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ACIIDS Conference 2022

Cancer
- Origin Story and Metabolism

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What are the chances of you getting hit by lightning in a year?

What are the chances of you getting hit by lightning in a year?

1 in 32,800 (source: Nat Geo)

What are the chances of you getting hit by lightning twice in a year?

What are the chances of you getting hit by lightning twice in a year?

1 in 1,100,000,000 (1.1bil or 1.1×10^9)

Winning Jackpot in Oz Lotto
1 in 45,379,620

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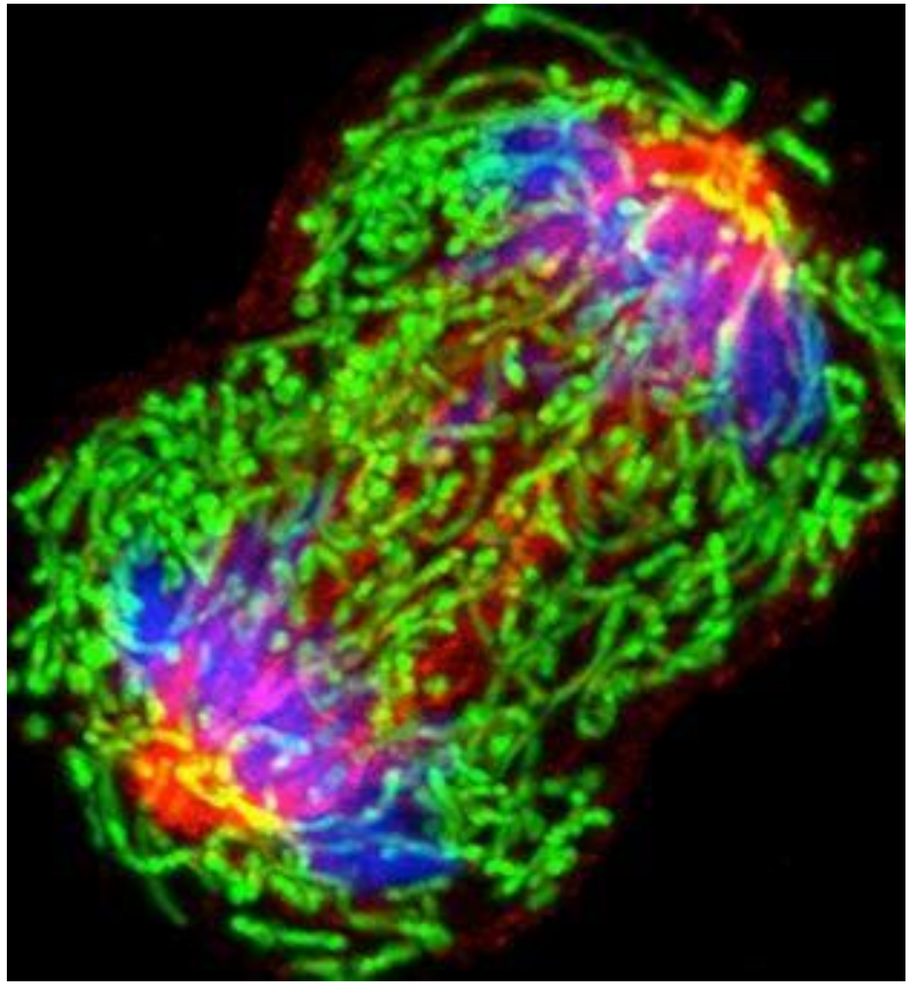
What is Cancer?



- We know the official story
- My Hypothesis: **Cancer is a dysfunction of Stem Cells**
- Resulting from a **Corrupted Microenvironment** and **Corrupted Cellular information**
- Dysfunctional Stem Cells reverts back to behaving like **Trophoblastic Cells**
- Not caused by random genetic mutations - mathematically improbable

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What are the hallmarks of ALL cancers?

- Rapid cell proliferation
- Tissue invasion
- Angiogenesis
- Immune evasion / suppression
- Differing energy metabolism to normal cells (eg. aerobic glycolysis, glutaminolysis)
- Stem-cell driven process

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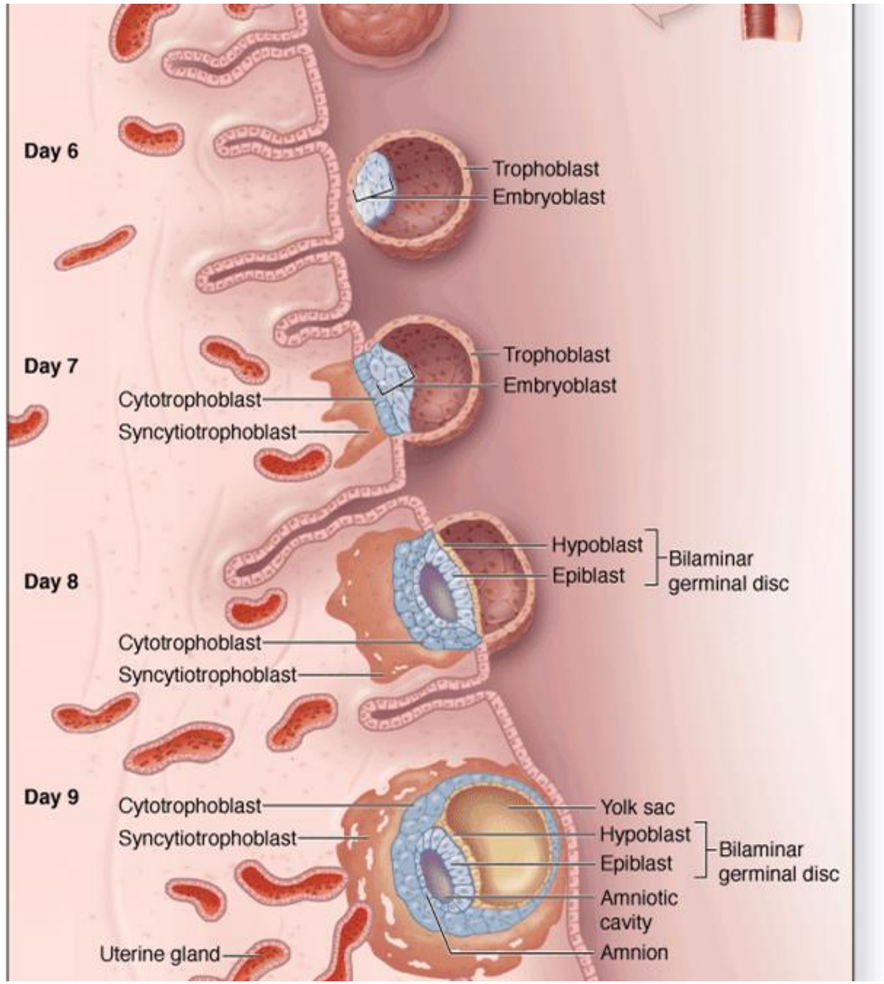
What happens during embryo implantation ?



- Rapid cell proliferation
- Tissue invasion
- Angiogenesis
- Immune evasion
- Unique energy metabolism (eg. aerobic glycolysis, glutaminolysis)
- Process driven by trophoblasts / stem cells

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Common features between cancer cells, trophoblasts and normal cells

Cell Behaviour	Cancer Cells	Trophoblasts (placental cells during implantation)	Somatic Cells (Normal Adult Cells)
Rapid Cell Replication	Y	Y	some cells eg dermis, mucosa
Invasive into surrounding tissues	Y	Y	X
Promotes Angiogenesis	Y	Y	X
Immune Evasion	Y	Y	Y
Driven by Stem Cells	Y	Y	X
Utilises Aerobic Glycolysis	Y	Y	some immune cells
Utilises Glutamine as fuel	Y	Y	X
Grows in Acidic environments	Y	Y	X
Grows in Estrogenic environments	Y	Y	X
High Mutation Rate	Y	Y	X

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Cancer and Pregnancy: Parallels in Growth, Invasion, and Immune Modulation and Implications for Cancer Therapeutic Agents

SHERNAN G. HOLTAN, MD; DOUGLAS J. CREEDON, MD, PHD; PAUL HALUSKA, MD, PHD; AND SVETOMIR N. MARKOVIC, MD, PHD

Many proliferative, invasive, and immune tolerance mechanisms that support normal human pregnancy are also exploited by malignancies to establish a nutrient supply and evade or edit the host immune response. In addition to the shared capacity for invading through normal tissues, both cancer cells and cells of the developing placenta create a microenvironment supportive of both immunologic privilege and angiogenesis. Systemic alterations in immunity are also detectable, particularly with respect to a helper T cell type 2 polarization evident in advanced cancers and midtrimester pregnancy. This review summarizes the similarities between growth and immune privilege in cancer and pregnancy and identifies areas for further investigation. Our PubMed search strategy included combinations of terms such as *immune tolerance*, *pregnancy*, *cancer*, *cytokines*, *angiogenesis*, and *invasion*. We did not place any restrictions on publication dates. The knowledge gained from analyzing similarities and differences between the physiologic state of pregnancy and the pathologic state of cancer could lead to identification of new potential targets for cancer therapeutic agents.

