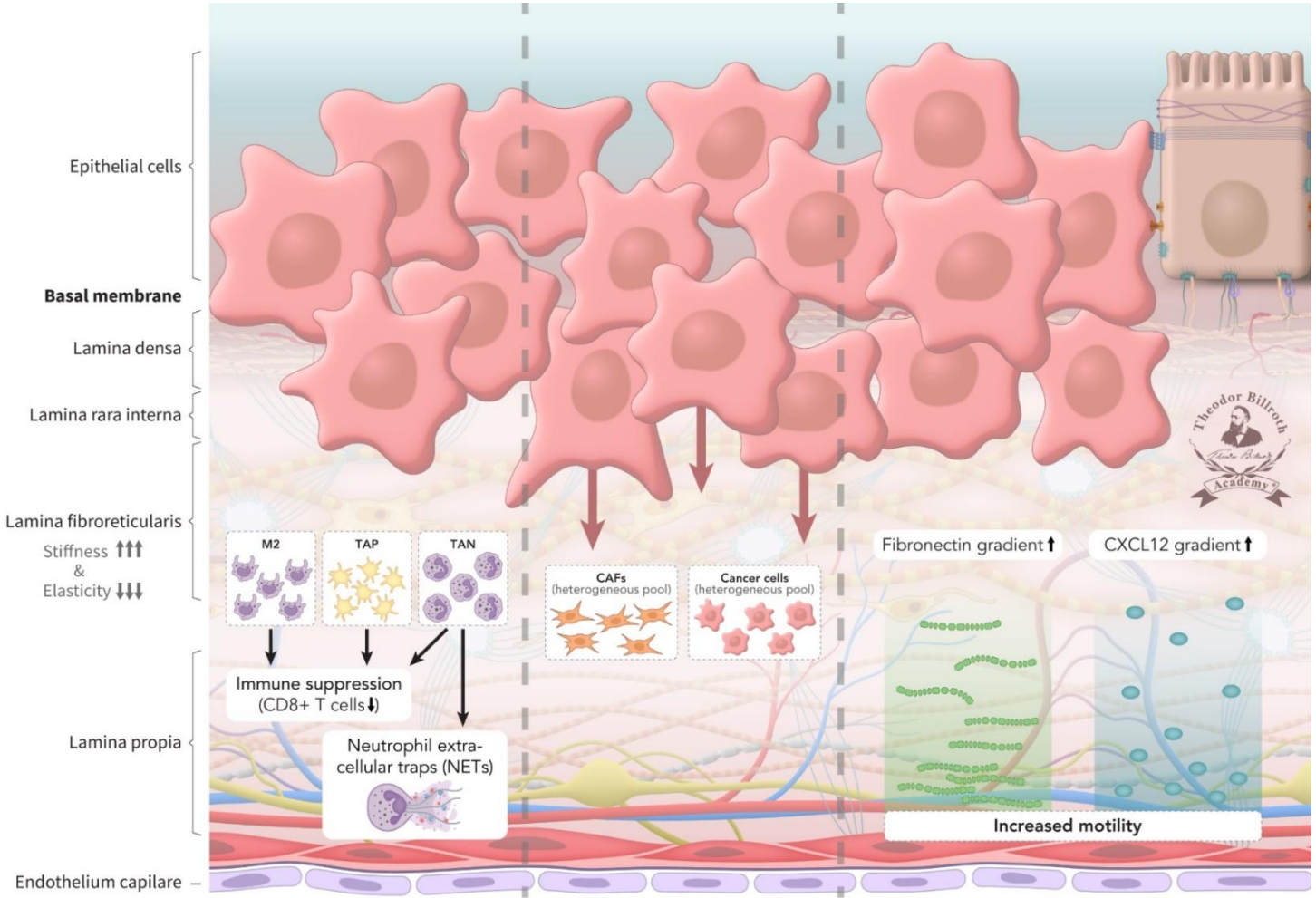
EPISTEMOLOGY OF THE ORIGIN OF CANCER – HIGHLIGHTS

ad Part III – Pre-Metastastic Niches (2025)

PMN-1 transformation to PMN-2: Tumor-associated cells (TACs) from tumor-associated macrophages (TAM), tumor-associated platelets (TAP), and tumor-associated neutrophils (TAN) transform from anti- tumorigenic to pro-tumorigenic TACs and local immunosuppression. CXCL12 and fibronectin gradient, lamellipodia, blebbing and extravesicular vesicles (EVs) facilitate mobility for CAFs and cancer cells migration towards the endothelium.

