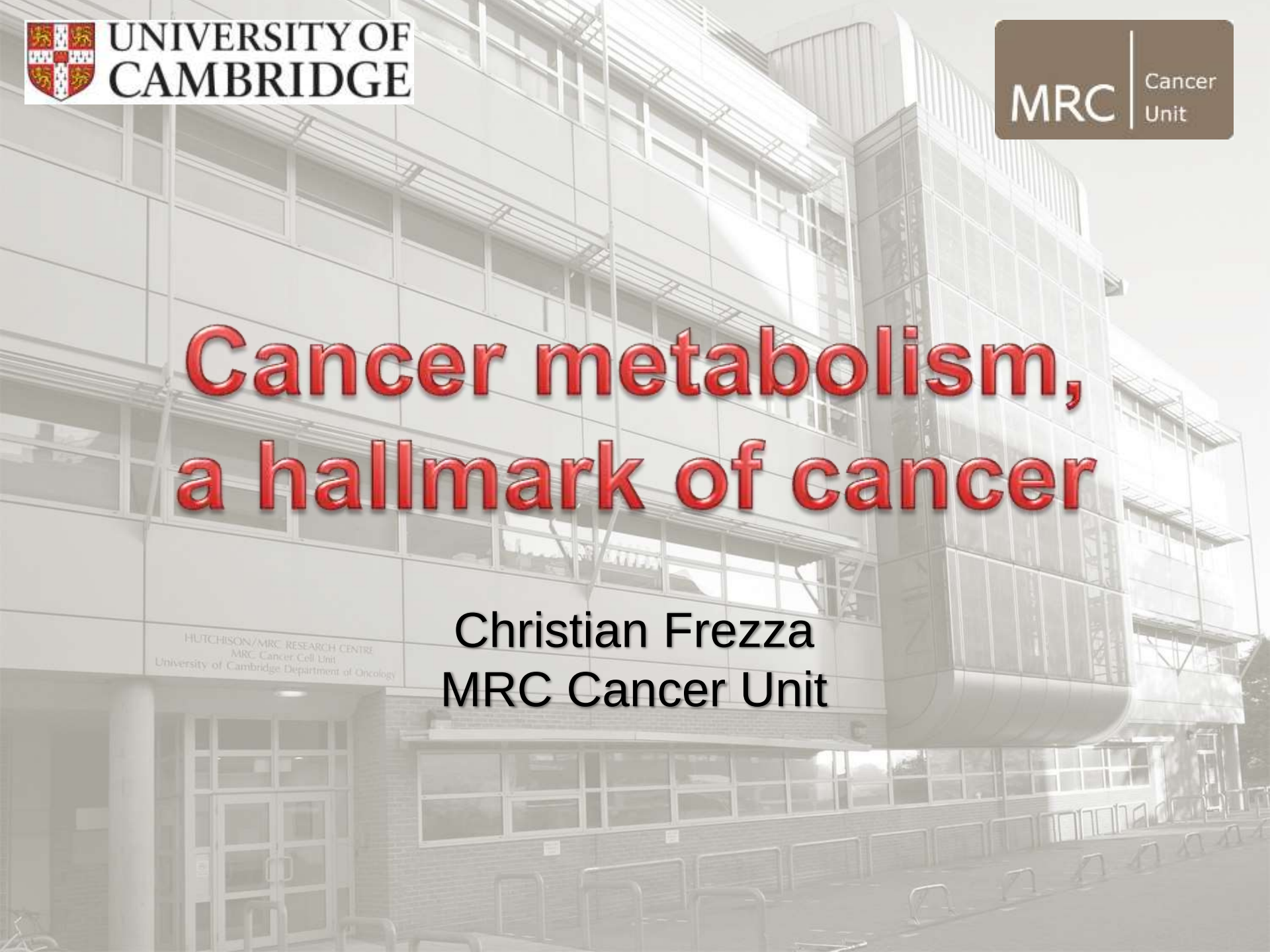


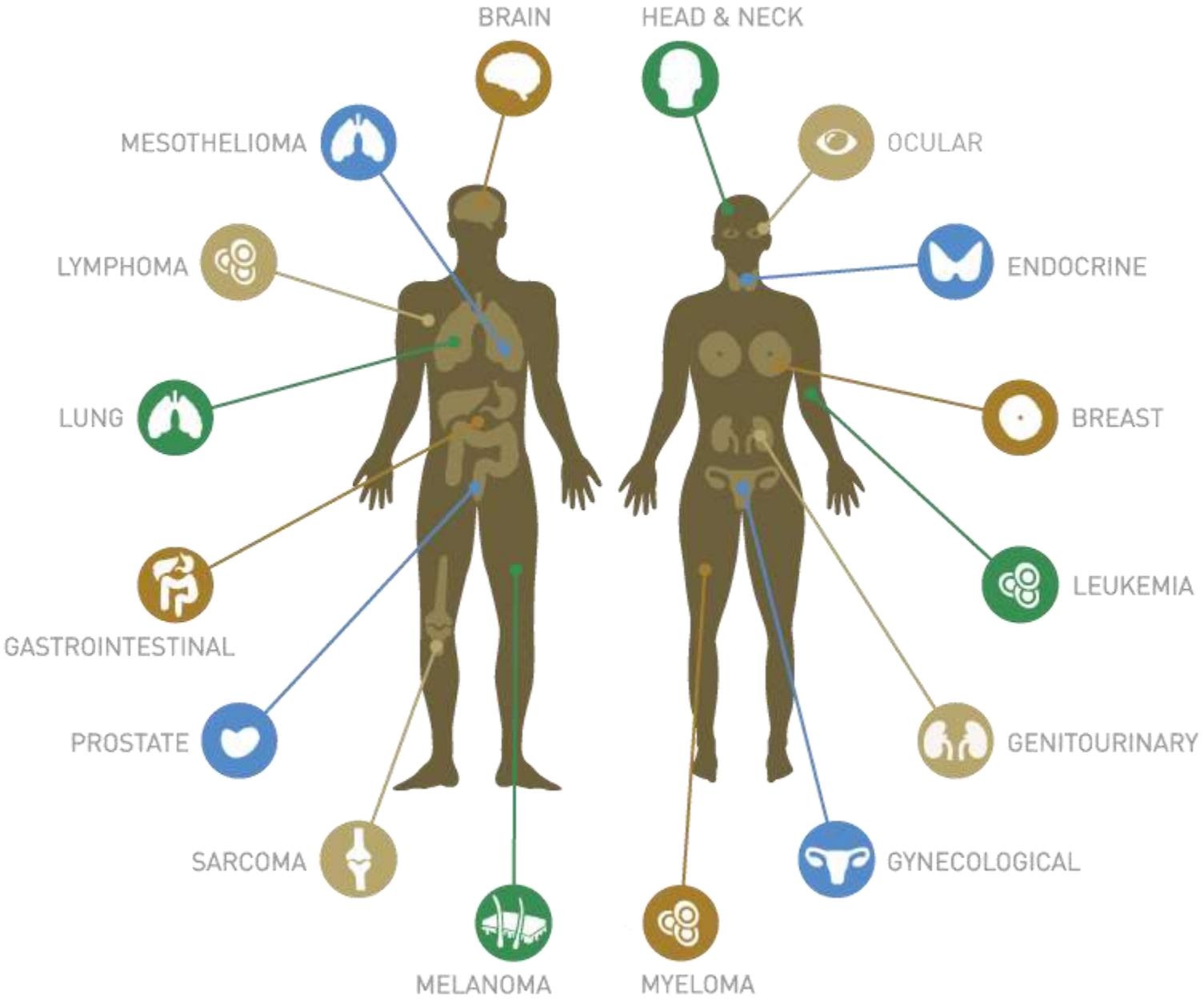
UNIVERSITY OF CAMBRIDGE

MRC Cancer Unit

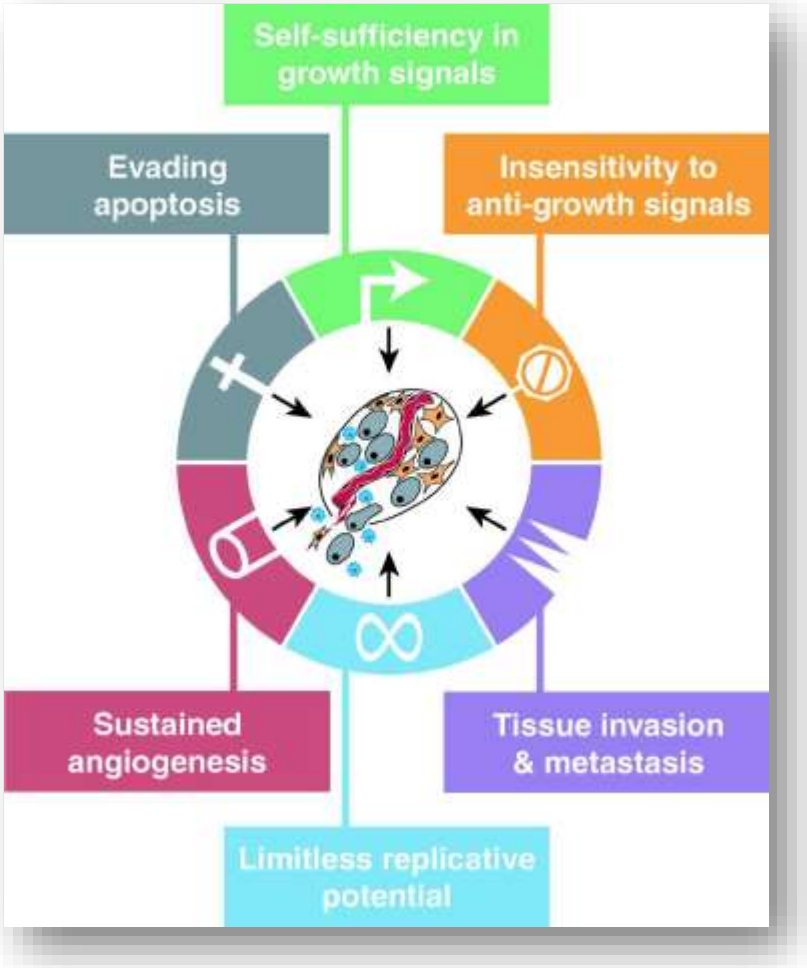
Cancer metabolism, a hallmark of cancer

Christian Frezza
MRC Cancer Unit

What is cancer?

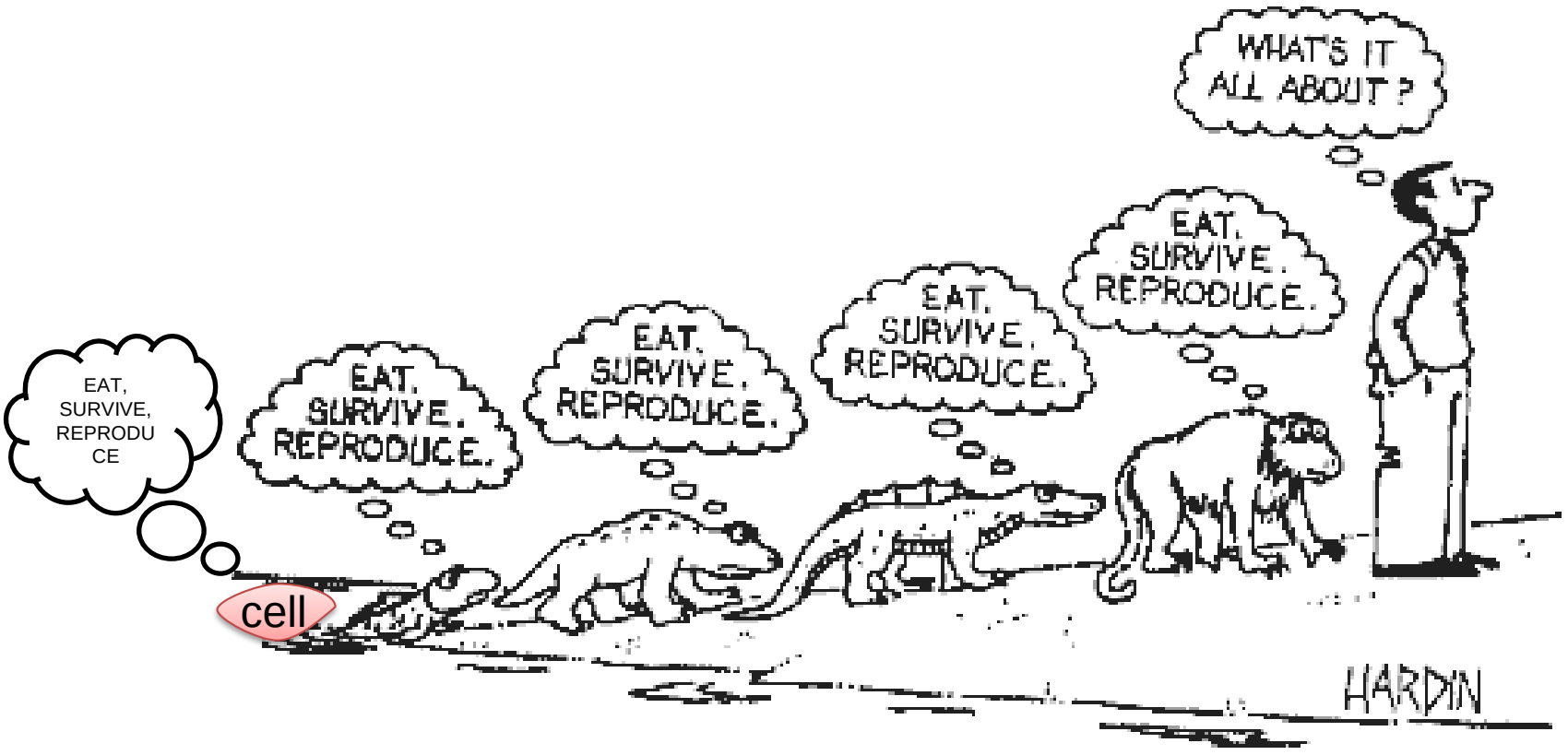


What is cancer?

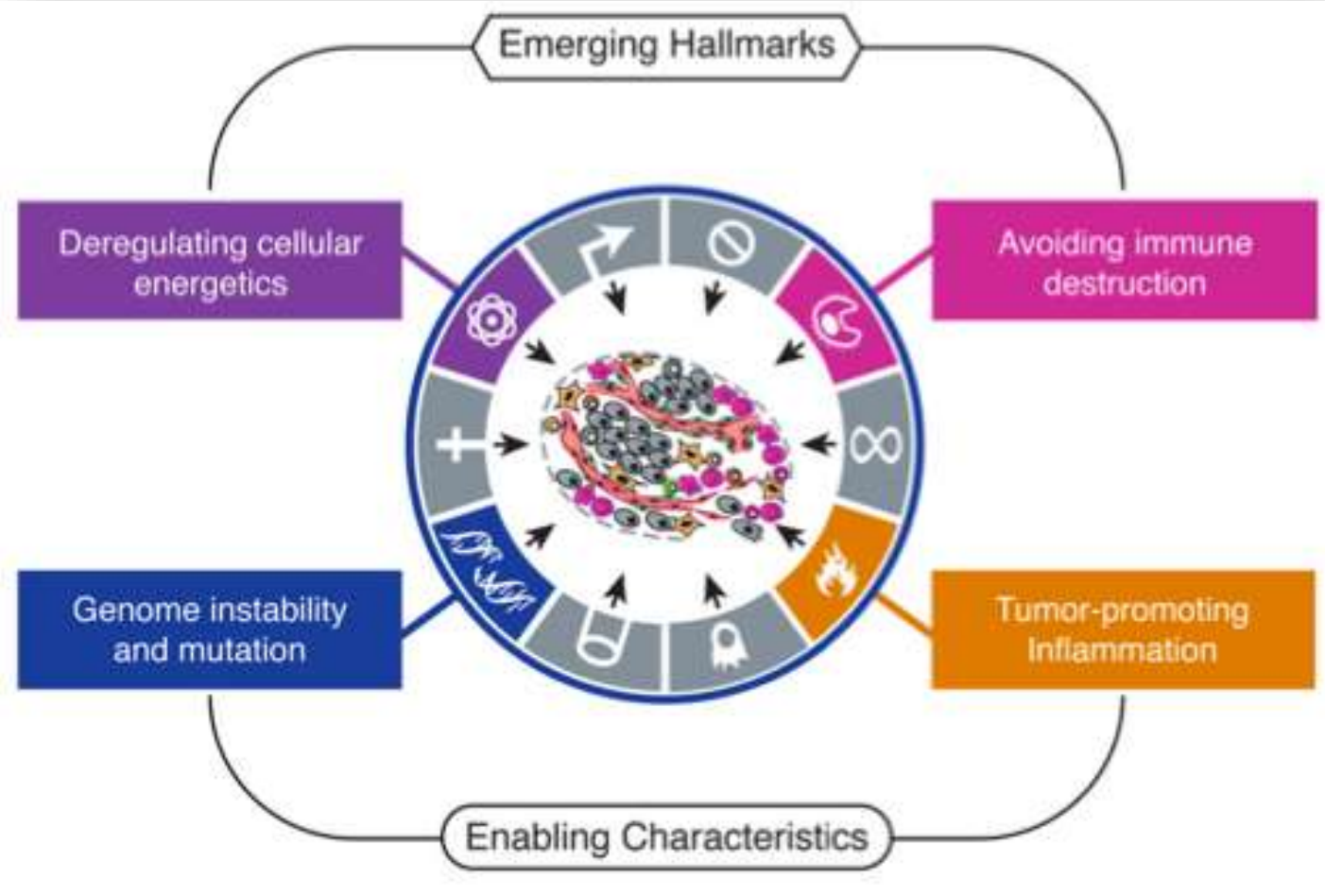


Douglas Hanahan, Robert A. Weinberg; The Hallmarks of Cancer
Cell, Volume 100, Issue 1, 7 January 2000, Pages 57–70

Cancer cells need energy to proliferate



Metabolism is an emerging hallmark of cancer



Douglas Hanahan, Robert A. Weinberg; Hallmarks of Cancer: next generation
Cell, Volume 144, Issue 5, p646–674, 4 March 2011

The timeline of cancer research

Muller observed aberrant metabolism in urine of cancer patients

Warburg observed the increased glycolysis in cancer cell

1890

1924

1912

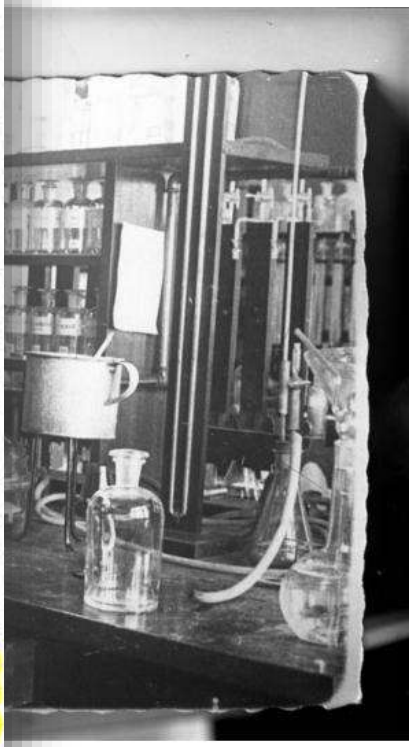
Wassermann hypothesised a role of deregulated respiration in cancer cell

100 Years Ago

Tissue Metabolism in Cancer.