***Mayo Clin Proc*. 2009;84(11):985-1000**

CTL = $CD8^+$ T cytotoxic lymphocyte; DC = dendritic cell; EVT = extravillous trophoblast; HLA = human leukocyte antigen; IL = interleukin; NK = natural killer; T_H1 = helper T cell type 1; T_H2 = helper T cell type 2; T_{reg} = regulatory T cell; uNK = uterine NK

sensitized against fetal Rh antigens, re-exposure to fetal Rh antigens with subsequent pregnancy may lead to hemolytic disease of the newborn and fetal death.[2] Such imperfections of shared mechanisms of immune tolerance between pregnancy and cancer suggest that cancer rejection via immunologic means may be possible, even considering the myriad mechanisms extending immunologic privilege to the fetus as well as cancer cells.

This review summarizes the parallels in proliferation, invasion, and immune privilege between cancer and pregnancy by first detailing shared characteristics of fetal-derived trophoblast cells of the placenta and tumor cells. It then describes the similarities between tolerogenic systems within the tumor microenvironment and the fetomaternal interface. Finally, it provides an overview of the evidence for systemic immune modulation in cancer and pregnancy and suggests the implications of these similarities in designing an integrated approach to cancer therapy. Our PubMed search strategy included combinations of terms such as *immune tolerance*, *pregnancy*, *cancer*, *cytokines*, *angiogenesis*, and

Holtan SG, et al. Mayo Clinic Proc 2009;84(11):985-1000. https://doi.org/10.4065/84.11.985

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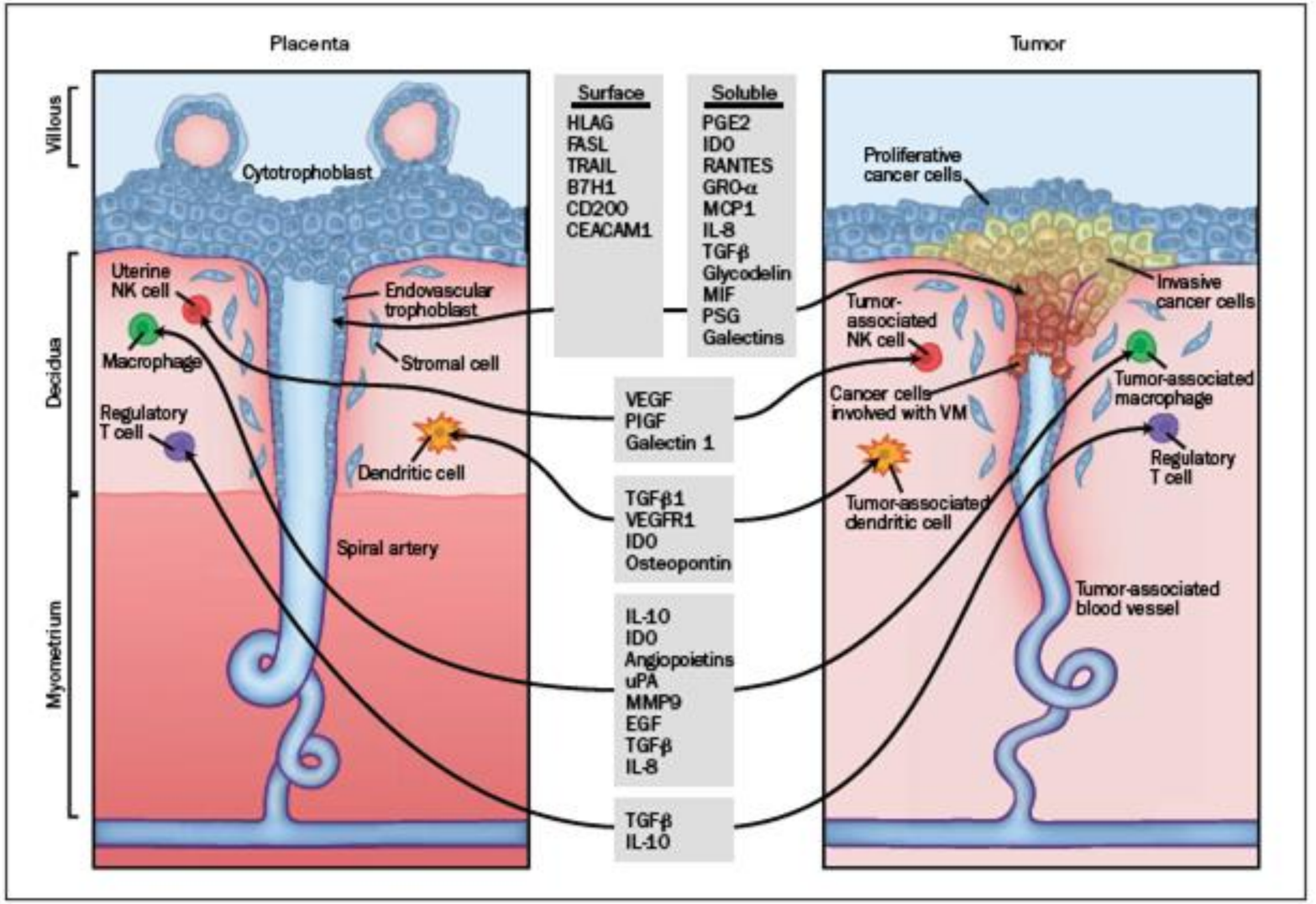

Similarities between the fetomaternal interface and tumour microenvironment. HLA – human leukocyte antigen, IL – interleukin, VM – vascular mimicry.

Holtan SG, et al. Mayo Clinic Proc 2009;84(11):985-1000. https://doi.org/10.4065/84.11.985

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TABLE 1. **Tumorlike Attributes of the Human Trophoblast Cells and a Selection of Representative Targeted Cancer Therapeutic Strategies in Use or Development**[a]

Shared trophoblast-tumor attribute	Mechanism	Targeted therapeutic strategy	Drug/compound name[b]
Self-sufficiency in growth signals	Activation of MAPK pathway	Inhibition of RAS-RAF-MEK-ERK signaling	Sorafenib; ARRY-142886; PLX-4032; XL281; RAF265; PD0325901[5]
	Activation of PI3K-AKT pathway	Inhibition of RAS-PI3K-AKT-MTOR signaling	Quercitin, XL147, and XL765; GDC-0941; BEZ235; PX-866[6]; sirolimus; everolimus; temsirolimus
	FAK activation	FAK inhibition	TAE226[7]; dasatinib
	HGF autocrine loop	HGF or C-MET inhibition	OA-5D5[8]; AMG-102[9]; SGX-523; PF-0234106; XL880
	EGF autocrine loop	EGF or EGFR inhibition	Erlotinib; cetuximab; panitumumab; XL647
	IGF autocrine loop	IGF or IGFR inhibition	AEW541[10]
	CSF autocrine loop	CSF1 or CSF1R inhibition	GW2580[11]; CYC10268[12]
	PDGF autocrine loop	PDGF or PDGFR inhibition	AZD2171; pazopanib; sorafenib; sunitinib; E7080; ZD6474; AG-013736
	VEGF autocrine loop	VEGF or VEGFR inhibition	Bevacizumab; RAF265; BMS-690514
Insensitivity to antigrowth signals	TGF-β pathway activation	TGF-β2 blockade	AP 12009[13]; LY-2157299[14]
	CDK	CDK inhibition	SNS-032[15]; AT7519[16]; flavopiridol
	SMAD	ALK inhibition leading to decreased SMAD phosphorylation	A 83-01[17]
Evasion of apoptosis	IGF1R signaling	IGF1R blockade	Concept reviewed by Werhova and Haluska[18]; R1507; CP-751,871[19,20]
	PDGFR signaling	PDGFR blockade	Imatinib; sorafenib; sunitinib; E7080; ZD6474; AG-013736; pazopanib
	BCL2	BCL2 inhibition	Oblimersen
	Survivin	Survivin inhibition	YM-155; terameprocol
	XIAP	XIAP antisense	AEG35156
	Endoreduplication	Maintain p53 integrity; Aurora kinase inhibition; induction of p21 (waf1/cip1)	Nutlin-3a (promotes endoreduplication)[21]; VX-680[22]; theaflavins[23]
Limitless replicative potential	Telomerase	Telomerase inhibition	GRN163L; RHPS4
	HGF–C-MET signaling	MET inhibition	PF-0234106
Sustained angiogenesis	VEGFR signaling	VEGF inhibition	Bevacizumab; sorafenib; sunitinib; E7080; ZD6474; AG-013736; pazopanib; IMC-1121B; AZD2171; CHIR-265; ABT-510; BMS-690514; XL880; aflibercept
	HIF-1α	HIF-1α inhibition	PX-478
	PGF	PGF inhibition	TB-403[24]
	FGF	FGF inhibition	PI-88
Tissue invasion	Integrins	α2 integrin inhibition; αv integrin inhibition; αvβ3 + αvβ5 integrin inhibition; αvβ3 integrin inhibition	E 7820; CNTO 95; cilengitide; abergrin (MEDI 522)
	MMPs	Down-regulation of MMPs	Curcumin[25]; Saponins[26]
	Wnt signaling	Cyclooxygenase-2 inhibition	Celecoxib[27]
	HSP27	3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibition	Lipophilic statin medications: atorvastatin, simvastatin, lovastatin, or fluvastatin[28]

- Shared mechanism / genetic expression for:
  - Growth signals
  - Evasion of apoptosis
  - Replication
  - Angiogenesis
  - Tissue invasion
  - Immune evasion

46 identical pathways between cancer cells and trophoblastic cells.