Modified figure from
Cell Physiol Biochem 2025
https://doi.org/10.33594/000000826

SUPPLEMENT
Cell Physiol Biochem 2025
https://www.cellphysiolbiochem.com/Articles/000672/



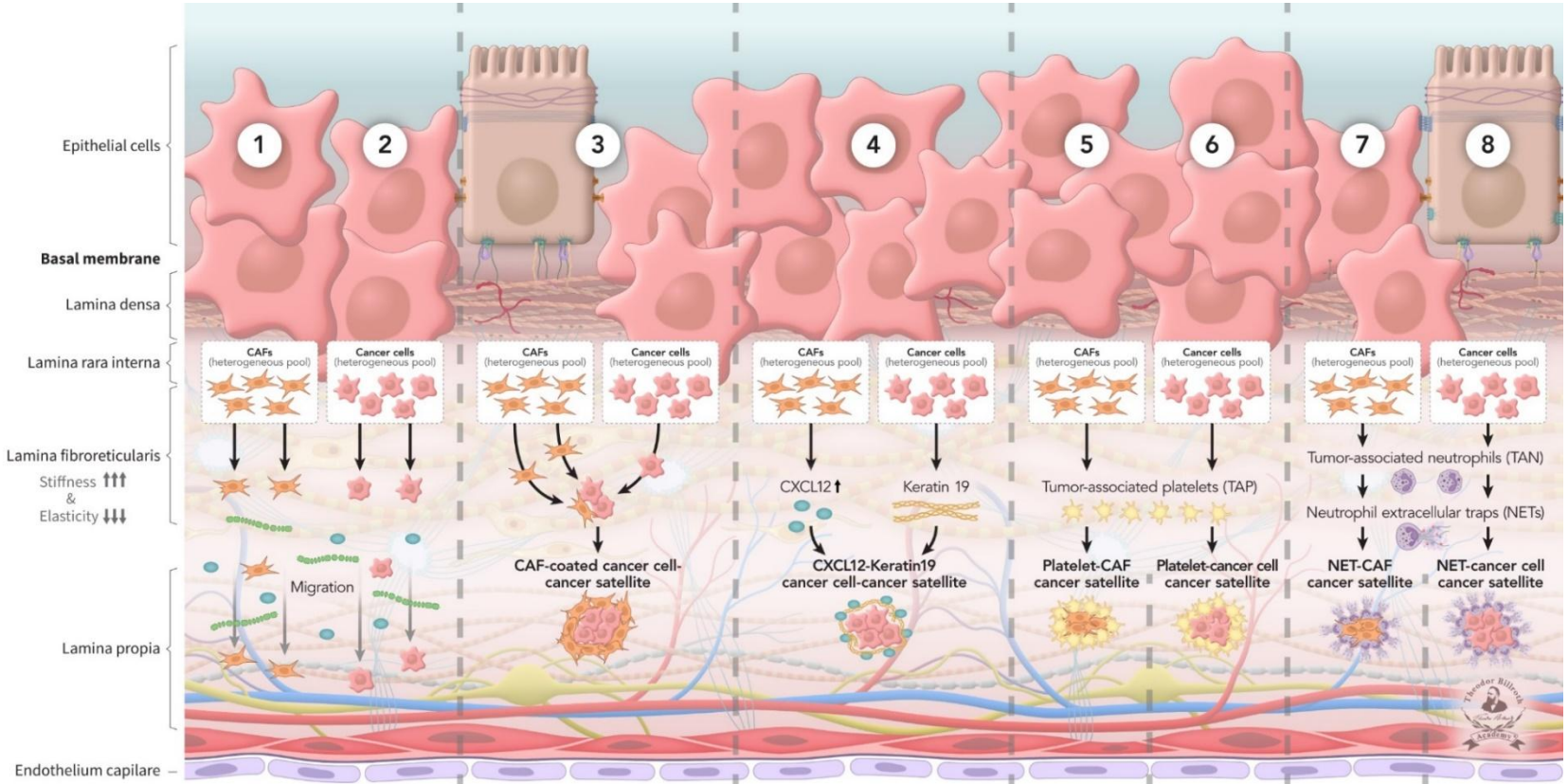
Epistemology of the Origin of Cancer – Highlights