Dr. F. Müller has made some careful comparative observations upon the urine in cases of cancer and other wasting diseases, and in simple starvation. He finds, according to the London *Lancet*, that in the cancerous the excretion of nitrogen far exceeds the amount ingested, and infers that this excess must in consequence be derived from the disintegration of the albuminoids of the body. However, in two out of seven cases this loss was not greater than occurred in other individuals similarly insufficiently nourished. The chlorides were, on the other hand, notably diminished,—a fact, he thinks, pointing to the source of the excreted nitrogen; viz., from the organ albumen, and not from the circulating albumen. Obviously, however, many diseases share, with carcinoma, in this disintegrating process, as Müller showed to be the case in chronic febrile affections, especially severe forms of malaria, in leukæmia, and pernicious anæmia. Previous observers do not coincide in their statements on this head as regards leukæmia. Voit and Pettenkofer found no marked evidence of increased metabolism in this affection, and Fleischer and Penzoldt concurred in this so far as regards mild cases. But in severe cases the last-named find the urea to be increased both absolutely and relatively. Sticker and Klemperer arrived at the same conclusion. Respecting pernicious anæmia, there is a concurrence of testimony in support of increased nitrogenous excretion. Reverting to cancer, this evidence, Müller thinks, goes to prove that malignant disease excites the formation of metabolic products which are poisonous to the organism. He points out that cachexia develops in the cases of malignant growths, no matter how limited, and without their involving any important organ; whereas a non-malignant tumor may attain great dimensions without affecting the excretion of urea. At the same time no such poison or ferment destructive of albumen can be isolated from cancerous tumors, although the fact pointed out by Feltz, that the urine of the cancerous is more toxic to animals than that of healthy individuals, is, with other facts, highly suggestive of that view.

JULY 18, 1890.] SCIENCE.

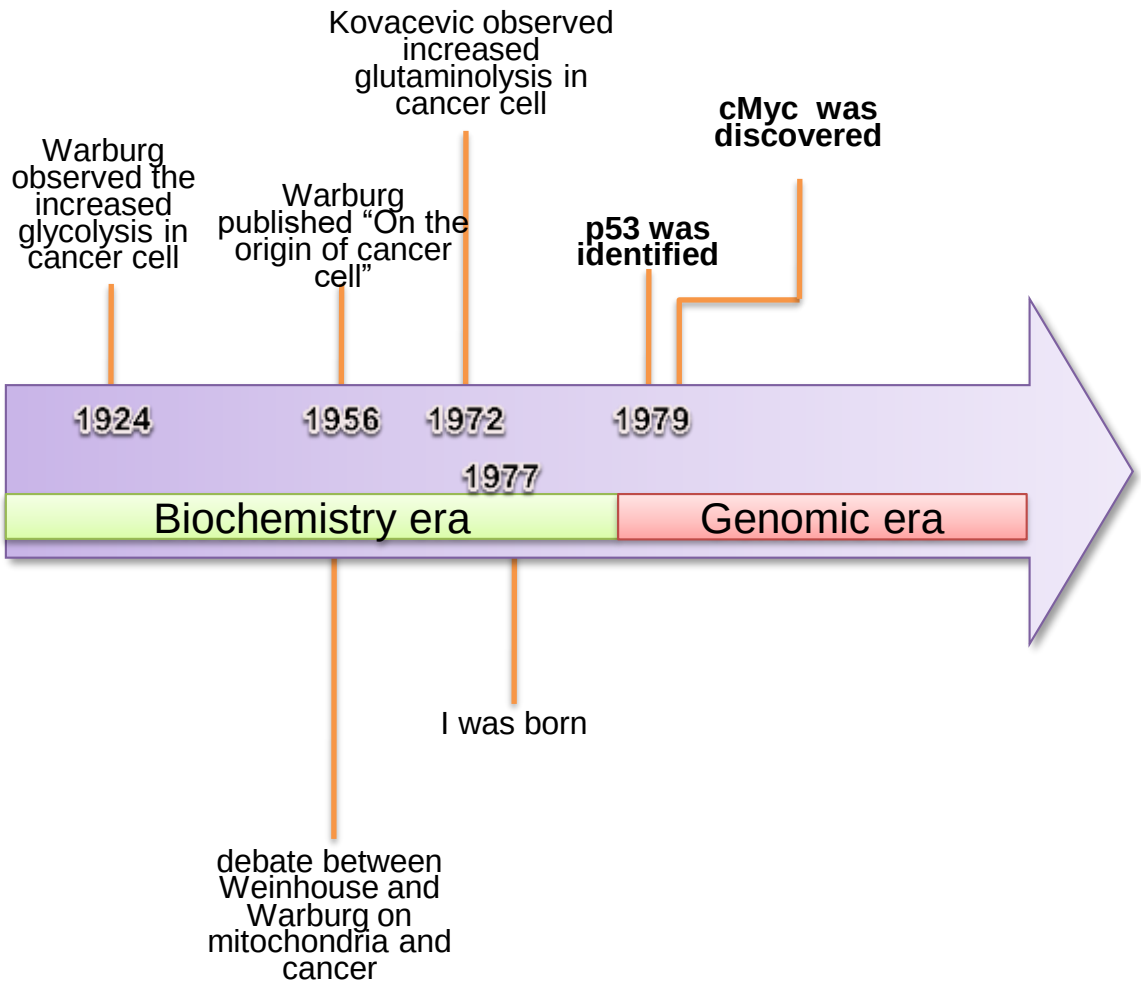


rg

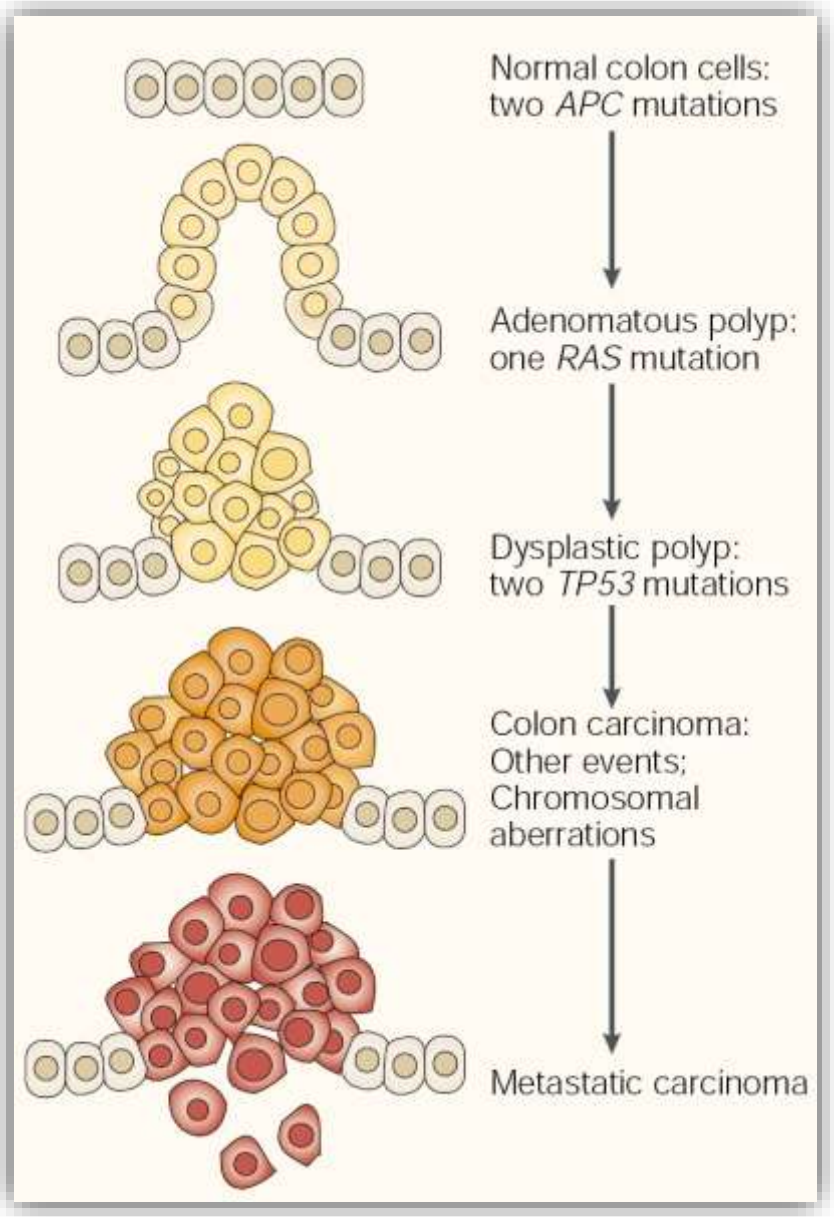
poisonous, and a certain number of mice succumb under the treatment.

From *Nature* 18 January 1912

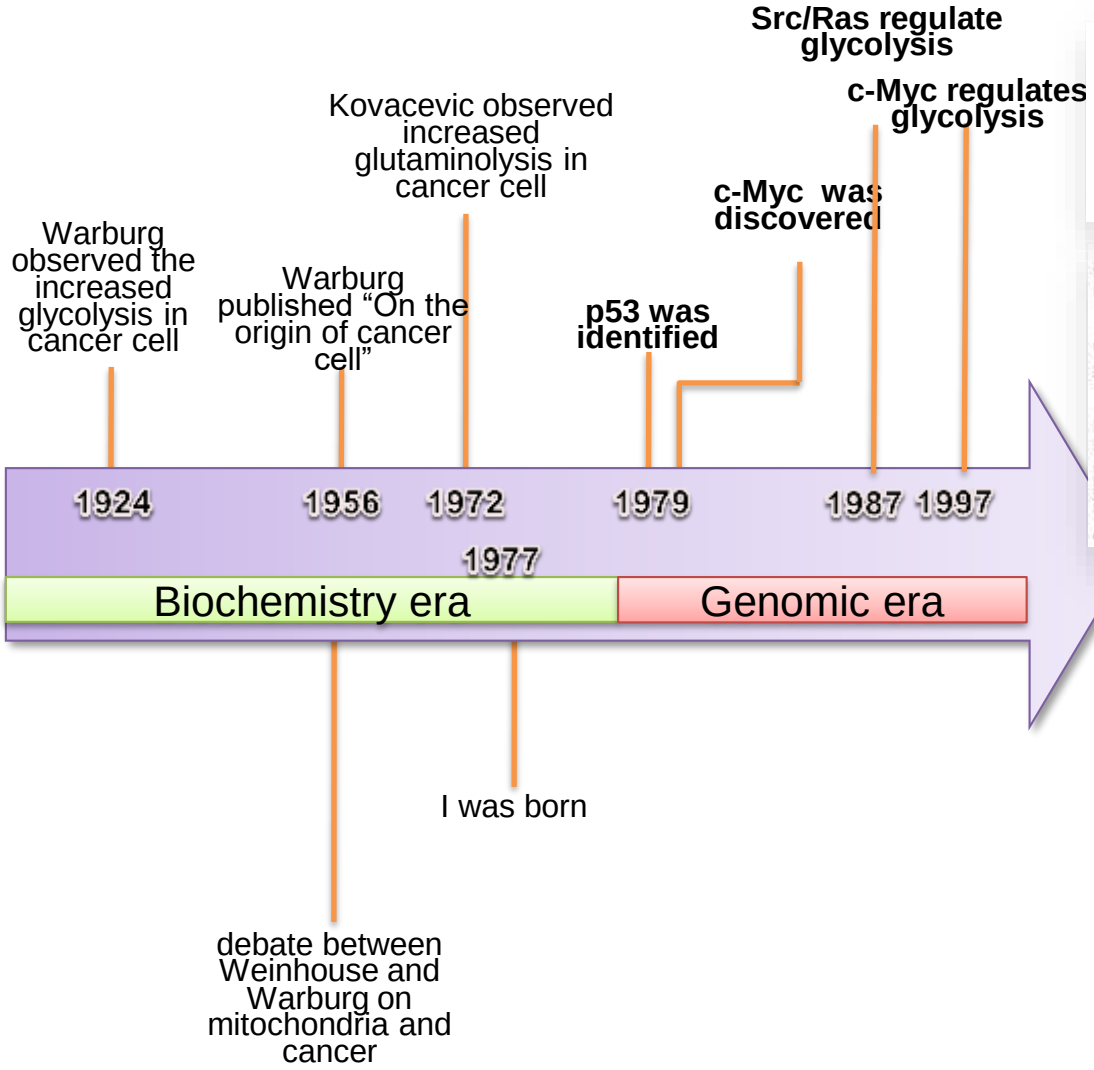
The timeline of cancer research



Cancer: a genetic disease



The timeline of cancer research



Elevated Levels of Glucose Transport and Transporter Messenger RNA Are Induced by *ras* or *src* Oncogenes

Jeffrey S. Flier,* Michael M. Mueckler, Patricia Usher, Harvey F. Lodish

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 6658–6663, June 1997
Biochemistry

c-Myc transactivation of *LDH-A*: Implications for tumor metabolism and growth

(oncogene/lactate dehydrogenase/hypoxia/tumorigenicity)

Hyunsuk Shim*, Christine Dolde†, Brian C. Lewis†, Chyi-Sun Wu*, Gerard Dang*, Richard A. Jungmann‡, Riccardo Dalla-Favera§, and Chi V. Dang*†¶||**

Departments of *Medicine and §Molecular Biology and Genetics, ¶The Johns Hopkins Oncology Center, and †Program in Human Genetics and Molecular Biology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205; ‡Department of Cellular and Molecular Biology and Cancer Center, Northwestern University Medical School, Chicago, IL 60611; and ||Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, NY 10032

Communicated by Michael Potter, National Institutes of Health, Bethesda, MD, April 28, 1997 (received for review February 11, 1997)