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Immune evasion	Decreased HLA class I expression	Increased HLA class I expression	Gamma irradiation[29]; samarium-153-ethylenediaminetetramethylenephosphonate[30]; DNA-demethylating agent 5-aza-2′-deoxycytidine[31]
	Nonclassical HLAG expression	Neutralization of soluble HLAG or reduced gene transcription of HLAG	None yet developed, but 5-aza-2′-deoxycytidine increases HLAG in leukemia cell lines with unknown clinical immunomodulatory impact[32]
	PGE2	Decreased PGE2 synthesis	Celecoxib[33]
	Complement regulatory proteins	Neutralization of miniantibodies to CD55 and CD59	MB55 and MB59 tested in mouse models only at time of writing of this manuscript[34]
	IDO	Decreased IDO expression, IDO blockade	Celecoxib,[35] 1-methyl D-tryptophan[36]
	CD44 expression (also soluble)	CD44 ligation	Anti-CD44 monoclonal antibodies[37]
	MUC1	MUC1 radioimmunotherapy	Radioimmunotherapy with MUC1 monoclonal antibody[38,39]
	Neuropilin 1 and 2	Neuropilin receptor blockade	None yet available, but concept reviewed by Mac Gabhann and Popel[40]
	B7H1	B7H1 blockade	None yet available, but concept reviewed by Thompson et al[41]

TABLE 1. **Continued**[a]

Shared trophoblast-tumor attribute	Mechanism	Targeted therapeutic strategy	Drug/compound name[b]
Immune evasion (continued)	FASL	Recombinant FASL	APO010[42]
	CCL5	CCL5 vaccine adjuvant	Engineered CCL5 superagonist[43]
	TRAILR	TRAILR2 agonist	Lexatumumab
	TIM3	TIM3 blockade	None yet available, but concept reviewed by Anderson[44]
	TLR	Synthetic TLR agonists	Ampligen (TLR3 agonist)[45]; imiquimod (TLR7 agonist)[46]
	Galectins	Galectin inhibition	GCS-100 (Galectin 3 antagonist)[47]; thiodigalactoside ester derivatives[48]
	CD200	CD200 antibody	ALXN6000[49]
	SDF1 (also known as CXCL12)	CXCR4 (CXCL12 receptor) antagonism	Plerixafor[50]; CTCE-9908[51]
	Osteopontin	Down-regulation of osteopontin expression	Small interfering RNA therapy[52]

[a] HLA = human leukocyte antigen. For expansion of all gene symbols, see Glossary of Genetics Terminology at the end of the article.
[b] Data regarding drug compounds are from *Mayo Clin Proc*,[53] unless a citation is given to indicate otherwise.

Chances of having cancer due to random DNA mutation (lottery numbers) is at least **1 in 10^{46} to 10^{77}** which is similar odds to getting struck by lightning **17x in a year -** so is it random?

At least 46 different pathways shared by a tumour and a trophoblast. The probability of a tumour sharing the same 46 pathways as that of a trophoblast through random mutation 1 in **10^{46} to 10^{77}.** (that is 10 with 77 zeros) - this would still be a gross underestimate! Chances of being hit by lightning in a year is 1 in 32,800. In comparison, the no. of atoms that make Earth is **1.3×10^{50}**

Holtan SG, et al. Mayo Clinic Proc 2009;84(11):985-1000. https://doi.org/10.4065/84.11.985

Placental energy metabolism in health and disease—significance of development and implications for preeclampsia

Irving L. M. H. Aye, PhD; Catherine E. Aiken, MD, PhD; D. Stephen Charnock-Jones, PhD; Gordon C. S. Smith, MD, PhD

The placenta is a highly metabolically active organ fulfilling the bioenergetic and biosynthetic needs to support its own rapid growth and that of the fetus. Placental metabolic dysfunction is a common occurrence in preeclampsia although its causal relationship to the pathophysiology is unclear. At the outset, this may simply be seen as an "engine out of fuel." However, placental metabolism plays a vital role beyond energy production and is linked to physiological and developmental processes. In this review, we discuss the metabolic basis for placental dysfunction and propose that the alterations in energy metabolism may explain many of the placental phenotypes of preeclampsia such as reduced placental and fetal growth, redox imbalance, oxidative stress, altered epigenetic and gene expression profiles, and the functional consequences of these aberrations. We propose that placental metabolic reprogramming reflects the dynamic physiological state allowing the tissue to adapt to developmental changes and respond to preeclampsia stress, whereas the inability to reprogram placental metabolism may result in severe preeclampsia phenotypes. Finally, we discuss common tested and novel therapeutic strategies for treating placental dysfunction in preeclampsia and their impact on placental energy metabolism as possible explanations into their potential benefits or harm.

Key words: epigenetics, fetal growth restriction, glycolysis, metabolism, metformin, mitochondria, placenta, preeclampsia, reactive oxygen species

Introduction

The placenta plays a vital role in the development and severity of preeclampsia. It has long been established that the presence of the placenta and not the fetus is necessary for preeclampsia. For example, molar pregnancies are susceptible to preeclampsia and the syndrome resolves on removal of the placenta.[1]

The prevailing hypothesis for the cause of preeclampsia centers on defective placentation and placental dysfunction. As such, preeclampsia shares common pathophysiology with other "disorders of placentation" often referred to as the "great obstetrical syndromes" that include spontaneous miscarriage, placental abruption, and fetal growth restriction (FGR).[2] Defective placentation in preeclampsia is characterized by abnormal trophoblast invasion and remodeling of the spiral arteries by extravillous trophoblast. Deficient spiral artery remodeling leads to a failure to establish an appropriate uteroplacental blood supply and therefore is thought to give rise to trophoblast damage that may be accompanied by an ischemia-reoxygenation type of injury[3] and placental stress (oxidative, endoplasmic reticulum [ER], and inflammatory). The maternal peripheral endothelial activation and systemic inflammatory response are then triggered by placentally released factors associated with placental stress.

Perturbations in placental metabolism and oxidative stress are universally observed in preeclampsia, although the cause-and-effect relationship is not clear. Placental energy metabolism intermediates are inversely correlated with levels of placenta-released soluble fms-like tyrosine kinase 1 (sFlt-1),[4] suggesting that the deficiency in energy metabolism correlates with preeclampsia

EMBRYOLOGY REVISION!

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Irving L.M.H. Aye, Catherine E. Aiken, D. Stephen Charnock-Jones, Gordon C.S. Smith, **Placental energy metabolism in health and disease—significance of development and implications for preeclampsia, American Journal of Obstetrics and Gynecology**, Volume 226, Issue 2, Supplement, **2022**, Pages S928-S944

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Bioenergetics in the placenta

- The placenta is a highly metabolically active organ fulfilling the bioenergetic and biosynthetic needs to support its own rapid growth and that of the fetus.
- >2.5 kg of ATP per day in a term placenta
- Glucose is the major nutrient source for energy generation in the placenta.
- Fatty acids and amino acids (glutamine) provide alternative fuel sources to feed into the TCA cycle via their conversion into the metabolic intermediate acetyl-CoA
- Long-held view of lactate as a metabolic waste product has since been revised.
- **30% of the glucose** from the maternal circulation **is converted into lactate** by the placenta, in **NORMOXIC** conditions (ie. **Aerobic Glycolysis** or **Warburg effect**).
- The production of lactate uncouples glycolysis and TCA cycle so that they can occur independently.

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Biosynthetic processes in the placenta

- Intermediates of energy metabolism are also essential for the **biosynthesis** of nucleotides, fatty acids, cholesterol, and amino acids to form biomass.
- Glycolysis acts as a metabolic hub connecting with its branched pathways to generate biosynthetic precursors.
- Pentose phosphate pathway (PPP) generate ribose 5-phosphate, a nucleotide precursor.
- Hexosamine biosynthetic pathway (HBP) generate uridine diphosphate N-acetylglucosamine (UDP-glcNAc), a key substrate for protein glycosylation.
- Dihydroxyacetone phosphate (DHAP) interconversion from fructose bisphosphate provides the glycerol backbone necessary for triglyceride synthesis.
- 3-phosphoglycerate can be used for serine and glycine synthesis, providing a source of methyl groups for one-carbon metabolic pathways that generate purines and glutathione.