ad Part III – Pre-Metastatic Niches (2025)

PMN-3 serves as pre-requisite that metastasis arise: 8 cancer satellites with Trojan horses enable immune escape, and disseminate (intravasation):

1. Cancer Cells, and
2. CAFs, migrating along CXCL12 and Fibronectin Gradient
3. CAFs surround Cancer Cells, and migrate.
4. CXCL12–Keratin 19 coated Cancer Cells migrate.
5. CAFs, and
6. Platelets surround Cancer Cells, and migrate.
7. Neutrophils formed NETs shield CAFs, and
8. Cancer Cells, for migration.

Summary: Metastasis in epithelial cancer occurs in parallel with carcinogenesis after PCN is transformed into pre-metastatic niches (PMNs), which are indispensable to the origin of metastasis. A series of eight heterogeneous cancer satellites develop, including Trojan horses (immune evasion), alongside reciprocally affecting sequences, which travel alone or in combination.



Modified figure from
Cell Physiol Biochem 2025
https://doi.org/10.33594/000000826

SUPPLEMENT
Cell Physiol Biochem 2025
https://www.cellphysiolbiochem.com/Articles/000672/

Epistemology of the Origin of Cancer – Highlights

ad Part I-to-III – Erosion of Healthcare and Scientific Integrity (2025)

Modified figure from
J Healthcare Leadership 2025
https://doi.org/10.2147/JHL.S506767

Development of cancers are frequently touted as "breakthroughs" in the media but, in reality, cancer costs explode, incidences are rising, and metastases and overall non-adjusted mortality rates have not changed substantially. Most cancers (80.5%) are epithelial whereas a minority (10%) are mesenchymal (e.g., sarcoma, myeloma, and leukemia) tumors, lymphatic system tumors (e.g., lymphoma and myeloma), central nervous system tumors, meningiomas, and mesotheliomas; the remainder form a highly heterogeneous group of other malignancies.