Cancer and Metabolism

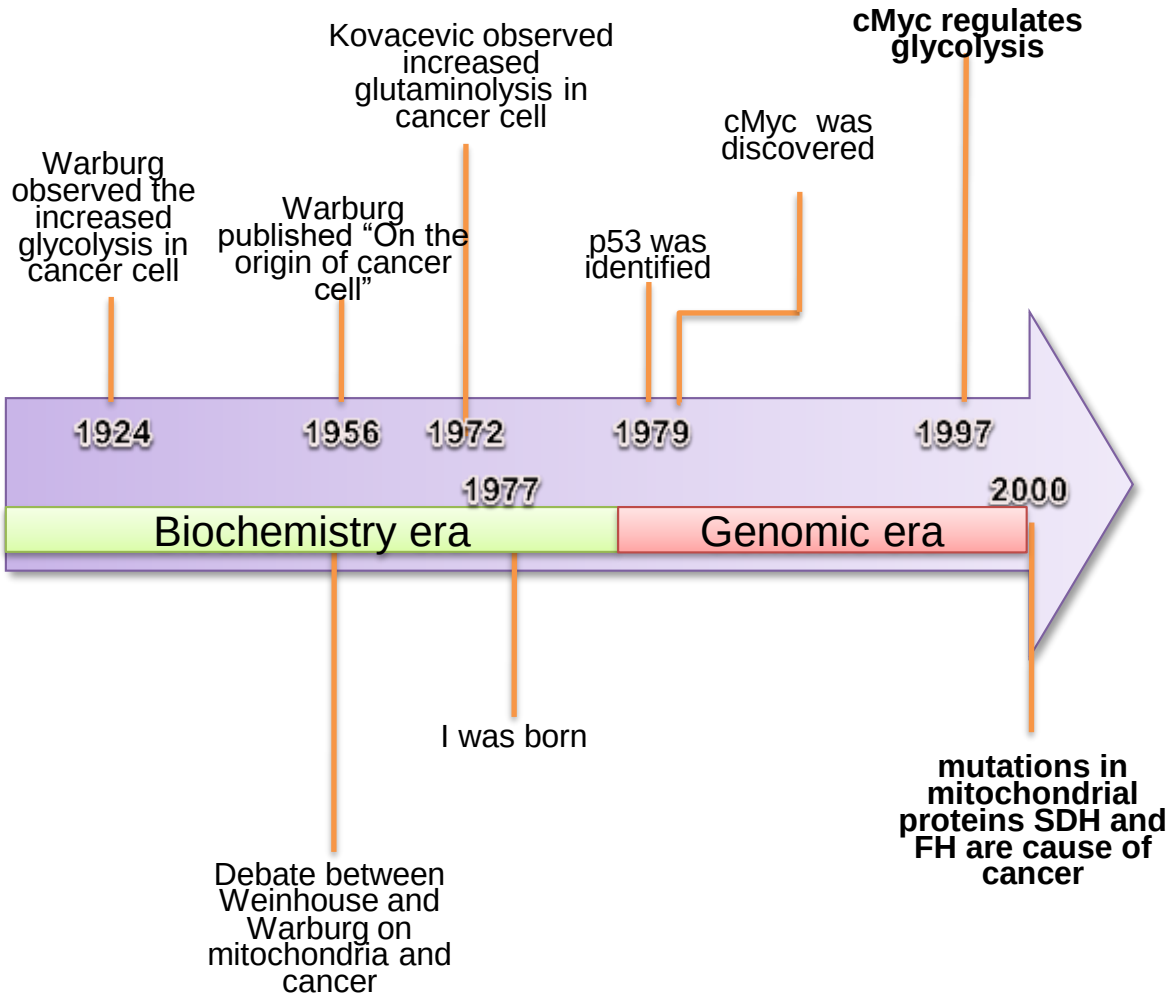
Metabolism

REVIEW

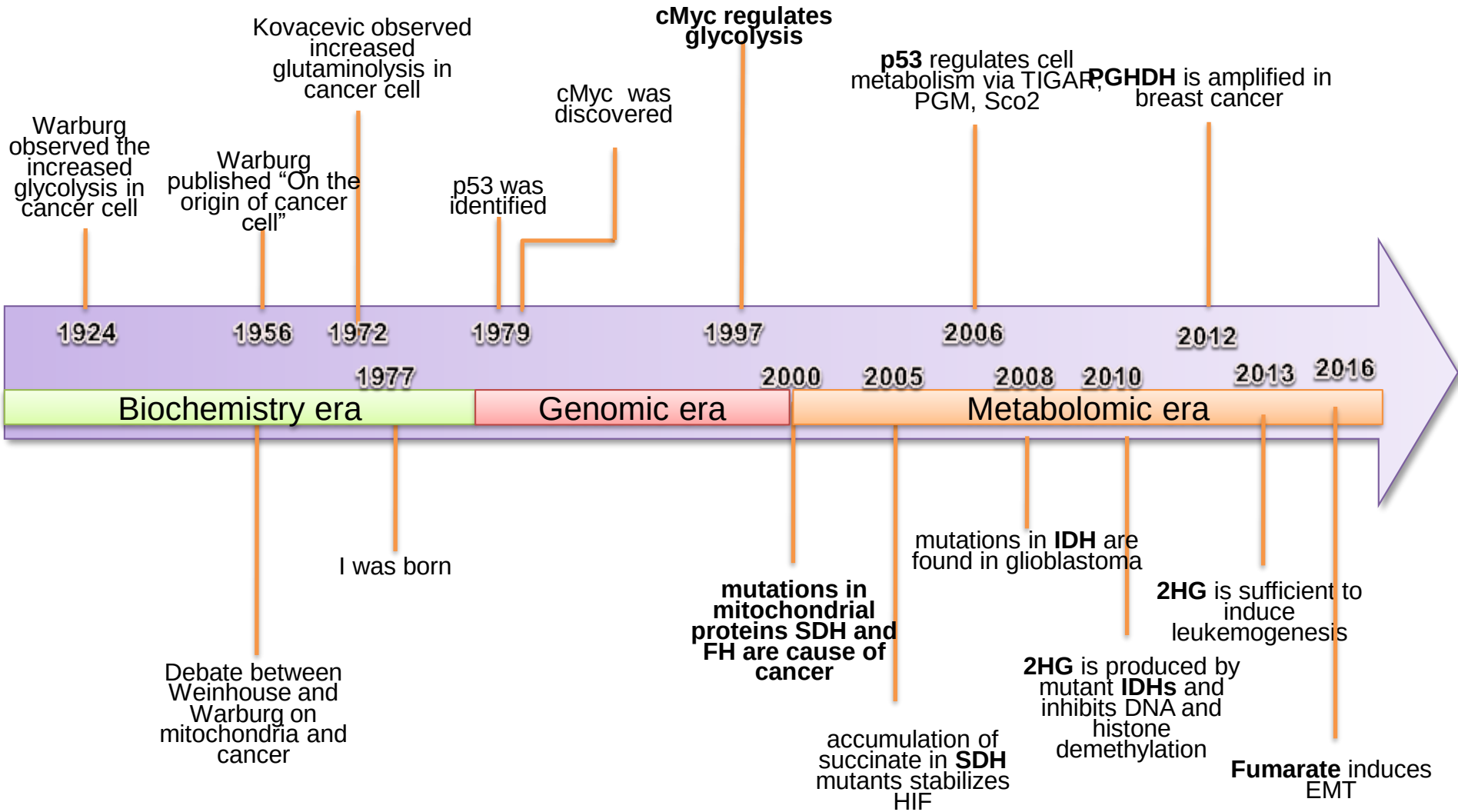
The Control of the Metabolic Switch in Cancers by Oncogenes and Tumor Suppressor Genes

Arnold J. Levine[1,2]* and Anna M. Puzio-Kuter[2]

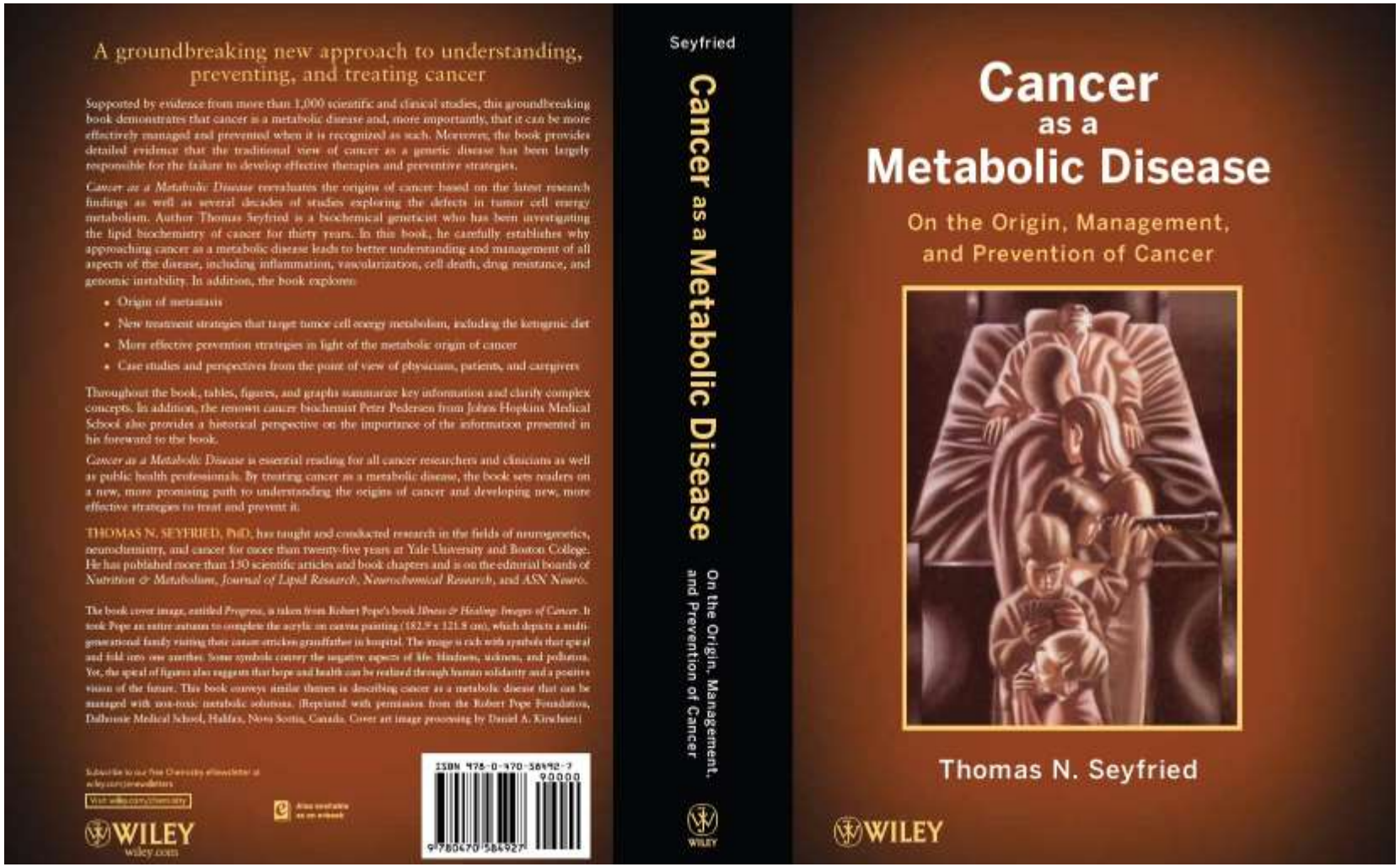
The timeline of cancer research



The timeline of cancer research



Cancer: a metabolic disease?



A groundbreaking new approach to understanding, preventing, and treating cancer

Supported by evidence from more than 1,000 scientific and clinical studies, this groundbreaking book demonstrates that cancer is a metabolic disease and, more importantly, that it can be more effectively managed and prevented when it is recognized as such. Moreover, the book provides detailed evidence that the traditional view of cancer as a genetic disease has been largely responsible for the failure to develop effective therapies and preventive strategies.

Cancer as a Metabolic Disease reevaluates the origins of cancer based on the latest research findings as well as several decades of studies exploring the defects in tumor cell energy metabolism. Author Thomas Seyfried is a biochemical geneticist who has been investigating the lipid biochemistry of cancer for thirty years. In this book, he carefully establishes why approaching cancer as a metabolic disease leads to better understanding and management of all aspects of the disease, including inflammation, vascularization, cell death, drug resistance, and genomic instability. In addition, the book explores:

- Origin of metastasis
- New treatment strategies that target tumor cell energy metabolism, including the ketogenic diet
- More effective prevention strategies in light of the metabolic origin of cancer
- Case studies and perspectives from the point of view of physicians, patients, and caregivers

Throughout the book, tables, figures, and graphs summarize key information and clarify complex concepts. In addition, the renown cancer biochemist Peter Pedersen from Johns Hopkins Medical School also provides a historical perspective on the importance of the information presented in his foreword to the book.

Cancer as a Metabolic Disease is essential reading for all cancer researchers and clinicians as well as public health professionals. By treating cancer as a metabolic disease, the book sets readers on a new, more promising path to understanding the origins of cancer and developing new, more effective strategies to treat and prevent it.

THOMAS N. SEYFRIED, PhD, has taught and conducted research in the fields of neurogenetics, neurochemistry, and cancer for more than twenty-five years at Yale University and Boston College. He has published more than 130 scientific articles and book chapters and is on the editorial boards of *Nutrition & Metabolism*, *Journal of Lipid Research*, *Neurochemical Research*, and *ASN Neuro*.

The book cover image, entitled *Progress*, is taken from Robert Pope's book *Illness & Healing: Images of Cancer*. It took Pope an entire autumn to complete the acrylic on canvas painting (182.9 x 121.8 cm), which depicts a multigenerational family visiting their cancer-stricken grandfather in hospital. The image is rich with symbols that spiral and fold into one another. Some symbols convey the negative aspects of life: blindness, sickness, and pollution. Yet, the spiral of figures also suggests that hope and health can be realized through human solidarity and a positive vision of the future. This book conveys similar themes in describing cancer as a metabolic disease that can be managed with non-toxic metabolic solutions. (Reprinted with permission from the Robert Pope Foundation, Dalhousie Medical School, Halifax, Nova Scotia, Canada. Cover art image processing by Daniel A. Kirschner.)

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Seyfried

Cancer as a Metabolic Disease

On the Origin, Management, and Prevention of Cancer

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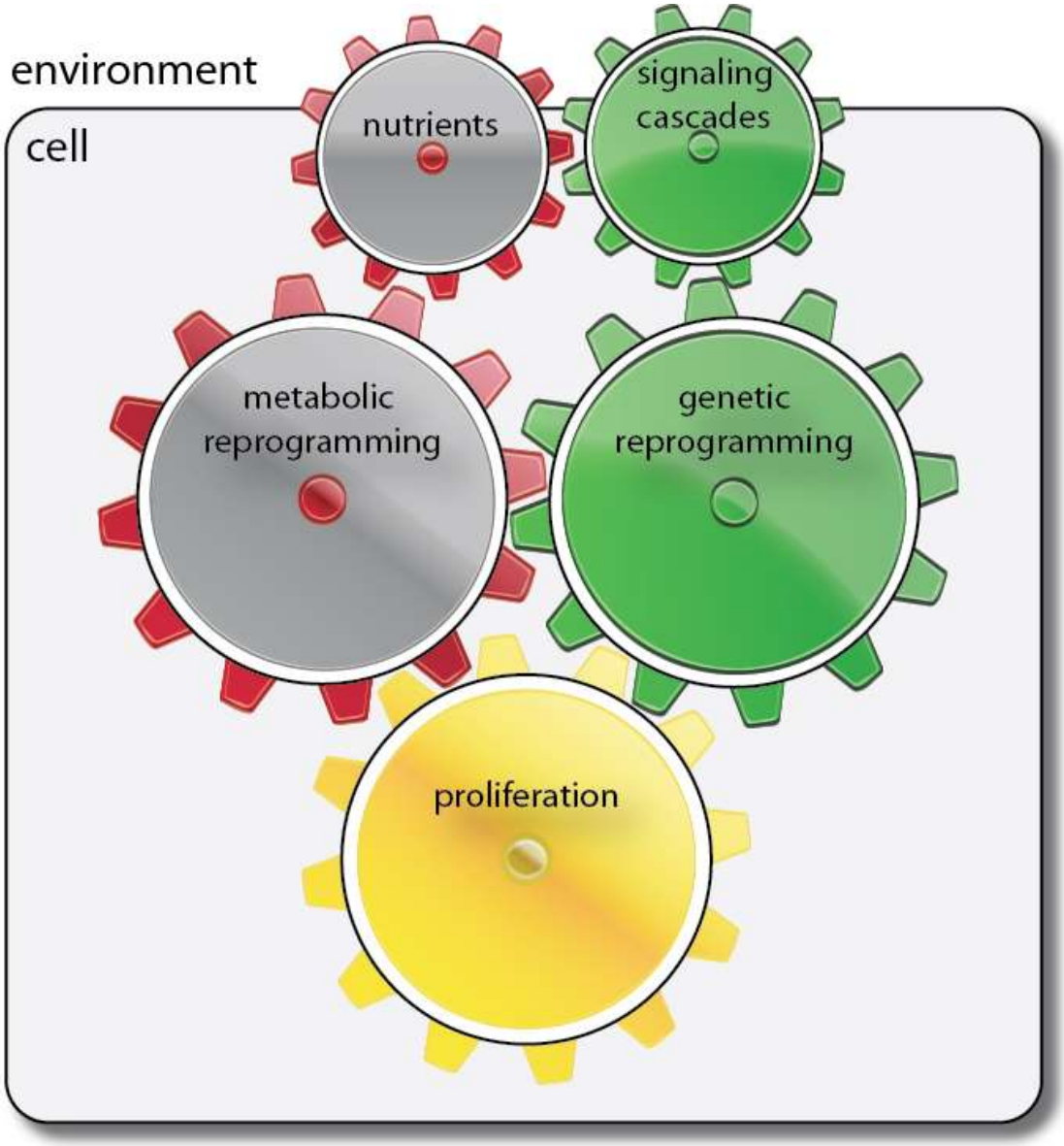
Cancer
as a
Metabolic Disease

On the Origin, Management, and Prevention of Cancer

Thomas N. Seyfried

WILEY

A system view of cancer

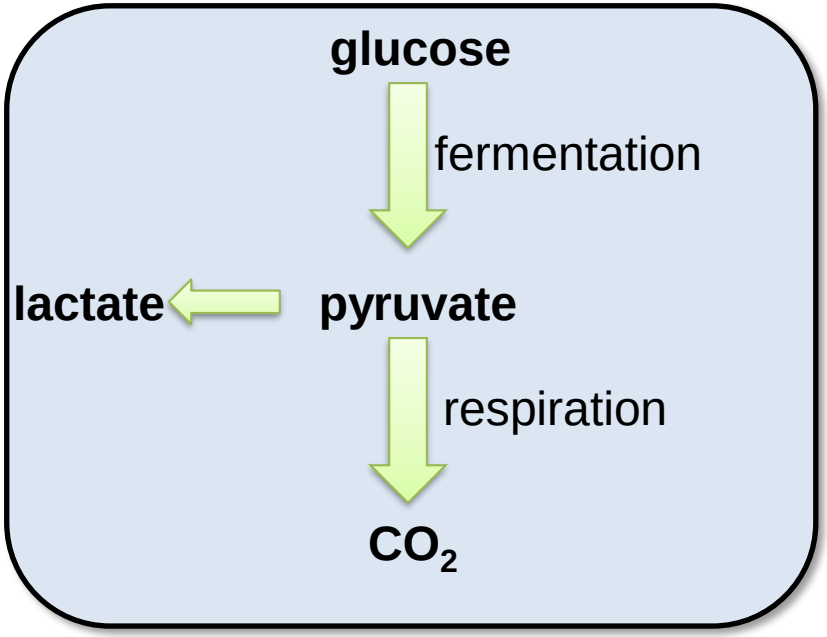


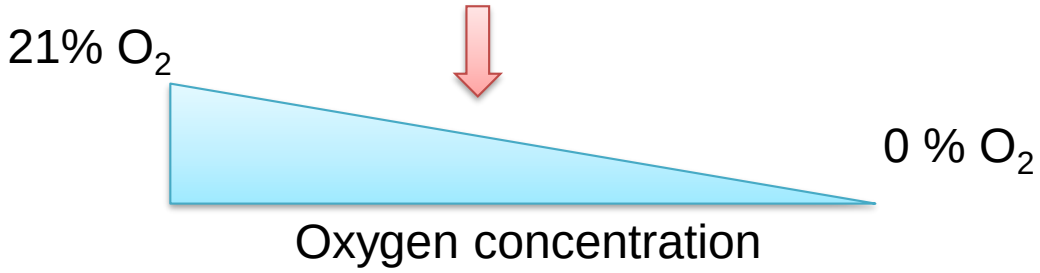
An historical perspective on

CANCER METABOLISM

Metabolism in the 19th century

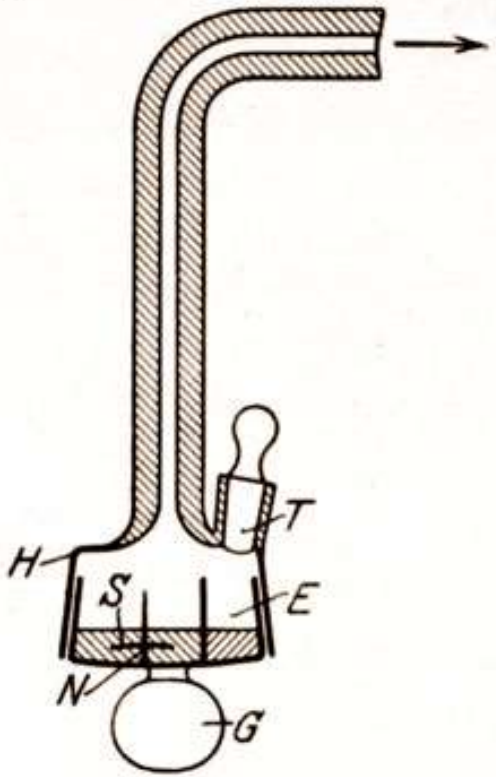
Pasteur effect





Warburg experiments

a



b

Tabelle I.