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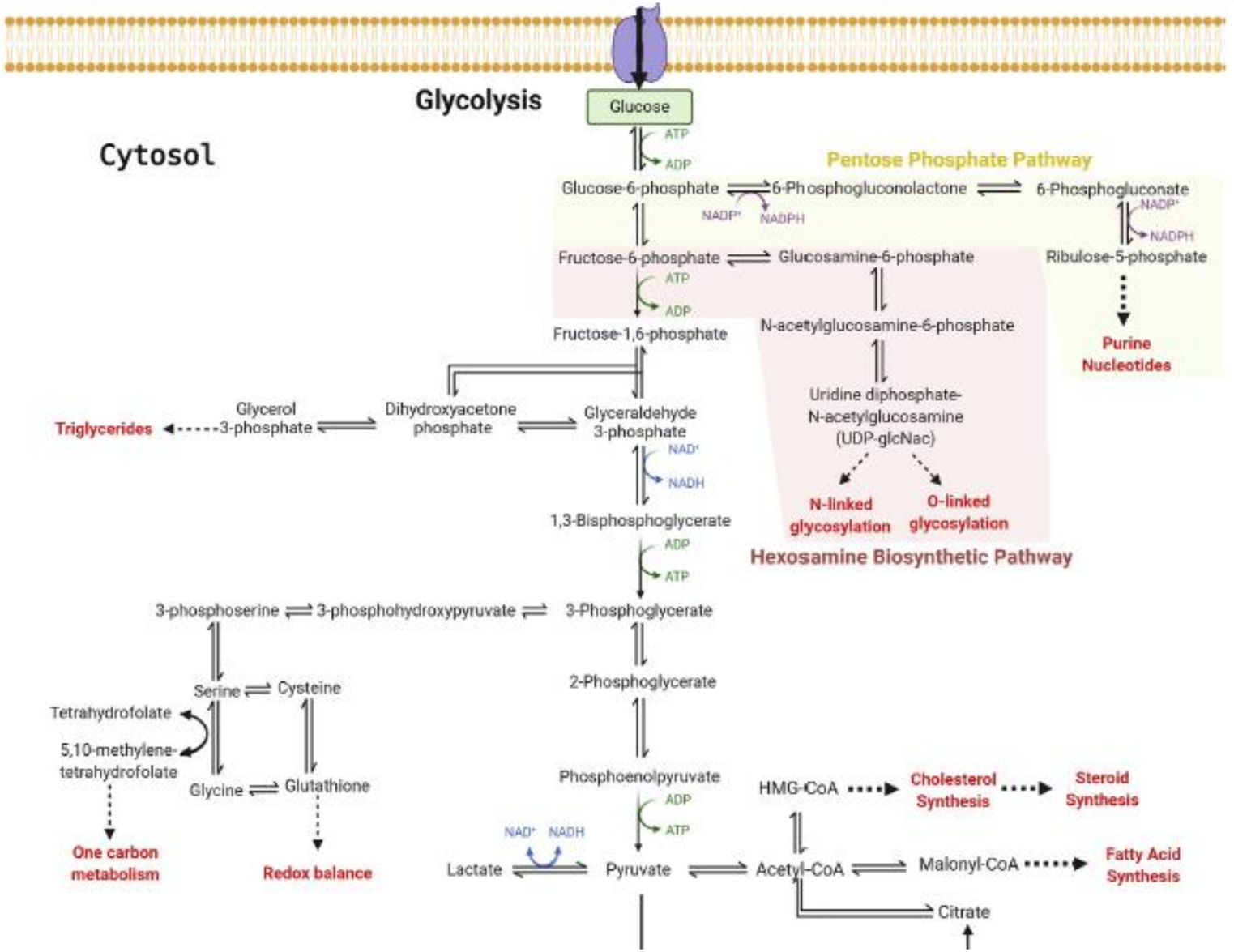
FIGURE 1
Central carbon metabolism and its contribution to bioenergetic and biosynthetic processes



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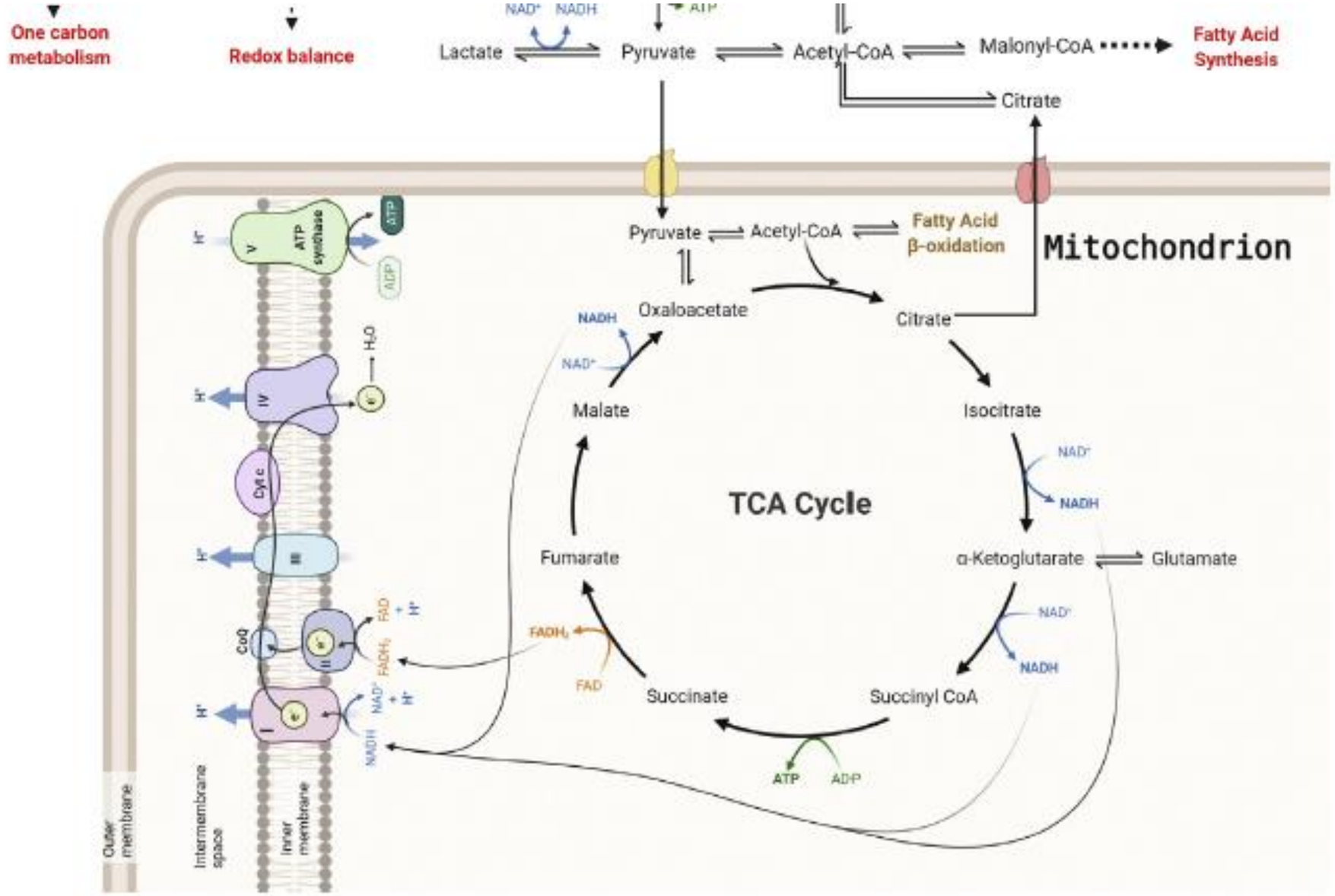

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Lactate production by the mammalian blastocyst: Manipulating the microenvironment for uterine implantation and invasion?

David K. Gardner

The mammalian blastocyst exhibits a high capacity for aerobic glycolysis, a metabolic characteristic of tumours. It has been considered that aerobic glycolysis is a means to ensure a high carbon flux to fulfil biosynthetic demands. Here, alternative explanations for this pattern of metabolism are considered. Lactate creates a microenvironment of low pH around the embryo to assist the disaggregation of uterine tissues to facilitate trophoblast invasion. Further it is proposed that lactate acts as a signalling molecule (especially at the reduced oxygen tension present at implantation) to elicit bioactive VEGF recruitment from uterine cells, to promote angiogenesis. Finally it is suggested that the region of high lactate/low pH created by the blastocyst modulates the activity of the local immune response, helping to create immune tolerance. Consequently, the mammalian blastocyst offers a model to study the role of microenvironments, and how metabolites and pH are used in signalling.