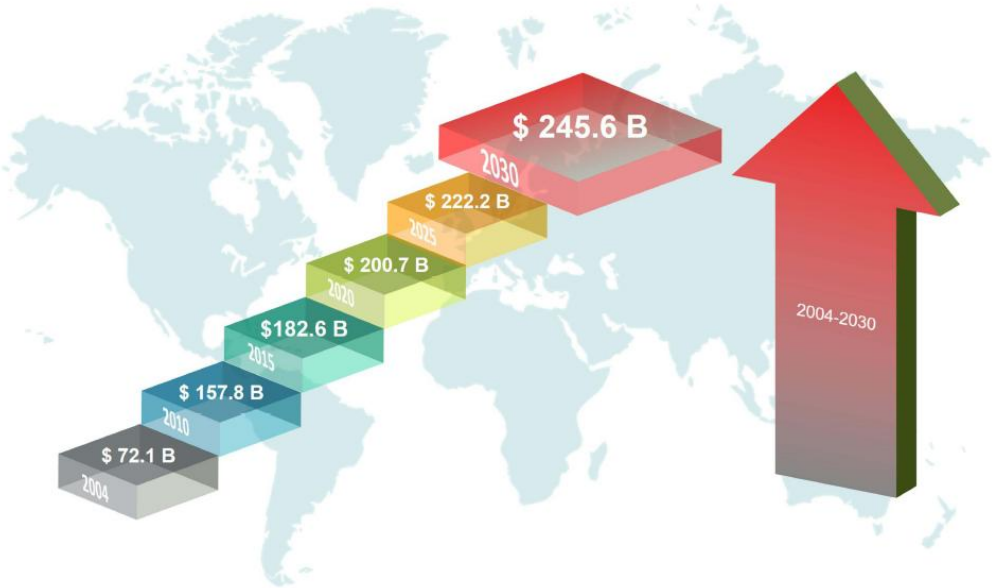


Table 1 Mass of All Cancers are Epithelial Cancers.

Epithelial Cancer Percentage	Cancer	Number	Percentage
80.5%	Gastrointestinal cancers	5,026,243	26%
	Gyneco-oncologic cancers	3,660,202	19%
	Uro-oncologic cancers	2,529,351	13.1%
	Lung cancers	2,206,771	11.4%
	Epithelial dermato-oncologic cancers	1,198,073	6.2%
	Head and neck cancers	933,931	4.8%

Note: Data from these studies.[6,25]