FLEXNER-JOBLINGsches Rattencarcinom.

37,5°. Ringerlösung. $C_{NaHCO_3} = 2{,}5 \cdot 10^{-2}$. 0,2 proz. Glucose. 5 proz. CO_2. $p_H = 7{,}66$.

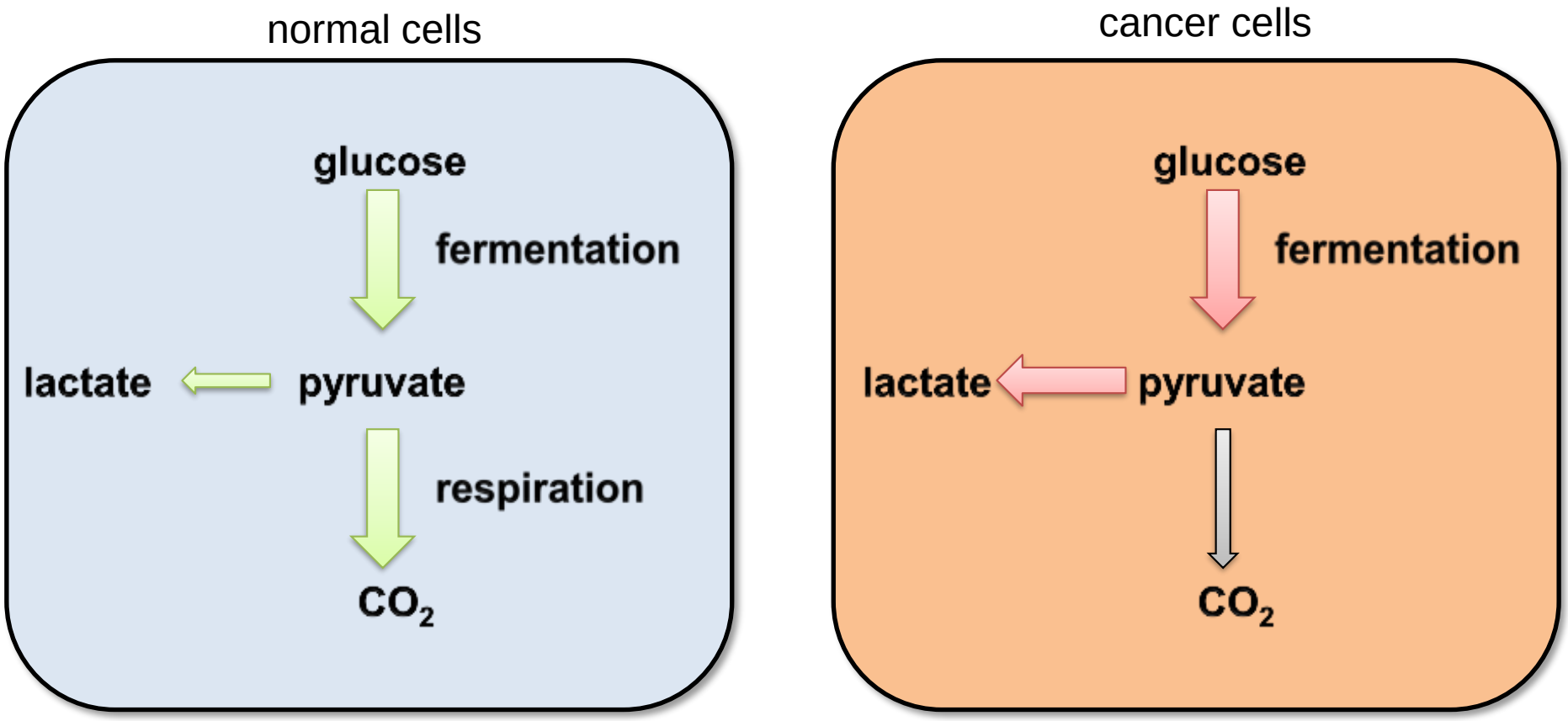
Nr.	I Q_{O_2} (Atmung)	II $Q^{O_2}_{CO_2}$ (Glykolyse in Sauerstoff)	III $Q^{N_2}_{CO_2}$ (Glykolyse in Stickstoff)	IV Hemmung d. Glykolyse durch Sauerstoff $\left(\frac{III-II}{III}\right)$ %	V MEYERHOF-Quotient $\left(\frac{III-II}{I}\right)$	VI Aerobe Glykolyse / Atmung $\left(\frac{II}{I}\right)$
1	— 4,5	+ 21	—	—	—	4,7
2	— 7,8	+ 28	—	—	—	3,6
3	— 11,5	+ 30	—	—	—	2,6
4	— 5,1	+ 18	—	—	—	3,6
5	— 7,5	+ 30,5	—	—	—	4,1
6	— 2,4	+ 17,7	—	—	—	7,4
7	— 4,1	+ 25,6	+ 30,8	18	1,3	5,1
8	— 3,5	+ 19	+ 26,8	29	2,2	5,4
9	— 7,5	+ 22,5	+ 34,6	35	1,6	3,0
10	— 12,8	+ 27	+ 34,5	22	0,6	2,1
11	— 11,8	+ 26	+ 34	24	0,7	2,2
12	— 10,4	+ 22,3	+ 25,3	12	0,3	2,1
13	— 2,5	+ 18,6	+ 28,3	34	3,9	7,6
14	— 9,0	+ 24	+ 30,8	21	0,73	2,7
15	— 11,5	+ 25,5	+ 33,8	25	0,72	2,2
16	— 6,7	+ 27,7	+ 37,0	25	1,4	4,2
17	— 5,5	+ 18	+ 25,6	30	1,4	3,3
18	— 8,9	+ 23,7	+ 27,3	13	0,4	2,7
19	— 4,1	+ 25,7	+ 33,8	24	2,0	6,4
Mittel:	— *7,2*	+ *25*	+ *31*	*23*	*1,3*	*3,9*

Nature Reviews | Cancer

Otto Warburg's contributions to current concepts of cancer metabolism

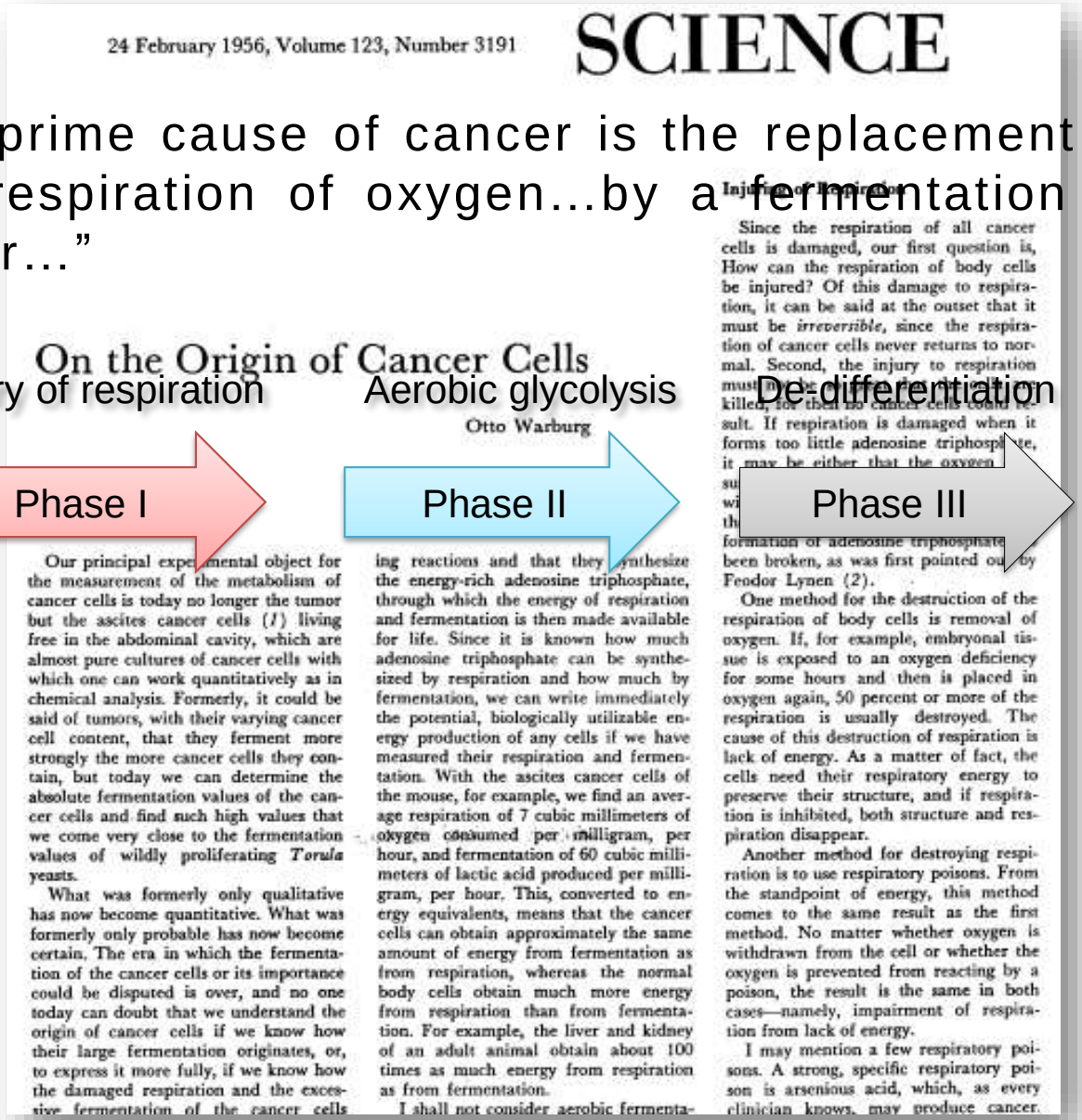
Willem H. Koppenol, Patricia L. Bounds* and Chi V. Dang‡*

Aerobic glycolysis in cancer cells



The Warburg hypothesis

The prime cause of cancer is the replacement of the respiration of oxygen...by a fermentation of sugar..."



24 February 1956, Volume 123, Number 3191 SCIENCE

On the Origin of Cancer Cells

Otto Warburg

Injury of respiration

Aerobic glycolysis

De-differentiation

Normal cell

Phase I

Phase II

Phase III

Cancer cell

Our principal experimental object for the measurement of the metabolism of cancer cells is today no longer the tumor but the ascites cancer cells (*1*) living free in the abdominal cavity, which are almost pure cultures of cancer cells with which one can work quantitatively as in chemical analysis. Formerly, it could be said of tumors, with their varying cancer cell content, that they ferment more strongly the more cancer cells they contain, but today we can determine the absolute fermentation values of the cancer cells and find such high values that we come very close to the fermentation values of wildly proliferating *Torula* yeasts.

What was formerly only qualitative has now become quantitative. What was formerly only probable has now become certain. The era in which the fermentation of the cancer cells or its importance could be disputed is over, and no one today can doubt that we understand the origin of cancer cells if we know how their large fermentation originates, or, to express it more fully, if we know how the damaged respiration and the excessive fermentation of the cancer cells

ing reactions and that they synthesize the energy-rich adenosine triphosphate, through which the energy of respiration and fermentation is then made available for life. Since it is known how much adenosine triphosphate can be synthesized by respiration and how much by fermentation, we can write immediately the potential, biologically utilizable energy production of any cells if we have measured their respiration and fermentation. With the ascites cancer cells of the mouse, for example, we find an average respiration of 7 cubic millimeters of oxygen consumed per milligram, per hour, and fermentation of 60 cubic millimeters of lactic acid produced per milligram, per hour. This, converted to energy equivalents, means that the cancer cells can obtain approximately the same amount of energy from fermentation as from respiration, whereas the normal body cells obtain much more energy from respiration than from fermentation. For example, the liver and kidney of an adult animal obtain about 100 times as much energy from respiration as from fermentation.

I shall not consider aerobic fermenta-

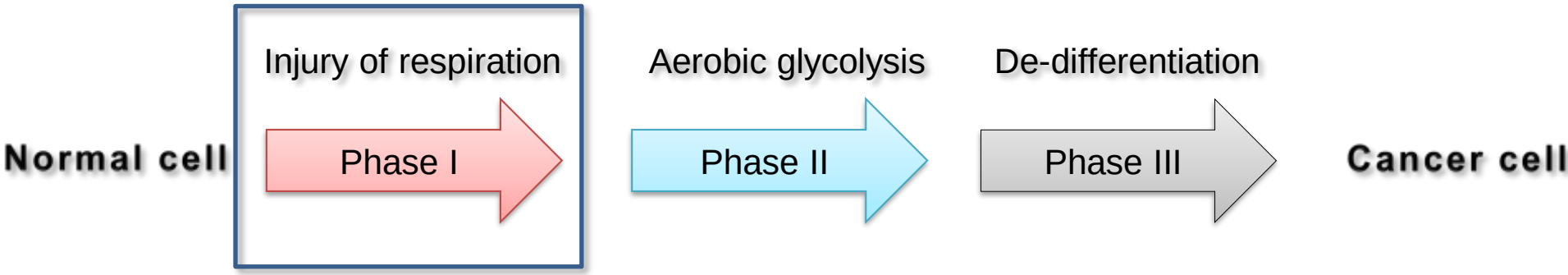
Since the respiration of all cancer cells is damaged, our first question is, How can the respiration of body cells be injured? Of this damage to respiration, it can be said at the outset that it must be *irreversible*, since the respiration of cancer cells never returns to normal. Second, the injury to respiration must [illegible] killed, for then no cancer cells could result. If respiration is damaged when it forms too little adenosine triphosphate, it may be either that the oxygen [illegible] formation of adenosine triphosphate [illegible] been broken, as was first pointed out by Feodor Lynen (*2*).

One method for the destruction of the respiration of body cells is removal of oxygen. If, for example, embryonal tissue is exposed to an oxygen deficiency for some hours and then is placed in oxygen again, 50 percent or more of the respiration is usually destroyed. The cause of this destruction of respiration is lack of energy. As a matter of fact, the cells need their respiratory energy to preserve their structure, and if respiration is inhibited, both structure and respiration disappear.

Another method for destroying respiration is to use respiratory poisons. From the standpoint of energy, this method comes to the same result as the first method. No matter whether oxygen is withdrawn from the cell or whether the oxygen is prevented from reacting by a poison, the result is the same in both cases—namely, impairment of respiration from lack of energy.

I may mention a few respiratory poisons. A strong, specific respiratory poison is arsenious acid, which, as every clinician knows, may produce cancer.

The Warburg hypothesis



Cancer cells originate from normal body cells in *two* phases. The first phase is the irreversible injuring of respiration. Just as there are many remote causes of plague—heat, insects, rats—but only one common cause, the plague bacillus, there are a great many remote causes of cancer—tar, rays, arsenic, pressure, urethane—but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration.

Is respiration injured in cancer cells?

”…there is no evidence…that the respiration in cancer cell is either quantitatively lowered or fails to lower glycolysis…”

Sidney Weinhouse

Weinhouse, Z. Krebsforsh, 1976

Is hypoxia the cause of mitochondrial dysfunction?