Keywords:
implantation; lactate; microenvironment; signalling

out the preimplantation period, but with major bouts of transcriptional activity around the 4- to 8-cell in the human, and a second round at the morula stage [1]. Of note, the early embryo during the first three cell cycles, similar to the unfertilised oocyte, cannot use glucose as the sole energy source, but rather requires pyruvate or sufficient aspartate and lactate to undergo the first cleavage division. The high ATP/ADP ratio of the early embryo [2], due to the low levels of energy requirements and biosynthesis during the first 48 hours of life, allosterically inhibits phosphofructokinase, thereby impairing glucose flux through the Embden-Meyeroff pathway (reviewed by [3]). A major change in physiology occurs around the 8- to 16-cell stage when the embryo creates the first trans-

Gardner DK. Bioessays. 2015;37(4):364-71. doi: 10.1002/bies.201400155.

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Multiple Biological Activities of Lactic Acid in Cancer: Influences on Tumor Growth, Angiogenesis and Metastasis

Suveera Dhup, Rajesh Kumar Dadhich, Paolo Ettore Porporato and Pierre Sonveaux*

Pole of Pharmacology, Institute of Experimental and Clinical Research (IREC), Université catholique de Louvain (UCL) Medical School, Brussels, Belgium

Abstract: High rate of glycolysis is a metabolic hallmark of cancer. While anaerobic glycolysis promotes energy production under hypoxia, aerobic glycolysis, the Warburg effect, offers a proliferative advantage through redirecting carbohydrate fluxes from energy production to biosynthetic pathways. To fulfill tumor cell needs, the glycolytic switch is associated with elevated glucose uptake and lactic acid release. Altered glucose metabolism is the basis of positron emission tomography using the glucose analogue tracer [^{18}F]-fluorodeoxyglucose, a widely used clinical application for tumor diagnosis and monitoring. On the other hand, high levels of lactate have been associated with poor clinical outcome in several types of human cancers. Although lactic acid was initially considered merely as an indicator of the glycolytic flux, many evidences originally from the study of normal tissue physiology and more recently transposed to the tumor situation indicate that lactic acid, i.e. the lactate anion and protons, directly contributes to tumor growth and progression. Here, we briefly review the current knowledge pertaining to lactic acidosis and metastasis, lactate shuttles, the influence of lactate on redox homeostasis, lactate signaling and lactate-induced angiogenesis in the cancer context. The monocarboxylate transporters MCT1 and MCT4 have now been confirmed as prominent facilitators of lactate exchanges between cancer cells with different metabolic behaviors and between cancer and stromal cells. We therefore address the function and regulation of MCTs, highlighting MCT1 as a novel anticancer target. MCT1 inhibition allows to simultaneously disrupt metabolic cooperativity and angiogenesis in cancer with a same agent, opening a new path for novel anticancer therapies.

Keywords: Tumor metabolism, hypoxia, Warburg effect, lactate, lactic acidosis, monocarboxylate transporters, hypoxia-inducible factor-1, nuclear factor-κB.

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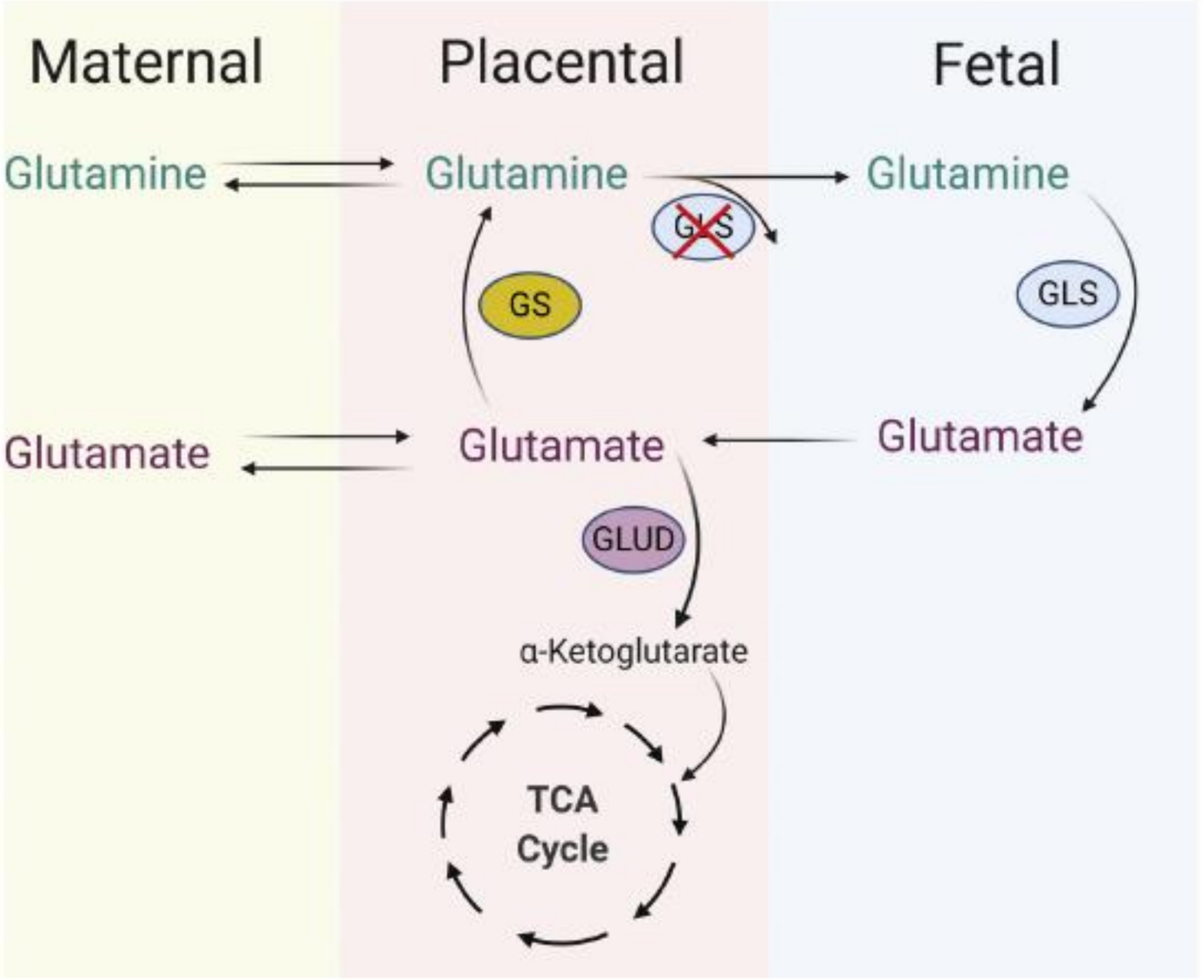
FIGURE 2
Placental-fetal glutamine-glutamate shuttle



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Glutamine is a major source of fuel in cancer, if not the main source in some instances

- Glutamine is the most abundant amino acid found in the body. It's made in the muscles and transferred by the blood into different organ systems.(1)
- Glutamine is a building block for making proteins in the body. It's also needed to make other amino acids and glucose (1)
- The intramuscular glutamine content corresponds to 50–60% of the total free amino acids found in the skeletal muscle tissue. Approximately 80% of the body glutamine is found in the skeletal muscle, and this concentration is 30 times higher than that recorded for human plasma(2)
- One of the main reasons for **cachexia** - cancer cells harvest glutamine from patient's muscles for fuel. Another reason is increased basal metabolic rate.
- Therefore, we should look at blocking glutamine metabolism to prevent cachexia.
- **IDEALLY, DO NOT GIVE L-GLUTAMINE SUPPLEMENTATION TO CANCER PATIENTS**

1. https://www.webmd.com/vitamins/ai/ingredientmono-878/glutamine
2. Cruzat, V., Macedo Rogero, M., Noel Keane, K., Curi, R., & Newsholme, P. (2018). Glutamine: Metabolism and Immune Function, Supplementation and Clinical Translation. Nutrients, 10(11), 1564. https://doi.org/10.3390/nu10111564

The Heterogeneity of Cancer Metabolism pp 13–32 | Cite as

Glutamine Metabolism in Cancer

Ting Li & Anne Le

Chapter

4770 Accesses | **1** Altmetric

Part of the Advances in Experimental Medicine and Biology book series (AEMB,volume 1063)

Sections | Figures

Abstract

Metabolism is the fundamental process for all cellular functions. For decades, there has been growing evidence with regard to the relationship between metabolism and malignant cell proliferation. Unlike normal differentiated cells, however, cancer cells have reprogrammed

Published: 29 July 2016

From Krebs to clinic: glutamine metabolism to cancer therapy

Brian J. Altman, Zachary E. Stine & Chi V. Dang

Nature Reviews Cancer **16**, 619–634 (2016) | Cite this article

57k Accesses | **723** Citations | **69** Altmetric | Metrics

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A Corrigendum to this article was published on 14 October 2016

This article has been updated

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Glutamine Addiction: A New Therapeutic Target in Cancer

David R. Wise and **Craig B. Thompson**
Department of Cancer Biology, Abramson Cancer Center, University of Pennsylvania, Room 450, BRB II/III, 421 Curie Boulevard, Philadelphia, PA 19104-6160, USA