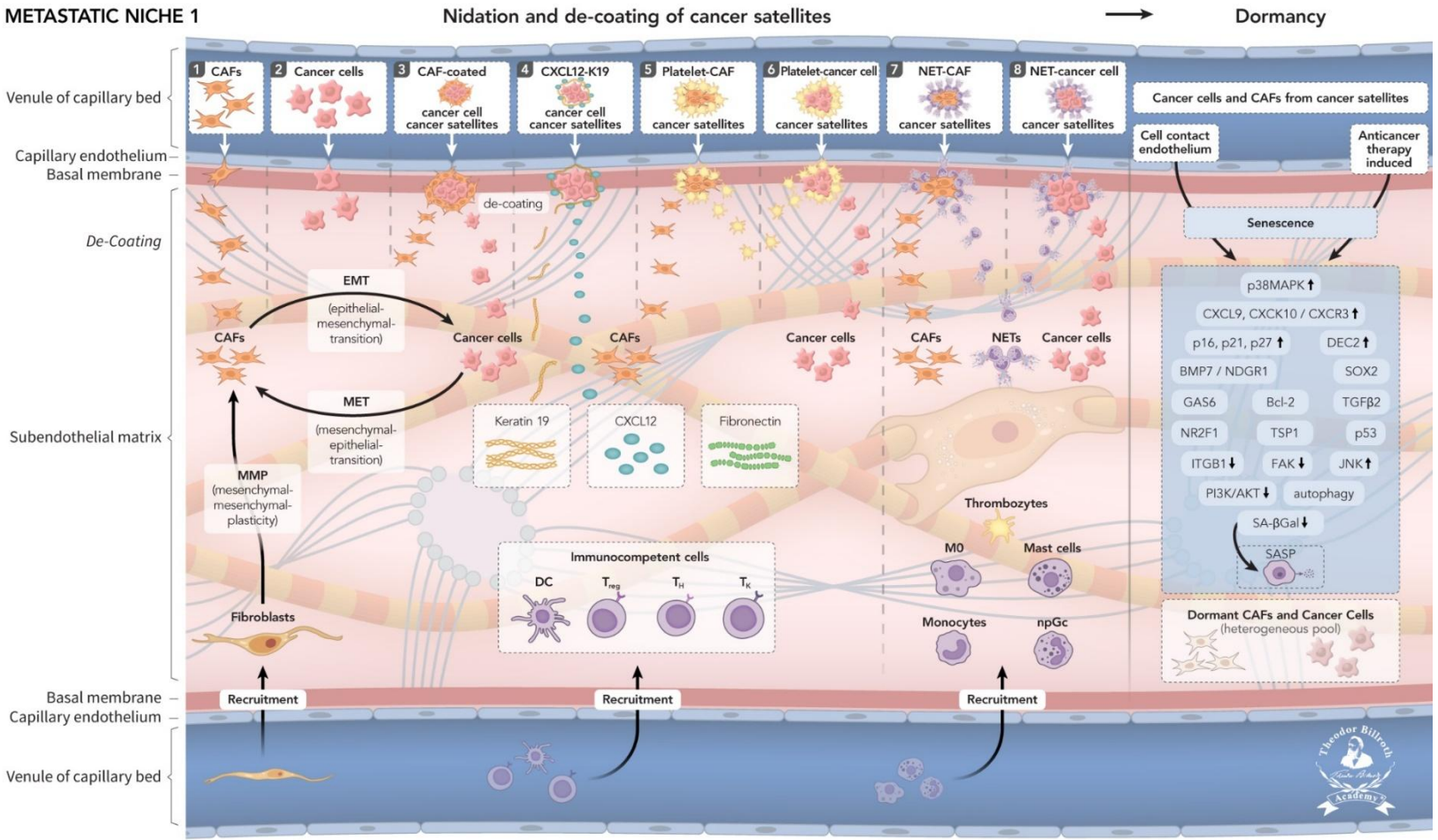
EPISTEMOLOGY OF THE ORIGIN OF CANCER – HIGHLIGHTS

4. Part IV – Metastastic Niches (2026)

Metastatic Niche 1 (MN-1) develops from Pre-Metastatic Niches (PMNs): Cancer satellites of MN-1 extravasate after traveling and nidate at the capillary bed following transendothelial migration when de-coating into its constituent parts occurs with cell epithelial-mesenchymal transition (EMT), mesenchymal-epithelial transition (MET), mesenchymal-mesenchymal plasticity (MMP), recruited immunocompetent cells, and dormancy.