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Biochemical and Biophysical Research Communications 313 (2004) 459–465
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Breakthroughs and Views

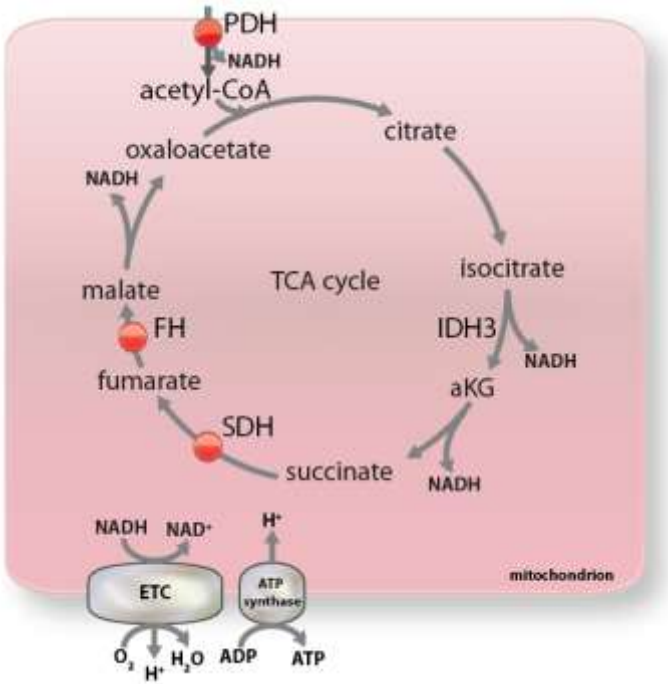
Cancer metabolism: facts, fantasy, and fiction☆

Xin Lin Zu* and Michael Guppy

Biochemistry and Molecular Biology, School of Biochemical and Chemical Science, University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia

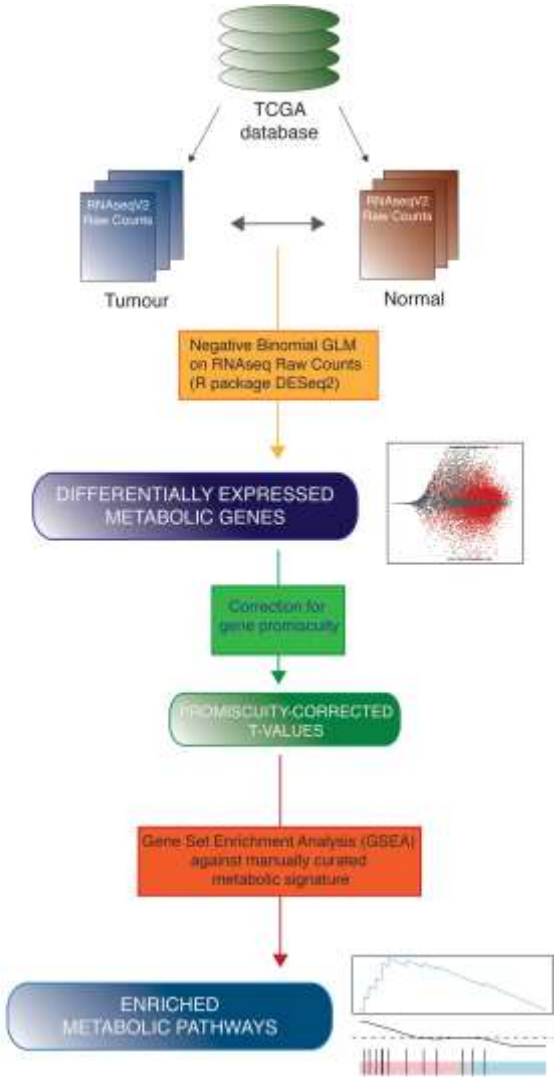
Received 19 November 2003

of a hypoxic core in tumours [57–59] and have led to the search for treatment strategies that exploit the hypoxic nature of tumours [60,61]. So perhaps tumours are glycolytic, but not inherently so, and not aerobically glycolytic, but anaerobically glycolytic as a result of a hypoxia-driven Pasteur effect. This would explain the



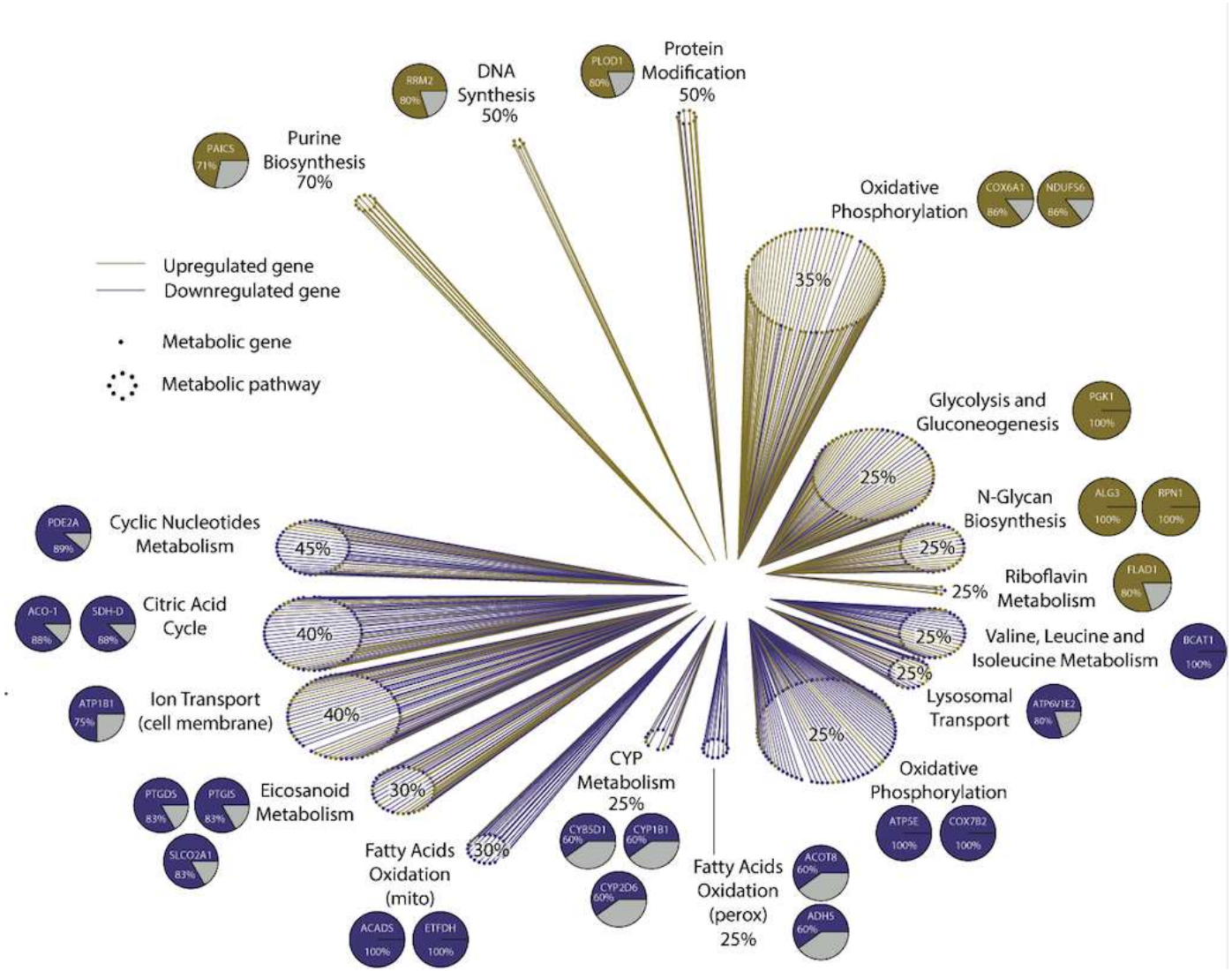
…all Warburg's experiment were performed using well oxygenated tissues

Metabolic changes in cancer vs normal tissues



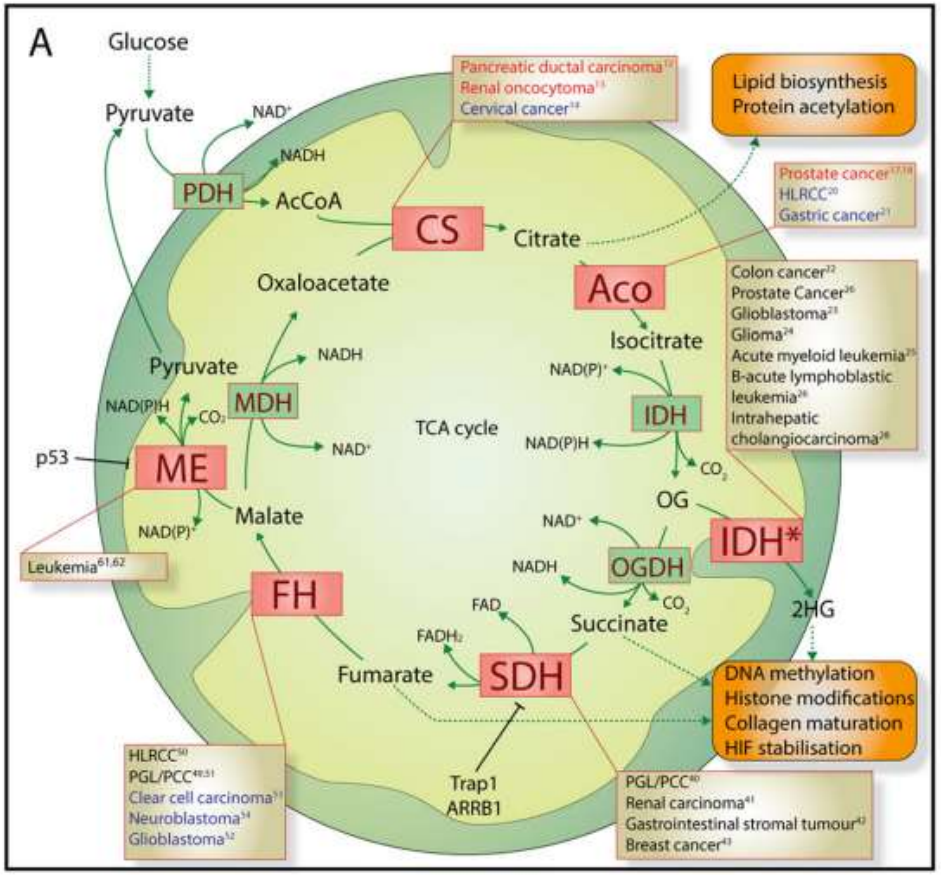
Gaude and Frezza, Nat Comms 2016

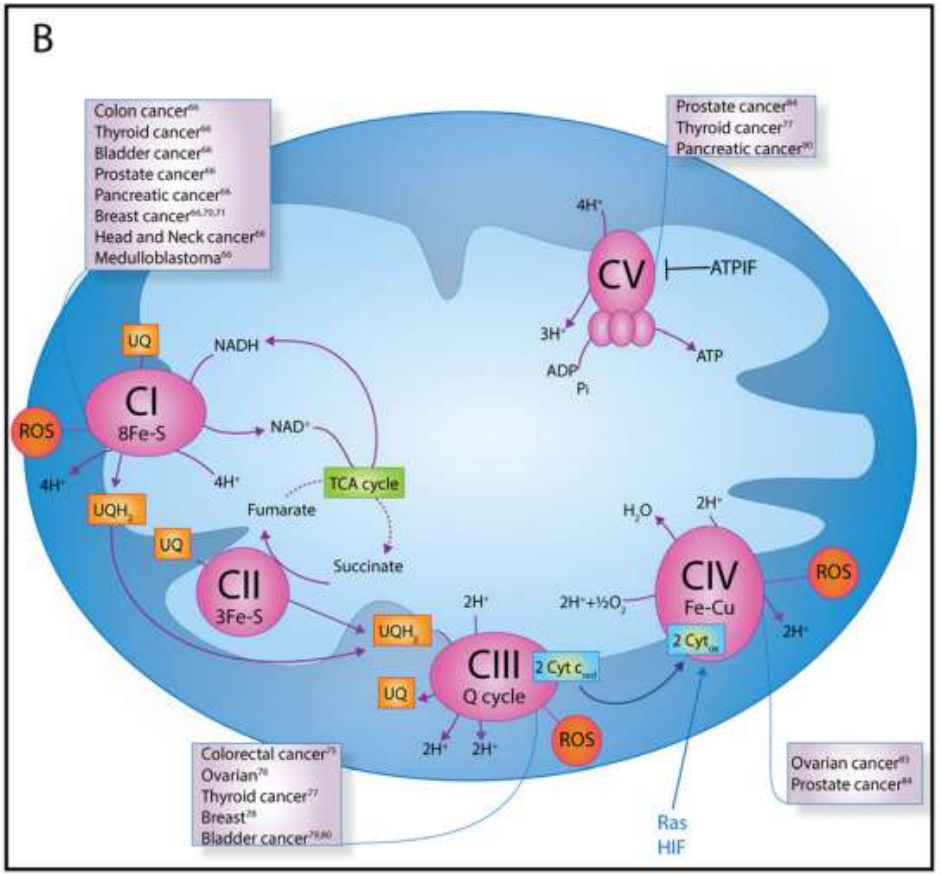
Mitochondrial genes are suppressed in cancer



Gaude and Frezza, Nat Comms 2016

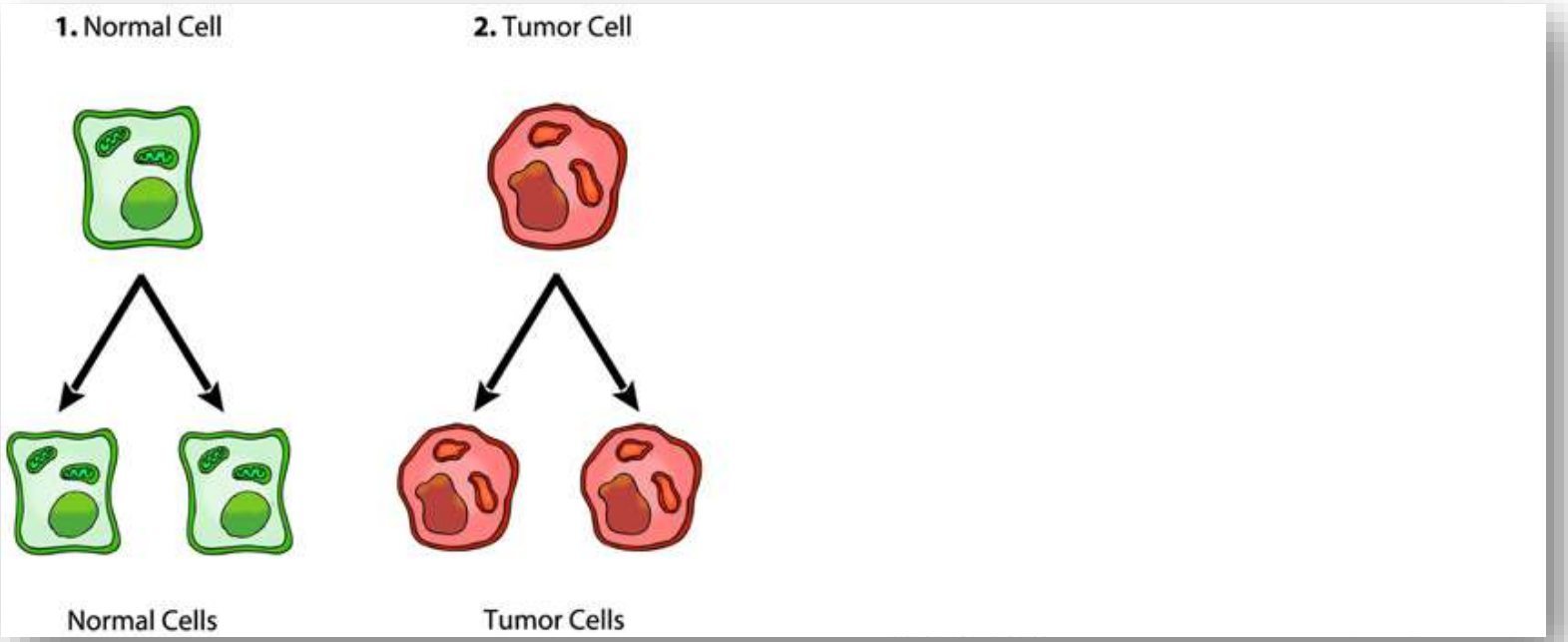
Mitochondrial genes as oncogenes and TSGs





Gaude and Frezza, Cancer & Metab, 2014

Oncogenic roles of dysfunctional mitochondria



Mitochondrial dysfunction can be oncogenic

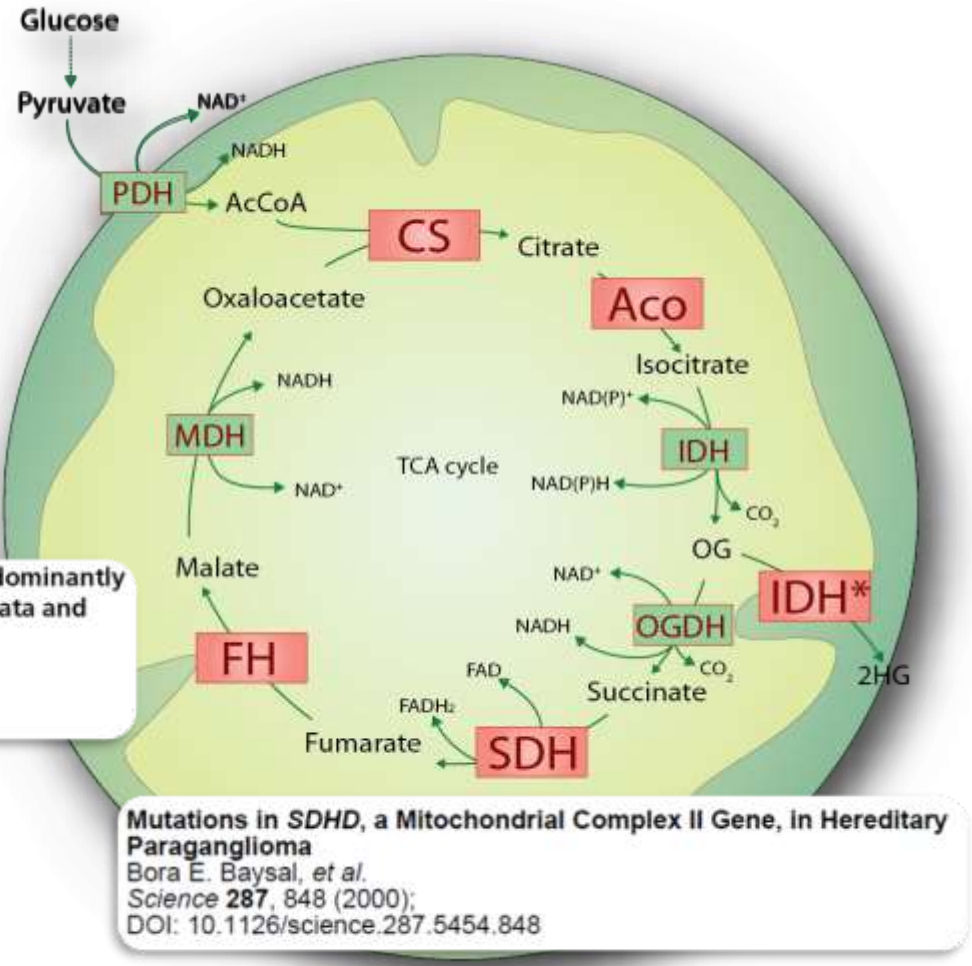
Inhibition of oxidative metabolism leads to p53 genetic inactivation and transformation in neural stem cells