Abstract

Most cancers depend on a high rate of aerobic glycolysis for their continued growth and survival. Paradoxically, some cancer cell lines also display addiction to glutamine despite the fact that glutamine is a nonessential amino acid that can be synthesized from glucose. The high rate of glutamine uptake exhibited by glutamine-dependent cells does not appear to result solely from its role as a nitrogen donor in nucleotide and amino acid biosynthesis. Instead, glutamine plays a required role in the uptake of essential amino acid and in maintaining activation of TOR kinase.

nature

Published: 27 March 2013

Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway

Jaekyoung Son, Costas A. Lyssiotis, Haoqiang Ying, Xiaoxu Wang, Sujun Hua, Matteo Ligorio, Rushika M. Perera, Cristina R. Ferrone, Edouard Mullarky, Ng Shyh-Chang, Ya'an Kang, Jason B. Fleming, Nabeel Bardeesy, John M. Asara, Marcia C. Haigis, Ronald A. DePinho, Lewis C. Cantley & Alec C. Kimmelman

Nature **496**, 101–105 (2013) | Cite this article

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A Corrigendum to this article was published on 12 June 2013

Abstract

Cancer cells have metabolic dependencies that distinguish them from their normal counterparts[1]. Among these dependencies is an increased use of the amino acid glutamine to

DO NOT GIVE L-GLUTAMINE SUPPLEMENTATION TO CANCER PATIENTS

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Immune Suppression in Pregnancy and Cancer: Parallels and Insights

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ARTICLE INFO

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ABSTRACT

Immune system has evolved to maintain homeostatic balance between effector and regulatory immunity, which is critical to both elicit an adequate protective response to fight pathogens and disease, such as cancer, and to prevent damage to healthy tissues. Transient immune suppression can occur under normal physiological conditions, such as during wound healing to enable repair of normal tissue, or for more extended periods of time during fetal development, where the balance is shifted towards regulatory immunity to prevent fetal rejection. Interestingly, tumors can exhibit patterns of immune suppression very similar to those observed during fetal development. Here some of the key aspects of normal patterns of immune suppression during pregnancy are reviewed, followed by a discussion of parallels that exist with tumor-related immune suppression and consequent potential therapeutic implications.

Kareva I. Transl Oncol. 2020;13(7):100759. doi: 10.1016/j.tranon.2020.100759.

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Article | Published: 10 March 2021

Inherent mosaicism and extensive mutation of human placentas

Tim H. H. Coorens, Thomas R. W. Oliver, Rashesh Sanghvi, Ulla Sovio, Emma Cook, Roser Vento-Tormo, Muzlifah Haniffa, Matthew D. Young, Raheleh Rahbari, Neil Sebire, Peter J. Campbell, D. Stephen Charnock-Jones, Gordon C. S. Smith & Sam Behjati

Nature **592**, 80–85 (2021) | Cite this article

22k Accesses | **51** Citations | **1241** Altmetric | Metrics

Did the placenta MUTATE itself into being??

An Author Correction to this article was published on 28 February 2022

This article has been updated

ASSOCIATION, NOT CAUSATION

Abstract

Placentas can exhibit chromosomal aberrations that are absent from the fetus[1]. The basis of this genetic segregation, which is known as confined placental mosaicism, remains unknown. Here we investigated the phylogeny of human placental cells as reconstructed from somatic mutations, using whole-genome sequencing of 86 bulk placental samples (with a median weight of 28 mg) and of 106 microdissections of placental tissue. We found that every bulk placental sample represents a clonal expansion that is genetically distinct, and exhibits a genomic landscape akin to that of childhood cancer in terms of mutation burden and

Placentas have a high rate of chromosomal aberrations and mutations

AND

Cancer cells have a high rate of chromosomal aberrations and mutations

Most likely reason = survival through genetic adaptability

Both Cancer and Embryo Implantation are Stem Cell Driven Processes

What are Cancer Stem Cells?

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Cancer Stem Cells

- First identified by Lapidot et al in 1994 in Toronto, from human Acute Myeloid Leukaemia (AML) – (Lapidot 1994)
- 'AML-initiating' cell was found to be 1:250000 cells in peripheral blood of AML patients. Rare!
- Available in-vitro assays could not identify CSCs at the time.
- Cells were identified using cell-surface-marker expression CD34+CD38-

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Cancer Stem Cells

- Landmark study
- New technique of transplanting 'AML-initiating' cell into immunodeficient (SCID) mice.
- The cells homed to the bone marrow and proliferated extensively in response to cytokine treatment, becoming identical to the AML cells in original human donor.
- However, when non-'AML-initiating' cell was transplanted, no tumour occurred.

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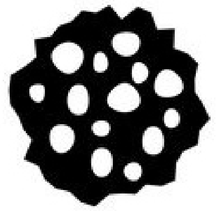
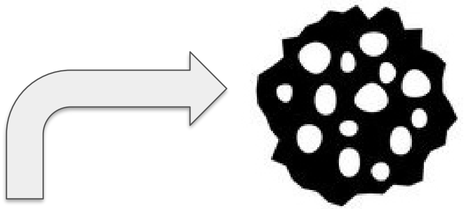
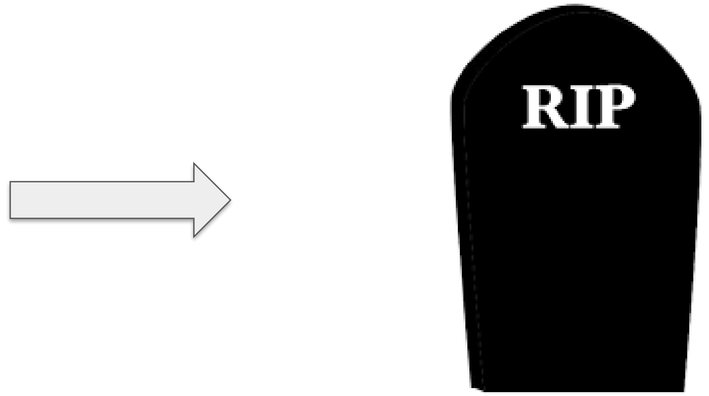


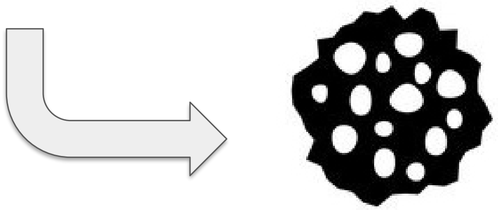
Human AML cells



CSCs AML cells
CD34+CD38-

Immunodeficient mice
(NOD/SCID)





Non-CSCs AML cells
CD34+CD38+

Immunodeficient mice
(NOD/SCID)

No Tumour

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Cancer Stem Cells

- According to 'The Year 2011 Working Conference on CSCs'
- "A subclass of neoplastic stem cells that propagate malignant clones indefinitely and produce an overt cancer"
  - **Pluripotent**
    - Ability to differentiate to many types of cells
  - **Initiate and Promote Tumour Growth (Tumorigenic)**
    - Tumour forming cancer cell vs non-tumour forming cancer cell
  - **Self-Renewal**
    - 'Immortal', perpetual ability to self-renew

Peter Valent 2012

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Cancer Stem Cells

- **Chemotherapy resistant**
  - Due to presence of drug pumps, DNA repair proteins, slow turnover. *(Dean, M., 2005)*
- **Radiotherapy resistant**
  - DNA repair proteins, Self-renewal ability, enhanced ROS defenses *(Maximilian Diehn 2006)*
- **Form metastasis / secondaries**
  - Cancer cells most likely to travel and start new colony *(Feng Li, 2007)*
- **Late recurrence**
  - One cell can survive conventional treatment and regrow many years later *(Peter Valent 2012)*
- **Constitute only 0.05-1% of the whole tumour[1]**

1. Bao, Bin, et al. "Overview of cancer stem cells (CSCs) and mechanisms of their regulation: implications for cancer therapy." *Current protocols in pharmacology* 61.1 (2013): 14-25.