Modified figure from
Cell Physiol Biochem 2026
https://doi.org/XX

SUPPLEMENT
Cell Physiol Biochem 2026
https://www.cellphysiolbiochem.com/XX



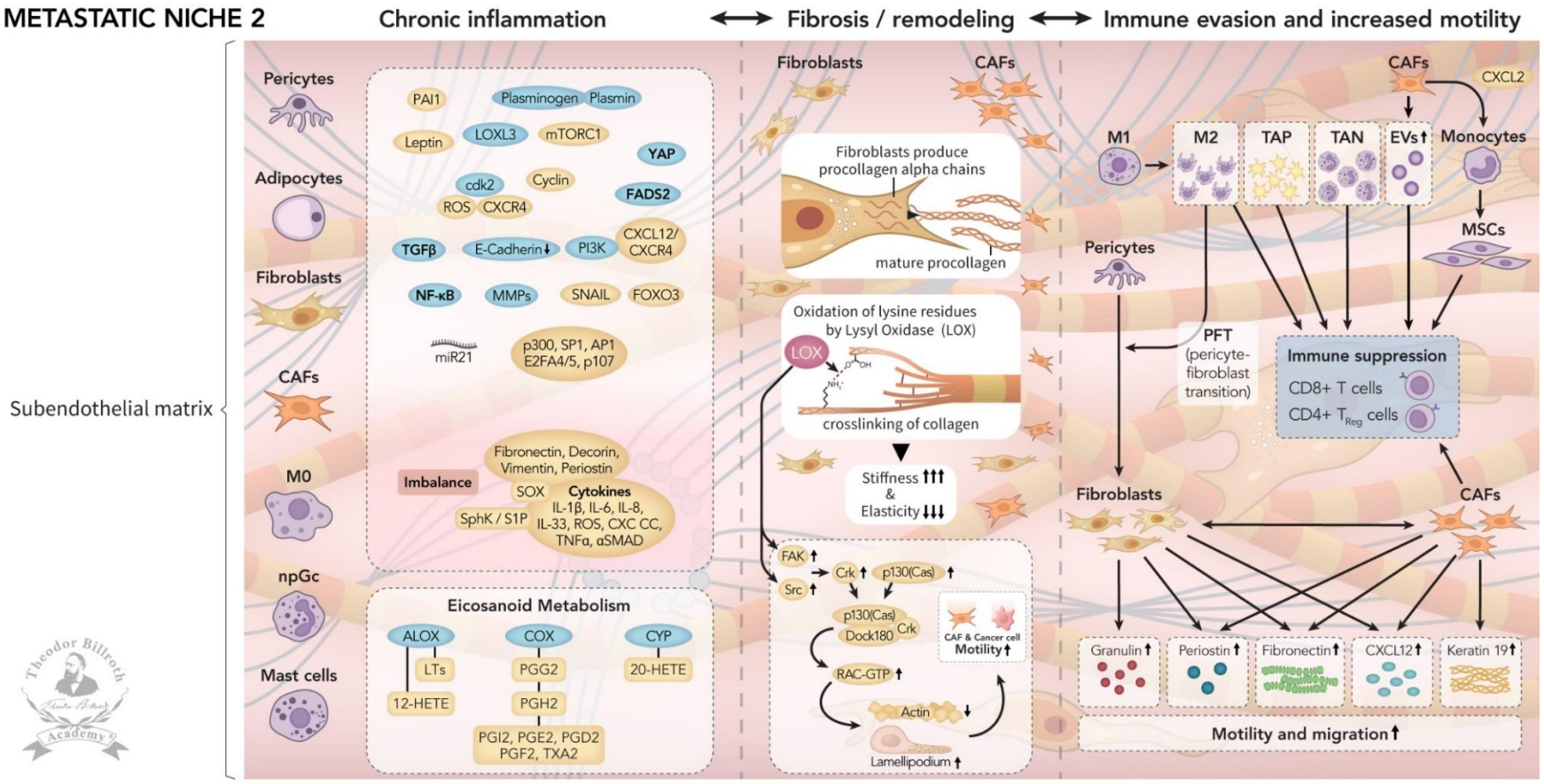
EPISTEMOLOGY OF THE ORIGIN OF CANCER – HIGHLIGHTS

ad Part IV – Metastastic Niches (2026)

MN-1 transformation to MN-2: Chronic inflammation, and remodeling through LOX leads to increase lamellipodia/motility. Recruited macrophages, platelets and neutrophils lead to pro-tumorigenic TACs: TAMs (M2), TAPs, and TANs. CAFs secrete EVs and CCL2 which leads into mesenchymal stem cells (MSCs), and immune suppression. These changes in the microenvironment result in consistent increases of granulosin, periostin, CXCL12, fibronectin, and KT19, which further increase motility and promote migration of non-dormant CAFs and cancer cells.

Modified figure from
Cell Physiol Biochem 2026
https://doi.org/XX

SUPPLEMENT
Cell Physiol Biochem 2026
https://www.cellphysiolbiochem.com/XX



EPISTEMOLOGY OF THE ORIGIN OF CANCER – HIGHLIGHTS

ad Part IV – Metastastic Niches (2026)

MN-3 predispose to metastases, or to dormancy: Increased cell plasticity induce newly developed metastasis-associated fibroblast (MAFs) to re-trigger dormancy. This is followed by increased heterogeneity leading to immune suppression and to newly developed metastatic cancer satellites:

1. Metastatic cancer cells, and
2. MAFs migrate along gradients
3. Metastatic cancer cells surrounded by MAFs
4. CXCL12 and Keratin 19 coats metastatic cancer cells
5. Platelets surround metastatic cancer cells and
6. MAFs
7. Neutrophil extracellular traps (NETs) shield metastatic cancer cells, and
8. MAFs