Stefano Bartesaghi[a], Vincenzo Graziano[a,b,1], Sara Galavotti[a,1], Nick V. Henriquez[c,1], Joanne Betts[a], Jayeta Saxena[a], Valentina Minieri[a], Deli A[a], Anna Karlsson[d], L. Miguel Martins[e], Melania Capasso[f], Pierluigi Nicotera[g], Sebastian Brandner[c], Vincenzo De Laurenzi[b], and Paolo Salomoni[a,2]

[a]Samantha Dickson Brain Cancer Unit, University College London Cancer Institute, London WC1E 6BT, United Kingdom; [b]Department of Experimental and Clinical Sciences, Aging Research Center (Centro Scienze dell'Invecchiamento), University G. d'Annunzio, 66013 Chieti-Pescara, Italy; [c]Institute of Neurology, University College London, London WC1N 3BG, United Kingdom; [d]Karolinska Institute, SE-171 77 Stockholm, Sweden; [e]Medical Research Council Toxicology Unit, Leicester LE1 7HB, United Kingdom; [f]Barts Cancer Institute, Queen Mary University, London E1 2AD, United Kingdom; and [g]Deutsches Zentrum für Neurodegenerative Erkrankungen, 53175 Bonn, Germany

Edited by Douglas R. Green, St. Jude Children's Research Hospital, Memphis, TN, and accepted by the Editorial Board December 10, 2014 (received for review July 11, 2014)

Mitochondrial tumour suppressors and oncometabolites



Germline mutations in *FH* predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer

The Multiple Leiomyoma Consortium

Published online: 25 February 2002; DOI: 10.1038/ng849

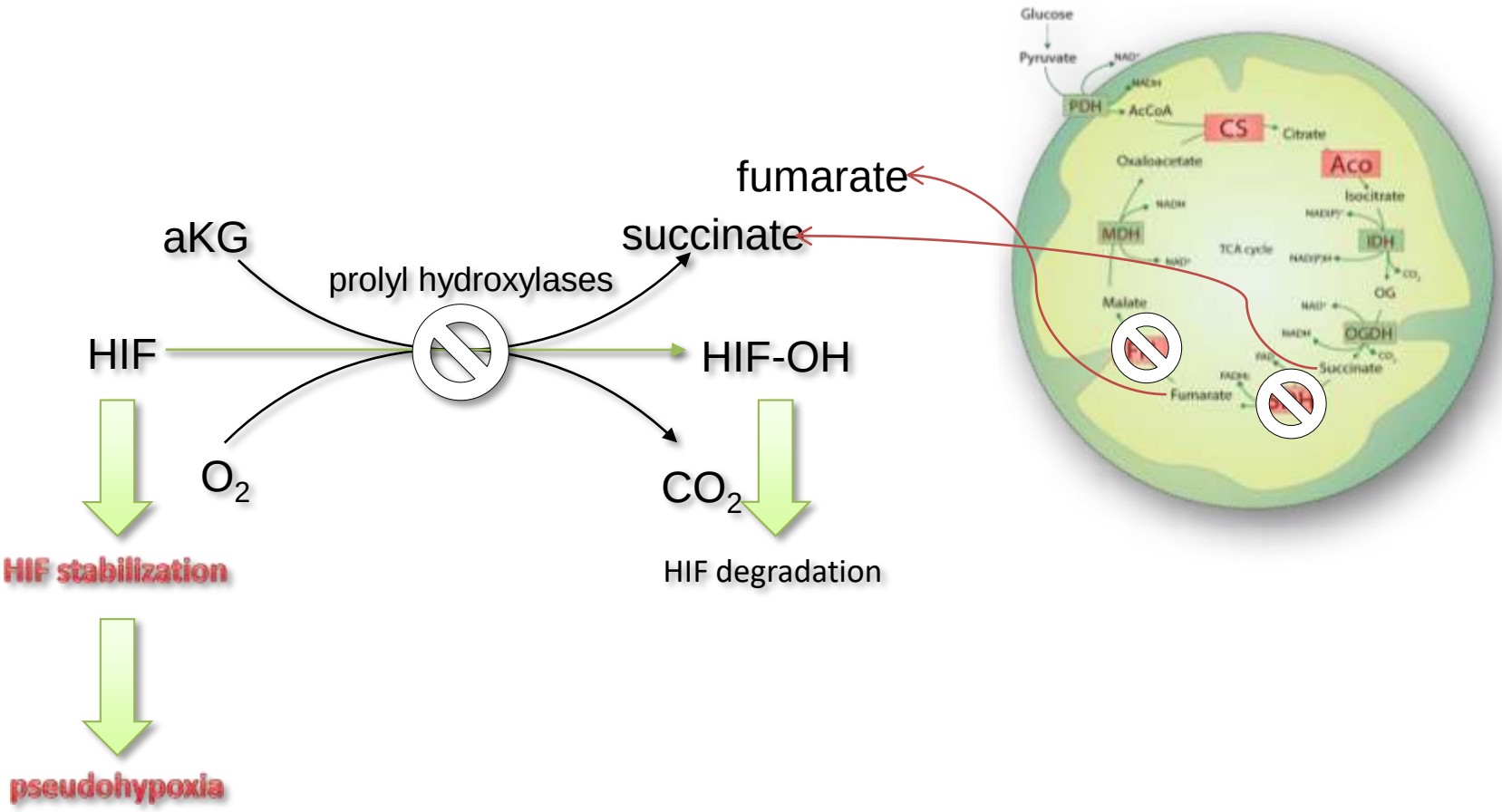
Mutations in *SDHD*, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma

Bora E. Baysal, *et al.*

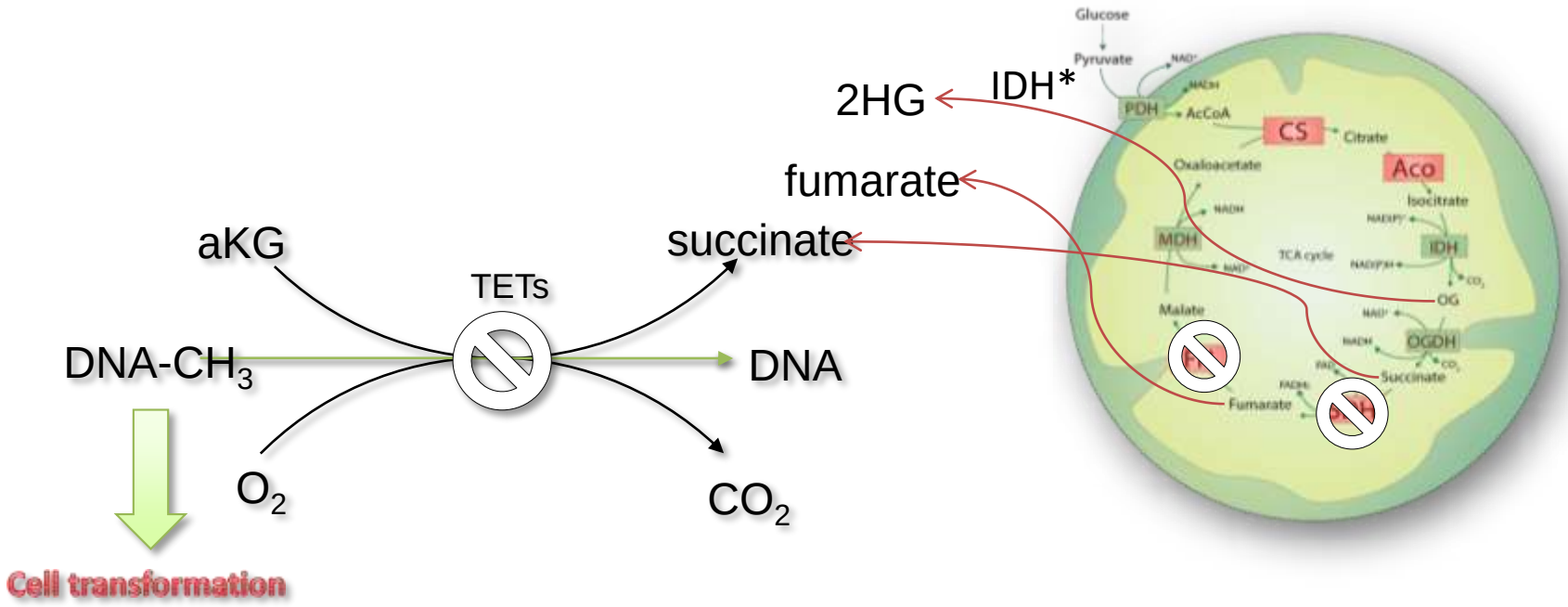
Science **287**, 848 (2000);

DOI: 10.1126/science.287.5454.848

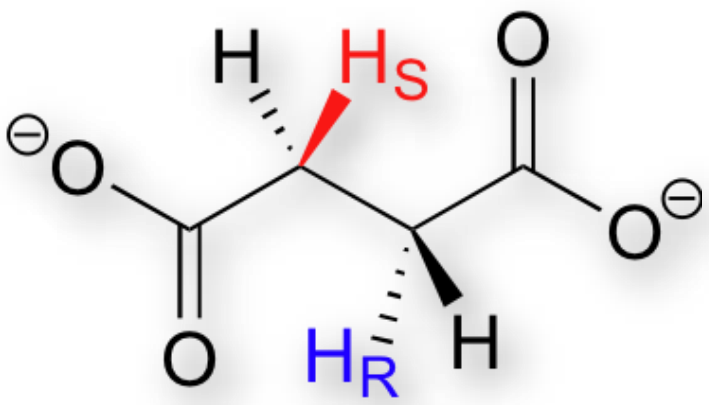
Succinate and fumarate activate HIF pathway



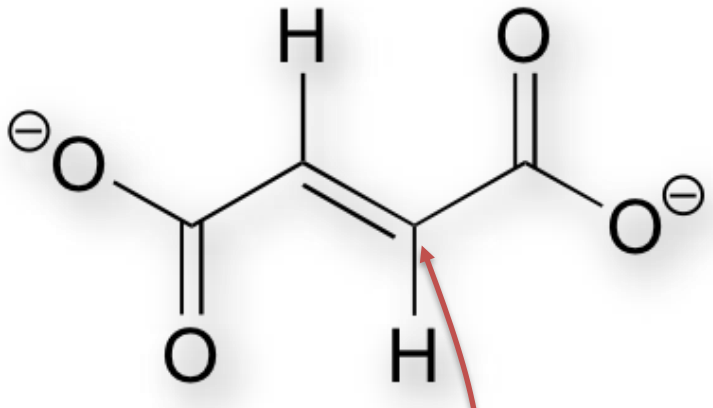
Succinate, fumarate, and 2HG as epigenetic modifiers



Fumarate and succination



succinate



fumarate

protein-SH

Succination of Keap1 activates Nrf2 pathway

fumarate

Keap1

Nrf2

Nrf2-Keap1

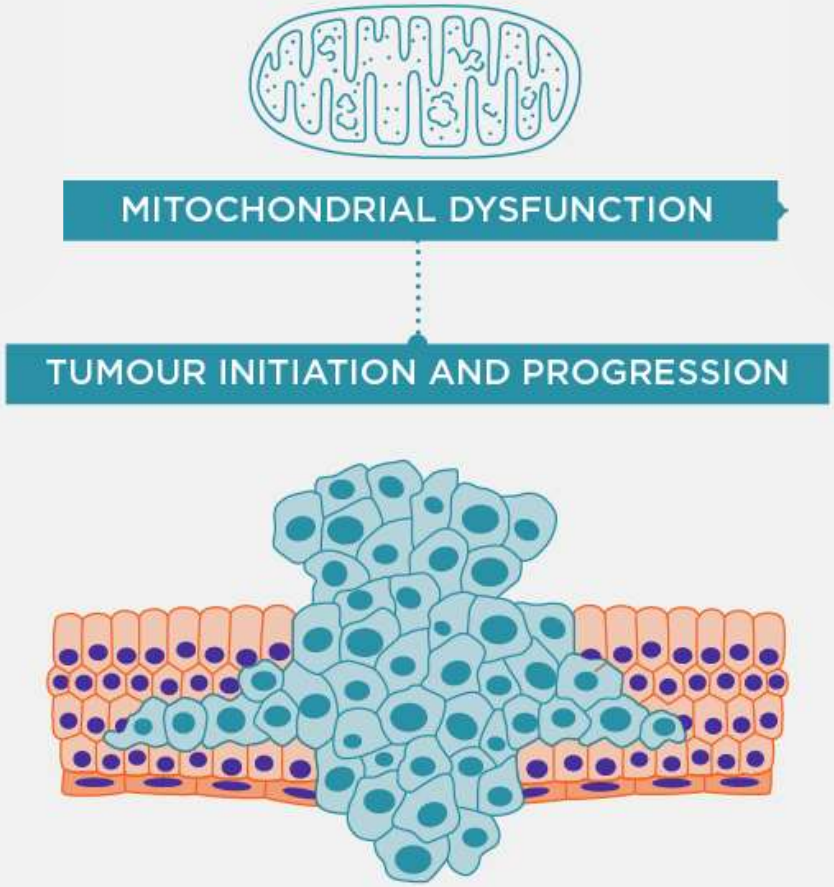
NRF2 stabilization

Nrf2 degradation

antioxidant response

The emerging concept of *oncometabolites*

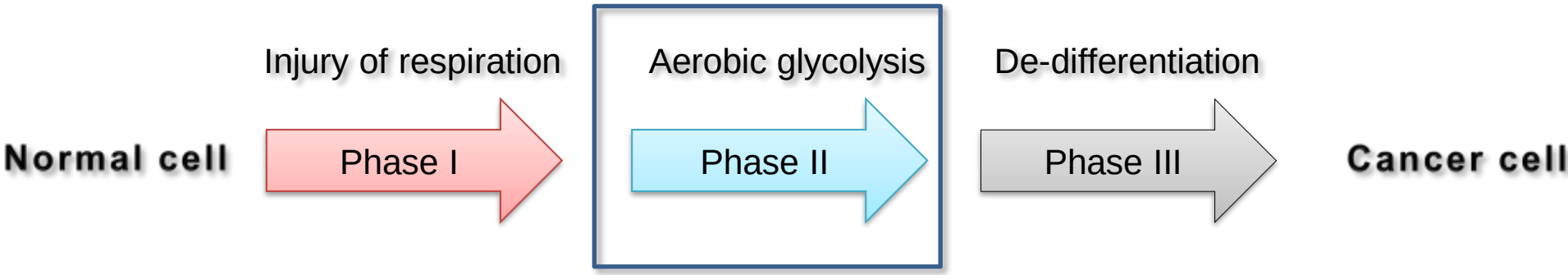
"the somatic mutation theory acts like a tranquilizer on those who believe in it" (Rous, 1959).



Mitochondria dysfunction in cancer?

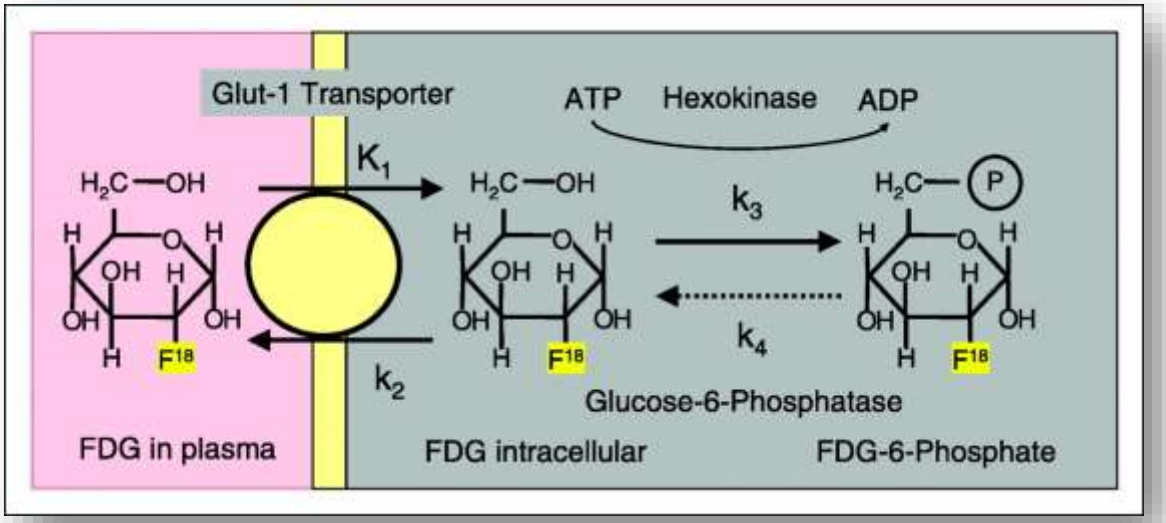
Mitochondrial function is rewired in cancer cells, but mitochondria are required for cancer cell growth and proliferation

The Warburg hypothesis



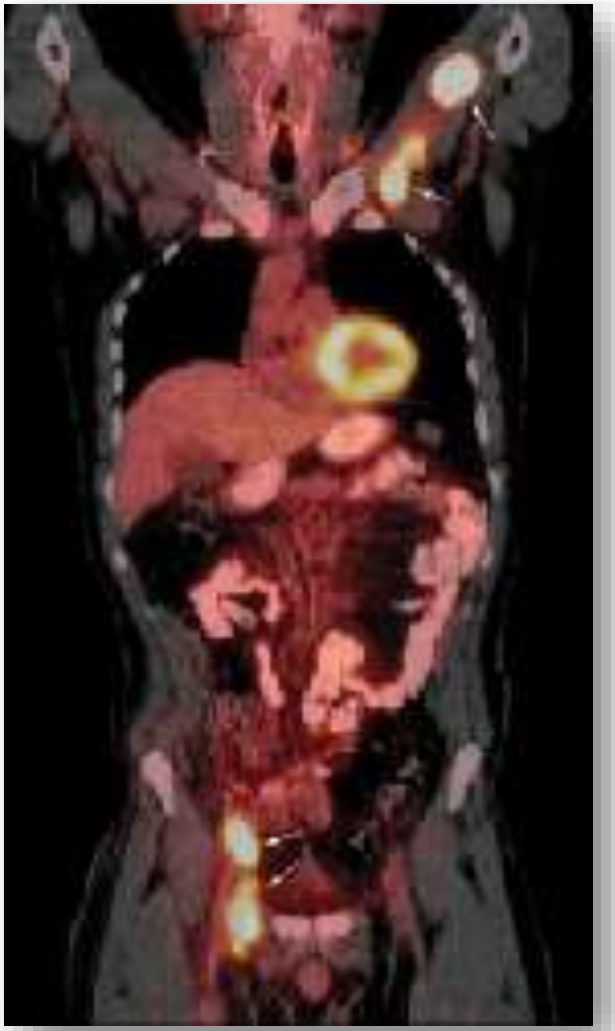
The irreversible injuring of respiration is followed, as the second phase of cancer formation, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish from lack of energy, while another part succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy, the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly—the cancer cells.