Cancer Markers - functional surface proteins in fetal and cancer cells

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Cancer Stem Cell Markers (assessed by RGCC Oncotrace)

- Nanog - embryonic transcription factor for self renewal and pluripotency (1)
- Sox2 - embryonic transcription factor for neural stem cells (2)
- Oct 4 - embryonic transcription factor for self renewal (3)
- CD133 - human embryonic stem cell transmembrane protein (4)
- CD44 - embryonic hematopoietic stem cell surface protein (5)

Other Cancer Markers

- CEA - carcinoembryonic antigen - intercellular adhesion molecule
- AFP - alpha fetoprotein - produced in large amounts by the fetus
- CA-125 - surface protein for materno-fetal tolerance, via suppressing NK cells(6)
- CA15.3 - part of MUC1 - surface protein important for embryo implantation(7)

1. Gawlik-Rzemieniewska, Natalia, and Ilona Bednarek. "The role of NANOG transcriptional factor in the development of malignant phenotype of cancer cells." *Cancer biology & therapy* 17.1 (2016): 1-10.
2. Ellis, Pam, et al. "SOX2, a persistent marker for multipotential neural stem cells derived from embryonic stem cells, the embryo or the adult." *Developmental neuroscience* 26.2-4 (2004): 148-165.
3. Stirparo, Giuliano G., et al. "OCT4 induces embryonic pluripotency via STAT3 signaling and metabolic mechanisms." *Proceedings of the National Academy of Sciences* 118.3 (2021): e2008890118.
4. Wang, Hua, et al. "Role of CD133 in human embryonic stem cell proliferation and teratoma formation." *Stem cell research & therapy* 11.1 (2020): 1-14.
5. Cao, Huimin, et al. "The role of CD44 in fetal and adult hematopoietic stem cell regulation." *Haematologica* 101.1 (2016): 26
6. .Scholler, Nathalie, and Nicole Urban. "CA125 in ovarian cancer." (2007): 513-523.
7. Wang, Xiangguo, et al. "Expression and function of MUC1 in uterine tissues during early pregnancy in sheep after natural oestrous or artificially-induced oestrous." *Theriogenology* 108 (2018): 339-347.

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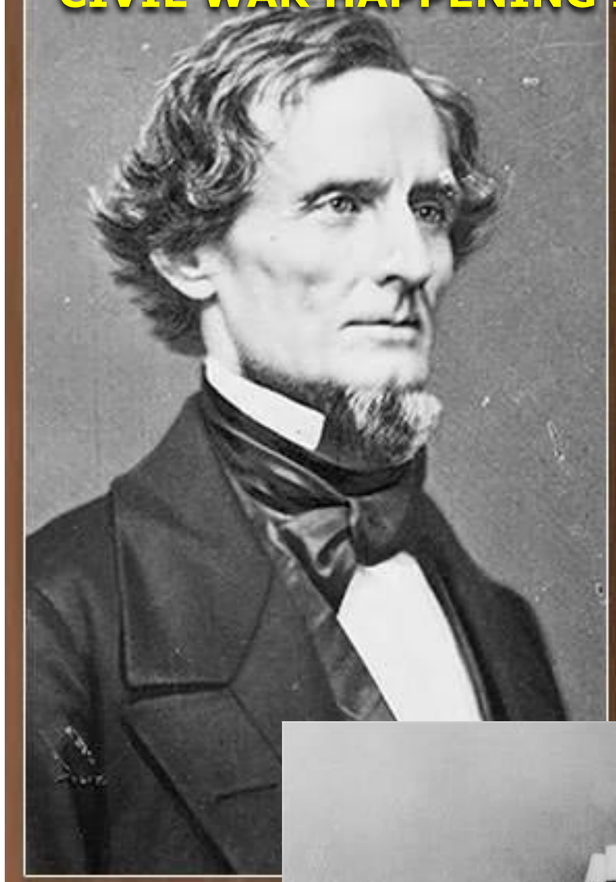
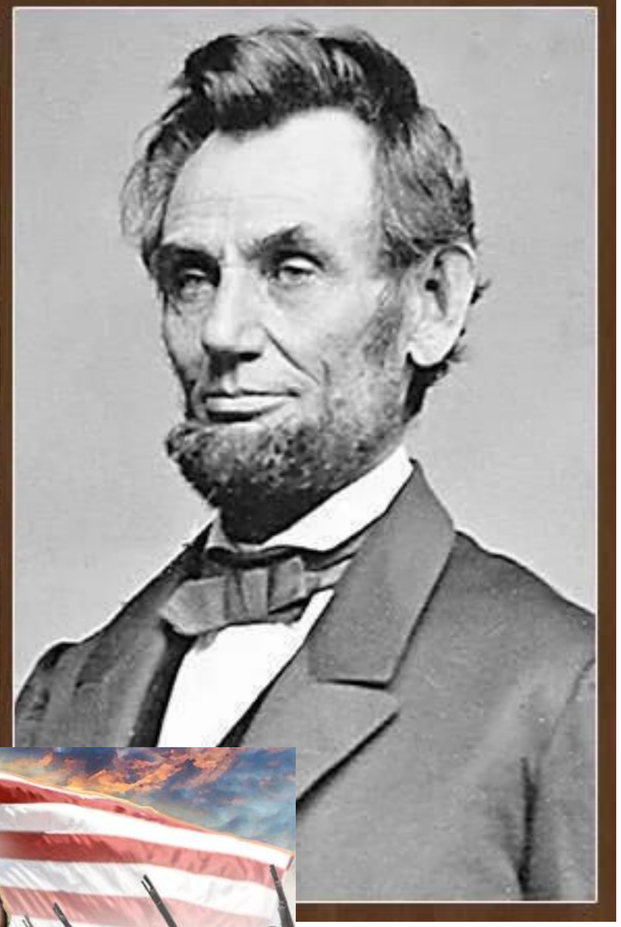
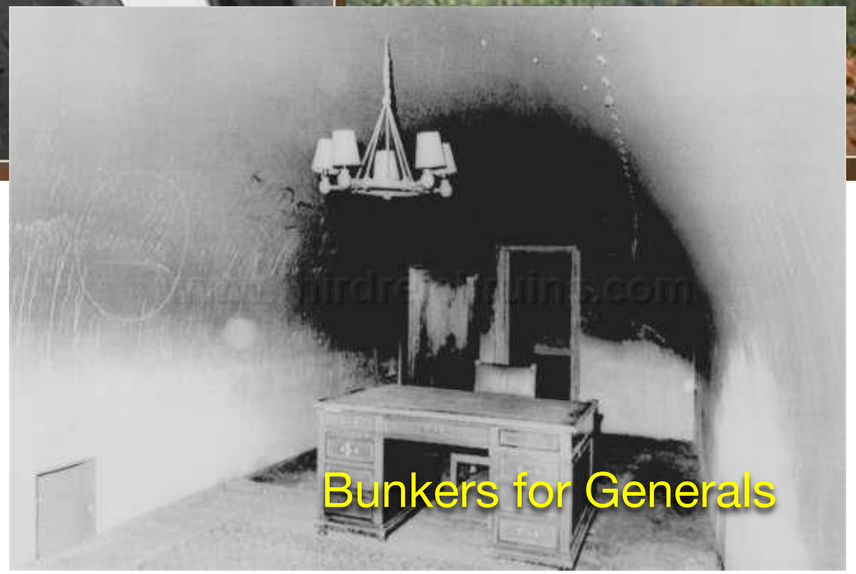
CIVIL WAR HAPPENING INSIDE THE PATIENT



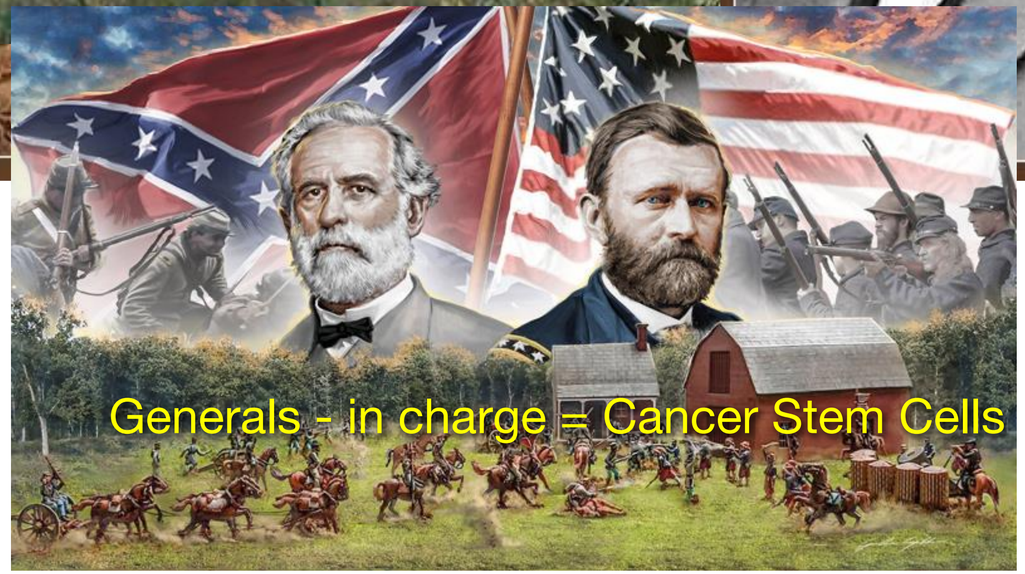
Foot soldiers = majority of cancer cells (non cancer stem cells)



In a population of 37 trillion cells, a faction has decided to revolt and break away from the Central Command / Govt and do their own thing. When attacked, they fight back, hence starting a **CIVIL WAR**



Bunkers for Generals



Generals - in charge = Cancer Stem Cells

HOLO-FRACTAL SYSTEMS - scale invariant

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What are (normal) stem cells?