Modified figure from
Cell Physiol Biochem 2026
https://doi.org/XX

SUPPLEMENT
Cell Physiol Biochem 2026
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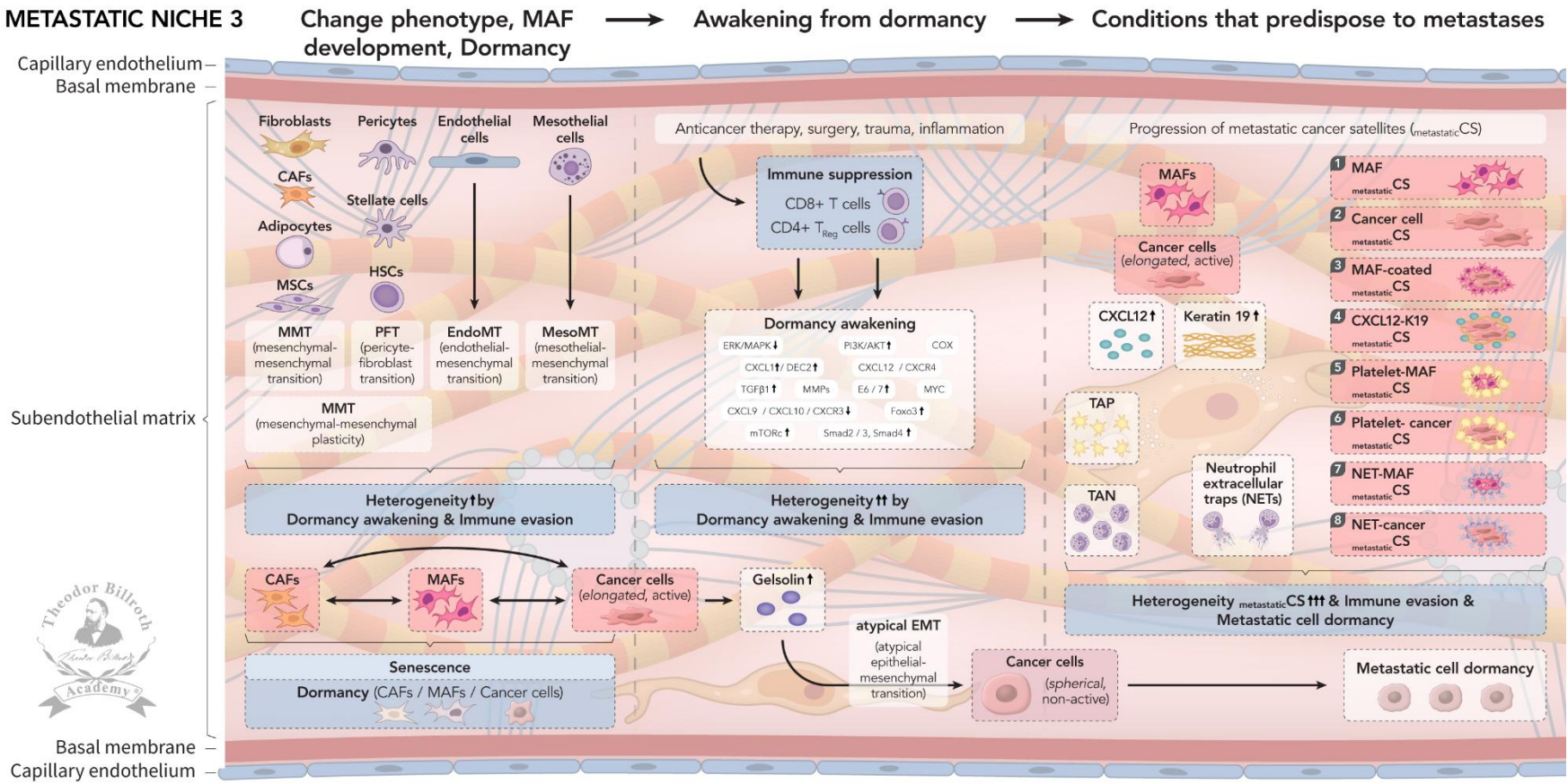
Summary: The sequence of steps that lead to the formation of the three metastastic niches are requisite conditions for metastases. It should be emphasized that metastasis is not a late event in cancer and, in fact, occurs concurrently with carcinogenesis. There is a vast heterogeneity of CAFs, MAFs, dormant and awakened cancer cells which progress to metastatic cancer satellites, and these help in fulfilling the conditions that predispose to metastases.



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Cell Physiol Biochem 2022 — Full Text — https://doi.org/10.33594/000000575

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