Aerobic glycolysis in cancer: increase in glucose uptake



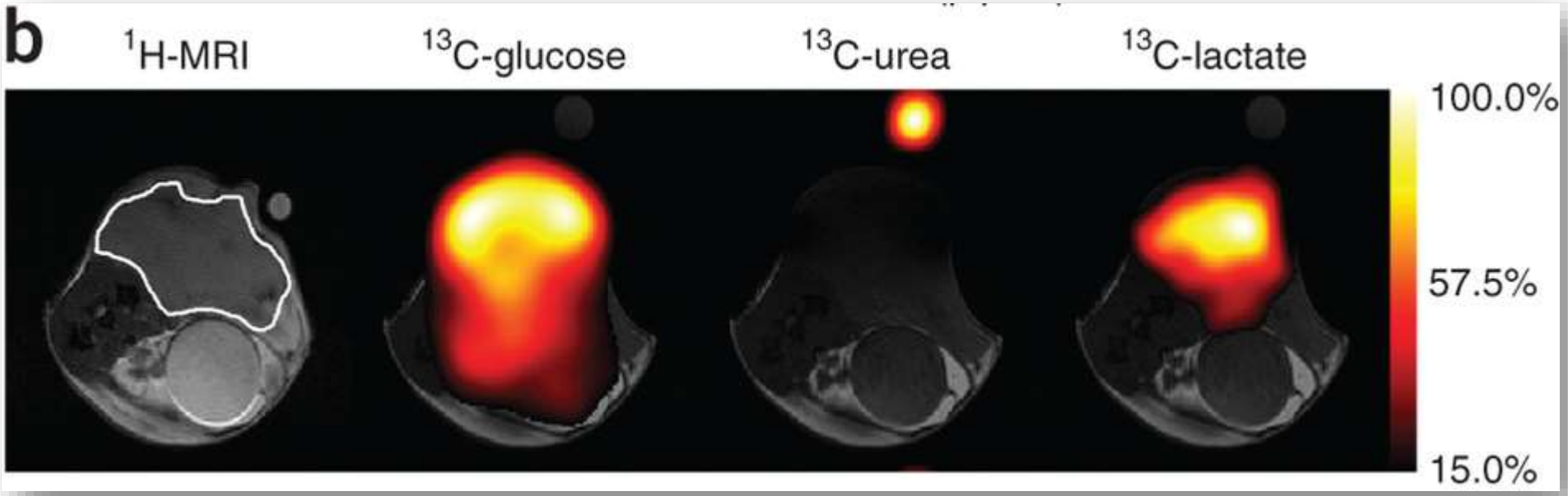
[^{18}F]flouro-2-deoxyglucose (FDG) Positron Emission Tomography (PET)

Aerobic glycolysis in cancer: increase in glucose uptake



Journal of the National Cancer Institute, Vol. 96, No. 24, December 15, 2004

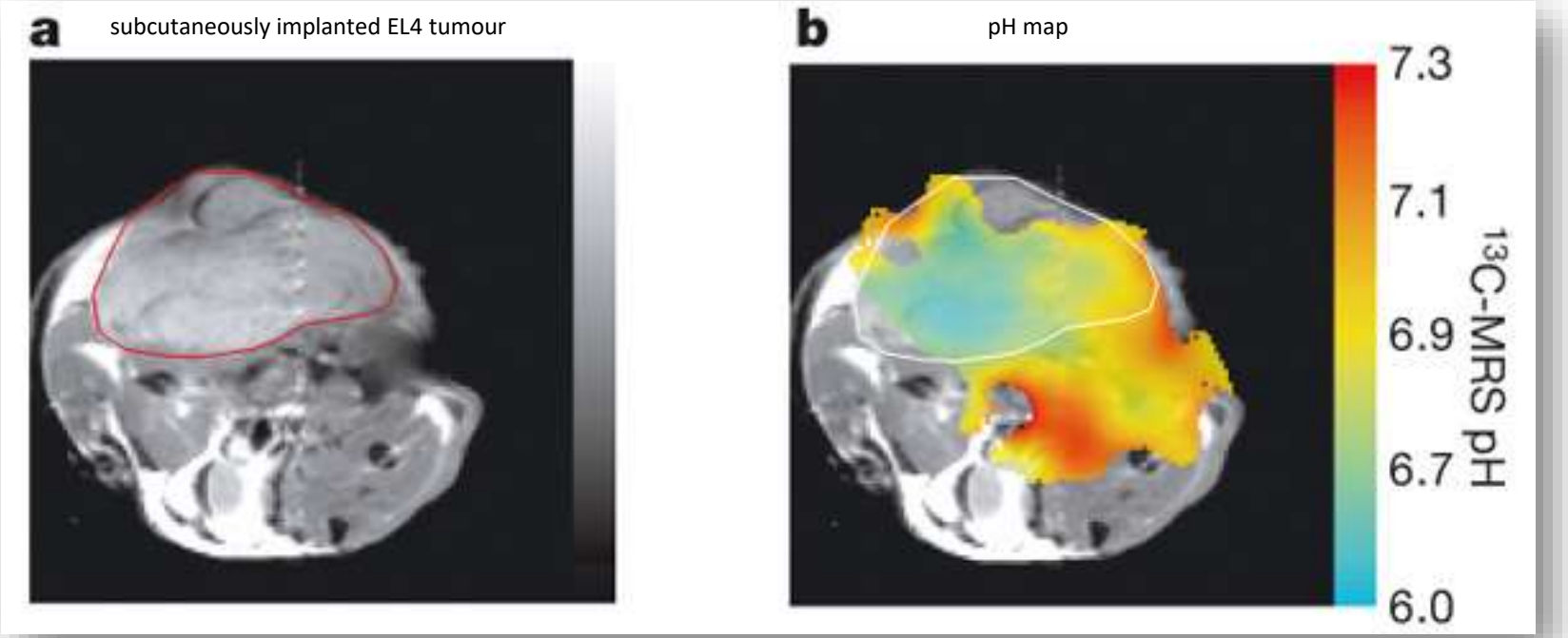
Aerobic glycolysis in cancer: hyperpolarised glucose



Magnetic resonance imaging of tumor glycolysis using hyperpolarized ^{13}C-labeled glucose

Tiago B Rodrigues[1], Eva M Serrao[1], Brett W C Kennedy[2], De-En Hu[2], Mikko I Kettunen[1–3] & Kevin M Brindle[1–3]

Aerobic glycolysis in cancer: increased lactate secretion



Magnetic resonance imaging of pH *in vivo* using hyperpolarized ^{13}C-labelled bicarbonate

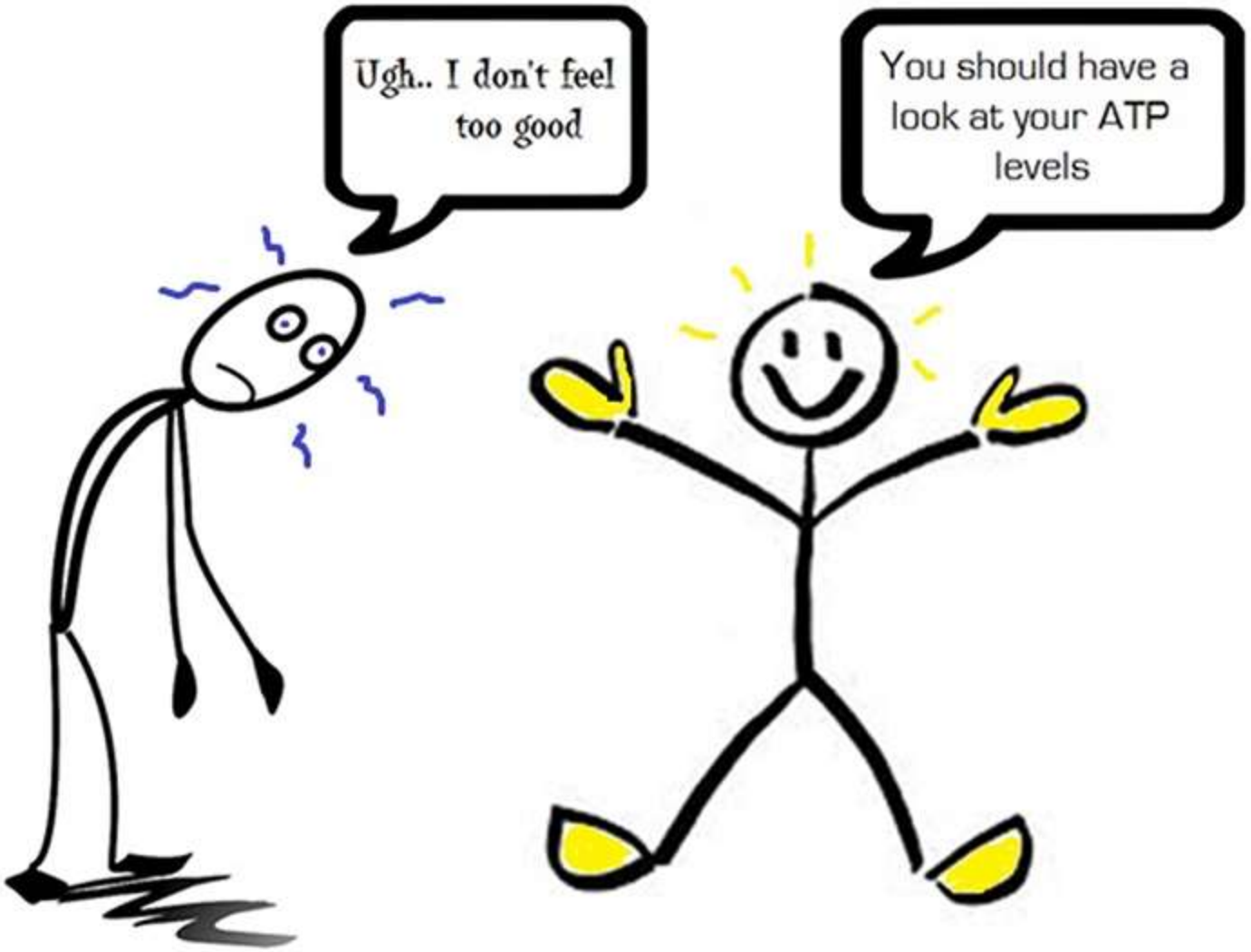
Ferdia A. Gallagher[1,2,3]*, Mikko I. Kettunen[1,2]*, Sam E. Day[1,2]†, De-En Hu[1,2], Jan Henrik Ardenkjær-Larsen[4], René in 't Zandt[5], Pernille R. Jensen[5], Magnus Karlsson[5], Klaes Golman[5], Mathilde H. Lerche[5] & Kevin M. Brindle[1,2]

Is glycolysis up-regulated in cancer?

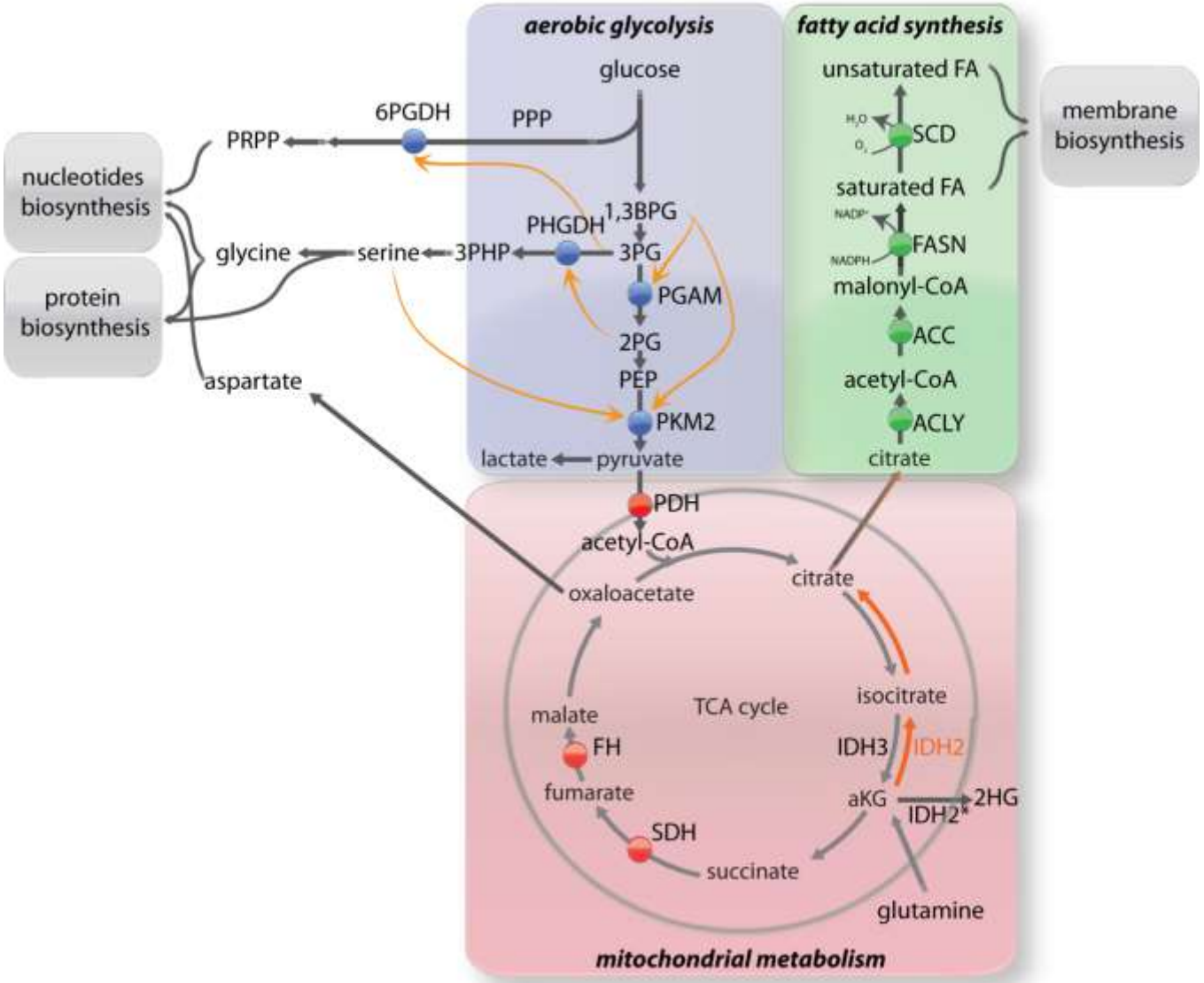
YES! aerobic glycolysis is a hallmark of cancer

Disclaimer: Aerobic glycolysis is a characteristic of most proliferating cells

Is it all about ATP?



Aerobic glycolysis supports proliferation



Aerobic glycolysis and migration

Published online: August 1,

Article

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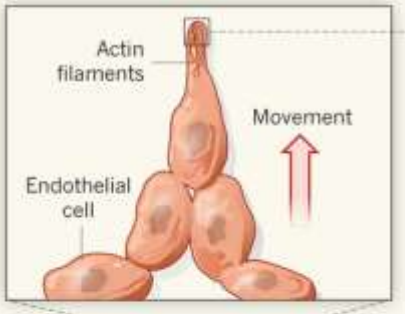
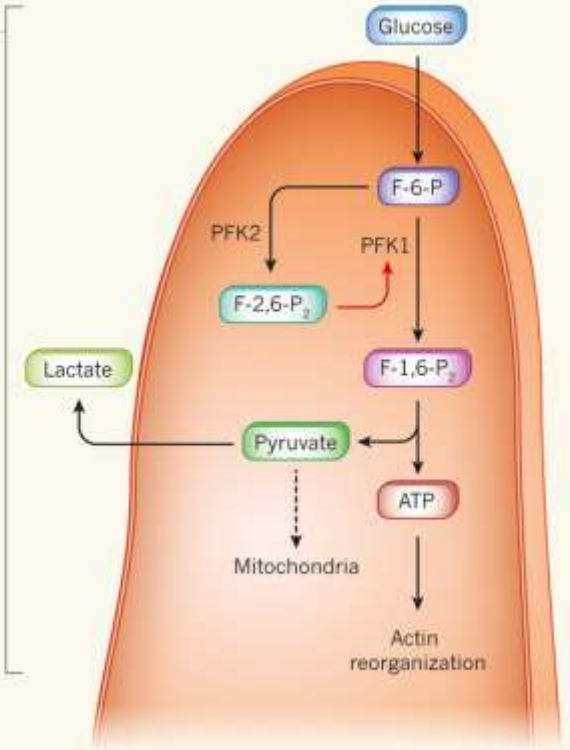
Keren Yizhak[1,*,†]
Christian Frezza





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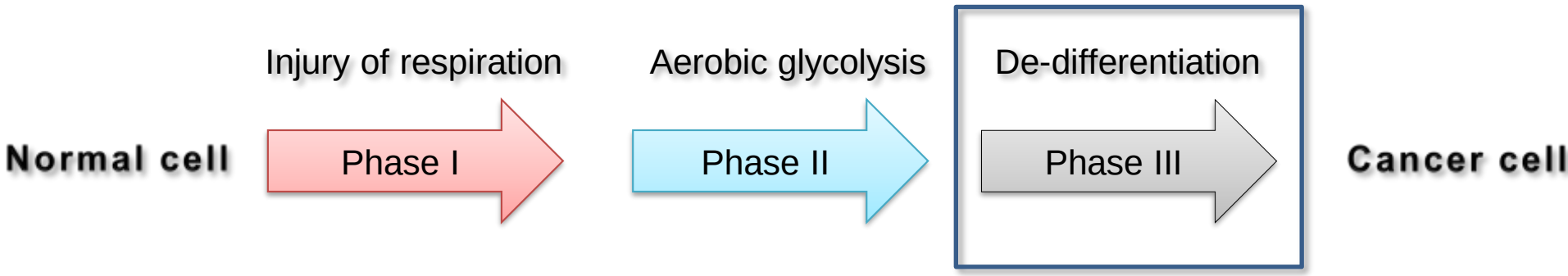
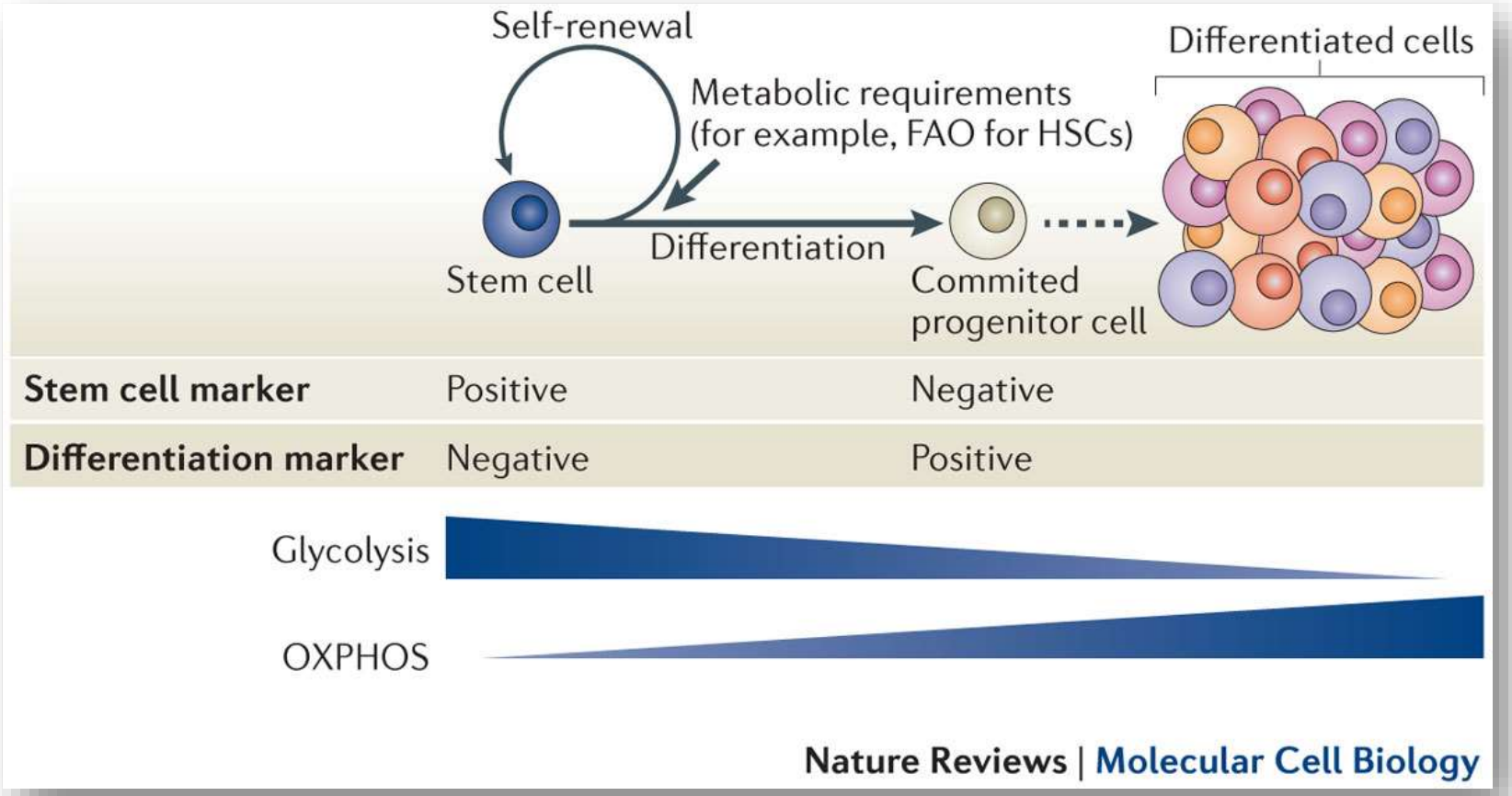
The Warburg hypothesis

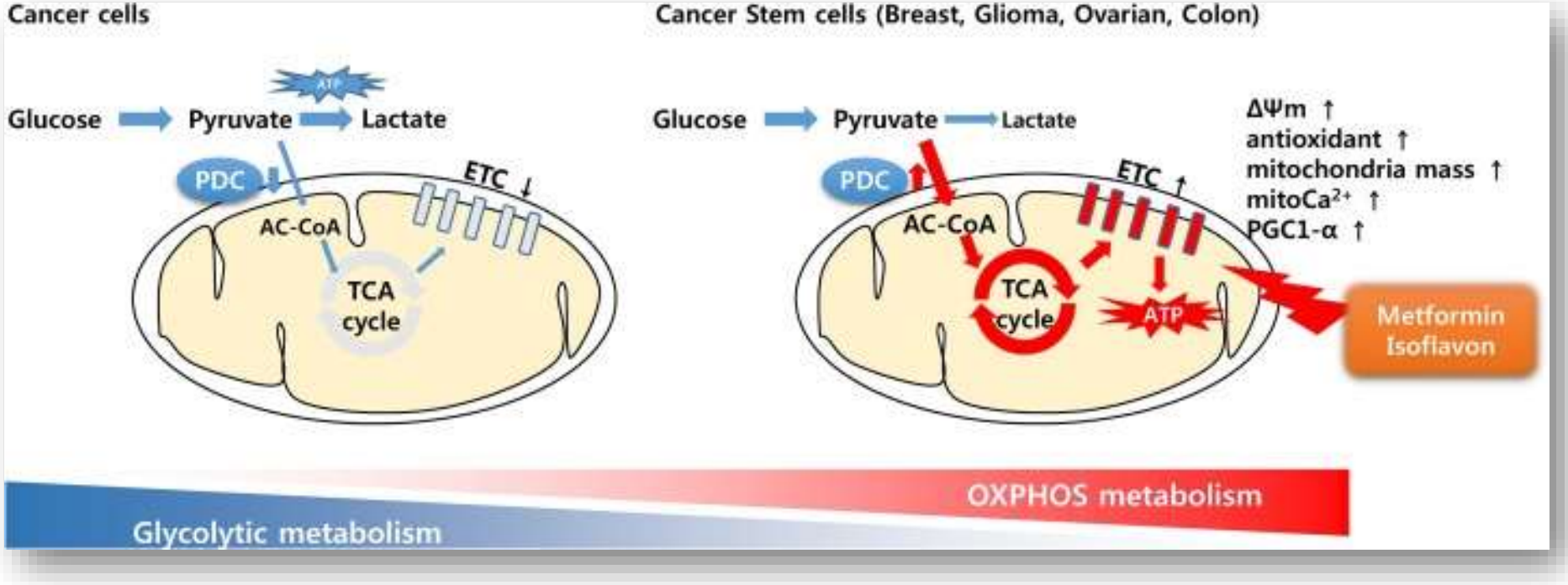


another part succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy, the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly—the cancer cells.

Aerobic glycolysis and "stemness"



Cancer stem cells and plasticity



Can we exploit altered cancer metabolism as therapeutic strategy?

The first example of targeting cancer metabolism?

The New England
Journal of Medicine

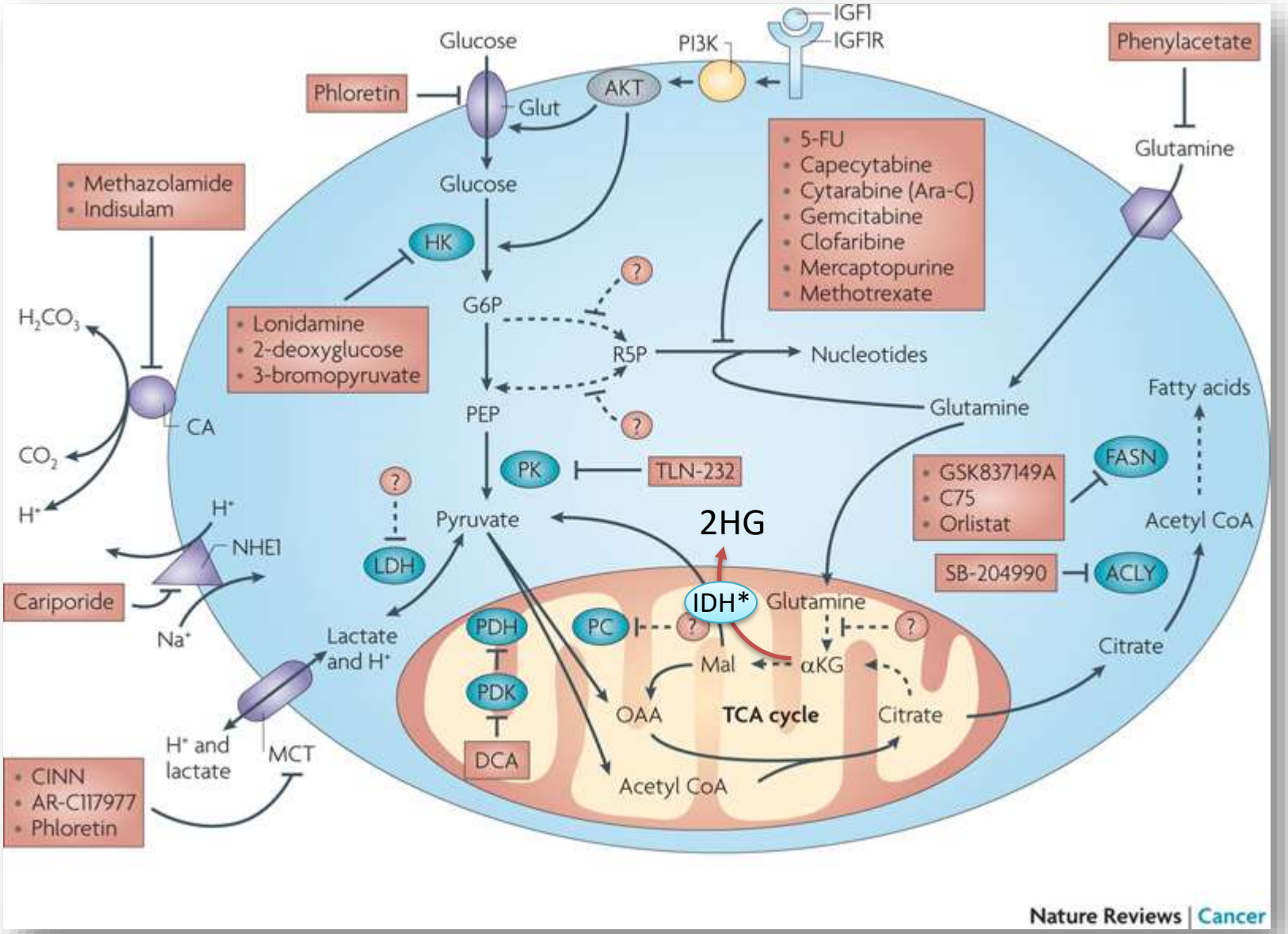
Volume 238 JUNE 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.‖

BOSTON

Targeting cancer metabolism



IDH and GLS inhibitors are in clinic

nature biotechnology

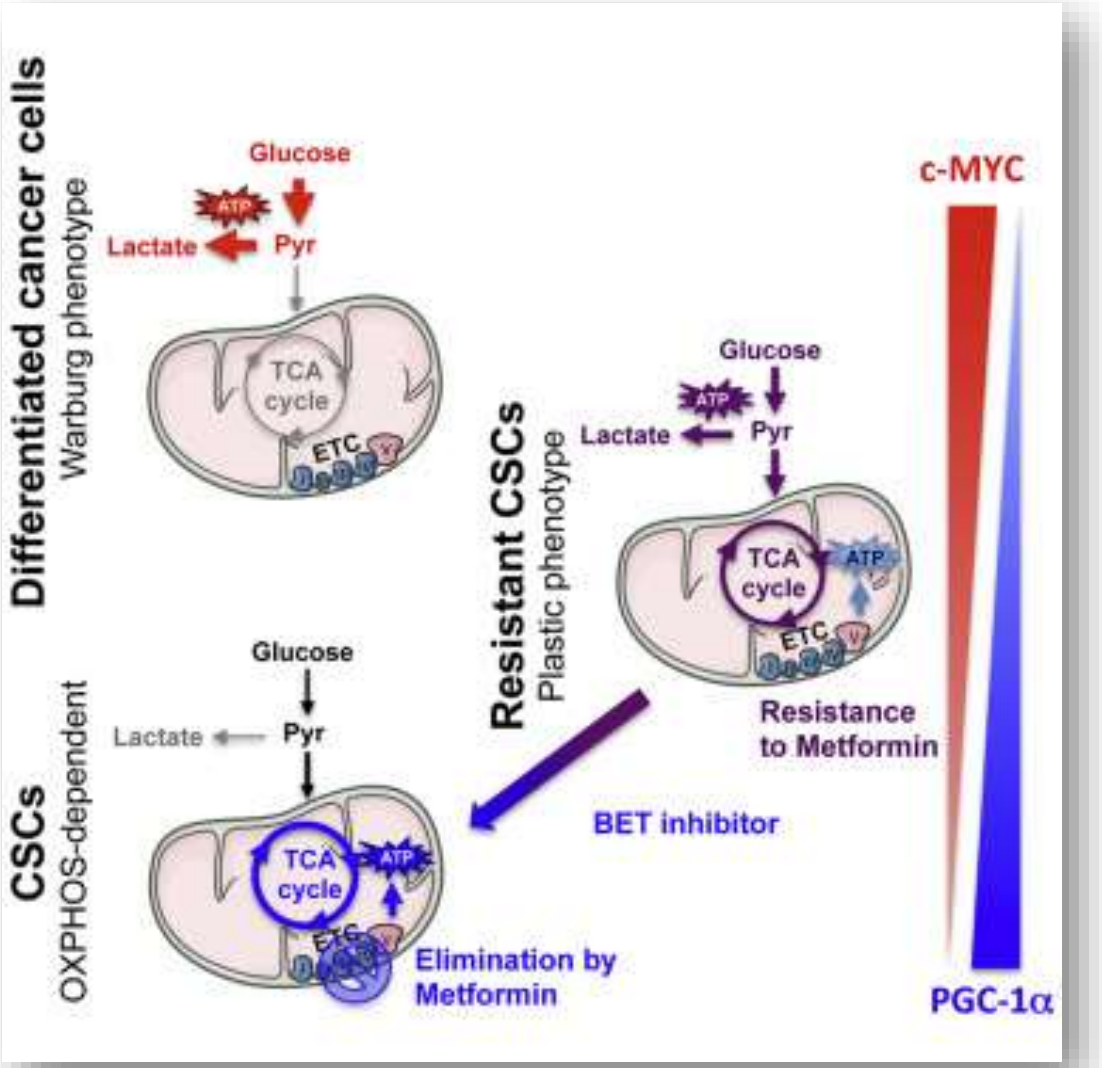
News

Cancer anabolic metabolism inhibitors move into clinic

Ken Garber

Company/location	Agent	Target	Indications	Status
Agios & Celgene	AG-221, AG-120, AG-881	IDH1 and IDH2	AML, MDS, solid tumors	Phase 3
Polaris Group/San Diego	ADI-PEG 20	Pegylated arginine deiminase	Hepatocellular carcinoma (HCC), others	Phase 3 in HCC missed primary endpoint
Cornerstone Pharmaceuticals/Cranbury, New Jersey	CPI-613	Pyruvate dehydrogenase	AML, MDS, solid tumors	Phase 2
Calithera Biosciences	CB-839	Glutaminase 1	RCC, breast cancer	Phase 1/2
3-V Biosciences	TVB-2640	Fatty acid synthase	Ovarian, breast, lung	Phase 2 pending
Novartis/Basel	IDH305	IDH1	Advanced cancers	Phase 1
Forma Therapeutics/Watertown, Massachusetts	FT-2102	IDH1	AML, MDS	Phase 1
Bayer/Leverkusen, Germany	BAY-1436032	IDH1	Solid tumors	Phase 1
Advanced Cancer Therapeutics/Louisville, Kentucky	PFK-158	PFKFB3	Solid tumors	Phase 1
Aeglea BioTherapeutics/ Austin, Texas	AEB-1102	Modified human arginase	AML, MDS, solid tumors	Phase 1

Resistance through metabolic reprogramming



Conclusions

Metabolism of cancer cells is different from that of normal cells

Dysregulated metabolism can drive oncogenic processes

Altered metabolism offers a therapeutic window to target cancer cells

Key references & links

- **O. Warburg**, On the origin of cancer cells, Science, 1956
- **JS. Flier et al.** Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. **Science**, **1987**
- **H. Shim et al. c**-Myc transactivation of *LDH-A*: Implications for tumor metabolism and growth, **PNAS**, 1998
- **D. Hanahan and RA. Weinberg**, Hallmarks of Cancer: next generation, **Cell**, 2011
- **Gaude and Frezza,** Tissue-specific and convergent metabolic transformation of cancer correlates with metastatic potential and patient survival, **Nat Comms**, 2016
- **Pavlova and Thompson**, The emerging hallmarks of cancer metabolism, **Cell Metabolism**, 2016

- https://www.facebook.com/CancerMetabolism/