- Main function is healing and repair.
- Normal adult stem cells differentiate depending on their niches (microenvironment)
- Functions mostly at night to perform repair and maintenance work, sleeps during the day, opposite to normal cells (night shift workers)
- Found in every tissue

"Normal stem cells are commonly defined as undifferentiated cells that have the capability to generate the specialized cells of the tissue they reside in (differentiation), along with undifferentiated daughter stem cells with tissue-maintaining potential (self-renewal)." – sciencedirect.com

Ferraro F, Celso CL, Scadden D. Adult stem cels and their niches. Adv Exp Med Biol. 2010;695:155-168. doi:10.1007/978-1-4419-7037-4_11

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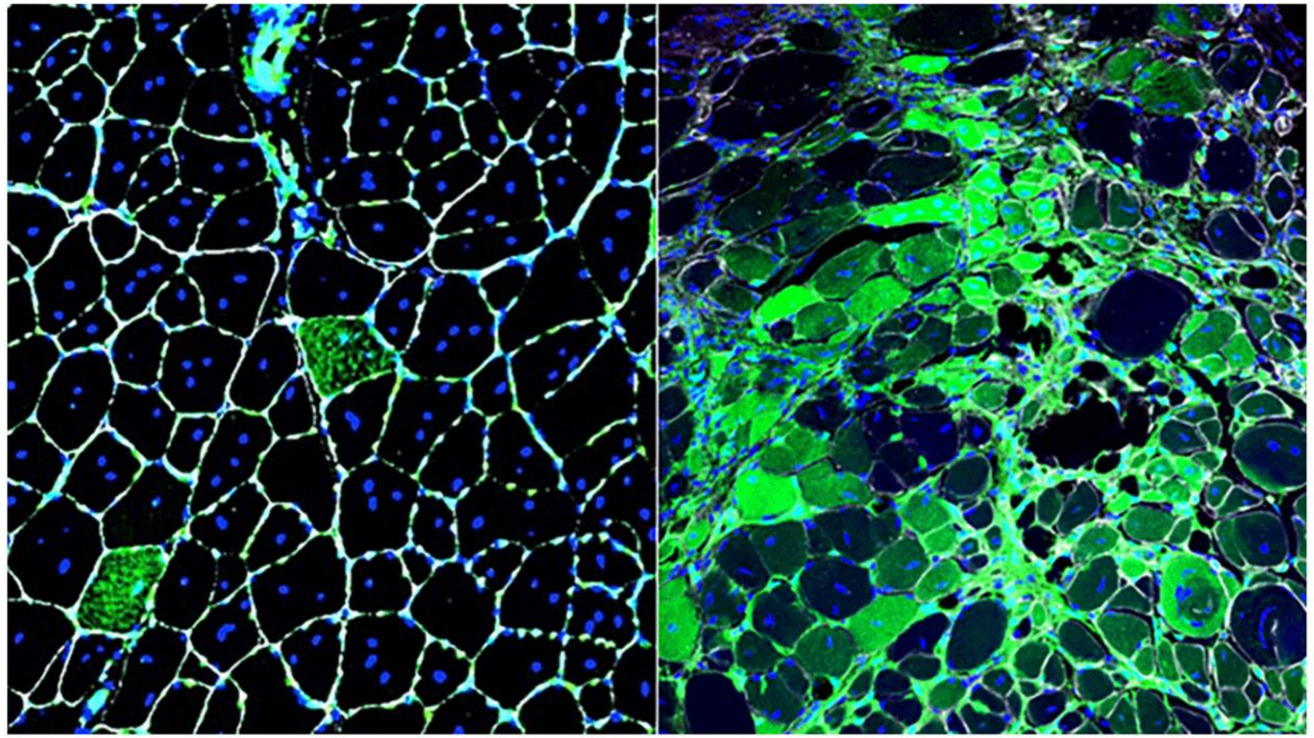
Research • April 18, 2019

'Super-Hero' Stem Cells Survive Radiation to Regrow Muscles

By Nicholas Weiler



Newly discovered radiation-resistant stem cells are normally rare and inactive (left), but they take on a major role in muscle repair when regular stem cells are damaged by radiation (right). *Credit: Brack lab / UCSF.*

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Annarita Scaramozza, PhD, discovered the small population of stem cells that activate after radiation.

"It was remarkable to see how these reserve cells that we'd previously overlooked were able to withstand levels of radiation that severely damaged all other stem cells, and then wake up and start regrowing the damaged muscles," Scaramozza said. "They were like superhero stem cells."

The results were published April 18 in *Cell Stem Cell*, alongside a second study showing that these resilient reserve stem cells are not just resistant to radiation, but also take over when regular stem cells are damaged by environmental toxins found in plastics and other pollutants.

Scaramozza and colleagues in the laboratory of Andrew Brack, PhD, also found that regular stem cells can be made radiation-resistant by treating them with anti-oxidizing agents that are well tolerated in humans.

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Cell Stem Cell

ARTICLE | VOLUME 24, ISSUE 6, P944-957.E5, JUNE 06, 2019

Lineage Tracing Reveals a Subset of Reserve Muscle Stem Cells Capable of Clonal Expansion under Stress

Annarita Scaramozza • Dongsu Park • Swapna Kollu • ... David T. Scadden • Colin Crist • Andrew S. Brack 9 • Show all authors • Show footnotes

Open Archive • Published: April 18, 2019 • DOI: https://doi.org/10.1016/j.stem.2019.03.020 •

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Highlights

- Mx1-Cre marks a subset of label-retaining muscle stem cells (SCs)
- Mx1-Cre^{+} muscle stem cells function as a radiotolerant reserve SC population
- Pax3 is enriched and required for clonal expansion of reserve SCs after radiation
- ROS levels endow radiotolerance of reserve SCs

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Normal Stem Cells and Cancer Stem Cells: The Niche Matters

Linheng Li[1,3] and William B. Neaves[1,2]

TUMOUR MICROENVIRONMENT !

[1]Stowers Institute for Medical Research and [2]University of Missouri-Kansas City School of Medicine, Kansas City, Missouri and [3]University of Kansas Medical Center, Kansas City, Kansas

Abstract

Scientists have tried for decades to understand cancer development in the context of therapeutic strategies. The realization that cancers may rely on "cancer stem cells" that share the self-renewal feature of normal stem cells has changed the perspective with regard to new approaches for treating the disease. In this review, we propose that one of the differences between normal stem cells and cancer stem cells is their degree of dependence on the stem cell niche, a specialized microenvironment in which stem cells reside. The stem cell niche in adult somatic tissues plays an essential role in maintaining stem cells or preventing tumorigenesis by providing primarily inhibitory signals for both proliferation and differentiation. However, the niche also provides transient signals for stem cell division to support ongoing tissue regeneration. The balance between proliferation-inhibiting and proliferation-promoting signals is the key to homeostatic regulation of stem cell maintenance versus tissue regeneration. Loss of the niche can lead to loss of stem cells, indicating the reliance of stem cells on niche signals. Therefore, cancer stem cells may arise from an intrinsic mutation, leading to self-sufficient cell proliferation, and/or may also involve deregulation or alteration of the niche by dominant proliferation-promoting signals. Furthermore, the molecular machinery used by normal stem cells for homing to or mobilizing from the niche may be "hijacked" by cancer stem cells for invasion and metastasis. We hope this examination of the interaction between stem cells and their niche will enhance understanding of the process of cancer development, inva-

In the early 1990s, clinical observations and genetic studies of a variety of cancers led to the hypothesis that six genetic mutations were required to convert a normal somatic cell into a cancer cell (3, 4). These six mutations included (*a*) self-sufficiency for growth signals, (*b*) insensitivity to antigrowth signals, (*c*) evasion of apoptosis, (*d*) limitless ability to replicate, (*e*) sustained angiogenesis, and (*f*) tissue invasion and metastasis.

However, not all cells in a given tissue are created equally in terms of their stage of development and their potential for proliferation and/or differentiation. Stem cells sit at the top of the developmental hierarchy, having the ability to self-renew and give rise to all the cell lineages in corresponding tissues. Stem cells divide to produce two daughter cells. One daughter remains a stem cell (self-renewal). The other daughter becomes a progenitor cell that undergoes expansion and further differentiation into mature cells. Stem cells have the highest potential for proliferation and a much longer life span compared with their progeny and therefore have a greater opportunity to accumulate genetic mutations (5). The realization that the adult body harbors small numbers of stem cells offered an alternative possibility for the origin of cancer. Perhaps only one or two mutations, such as self-sufficiency in growth or insensitivity to antigrowth signals, are needed for stem cells to initiate tumorigenesis rather than six mutations, a rare event in any type of cell.

The thought that cancer might originate in stem cells harkens back to the 19th century concept of "embryonal rest" (6, 7). Over a century later, one recognizes the similarity between the old belief that cancer arises from embryonal rests and the contemporary view that some forms of cancer originate in adult stem cells. In

Li L, et al. Cancer Res. 2006;66(9):4553-7. doi: 10.1158/0008-5472.CAN-05-3986.

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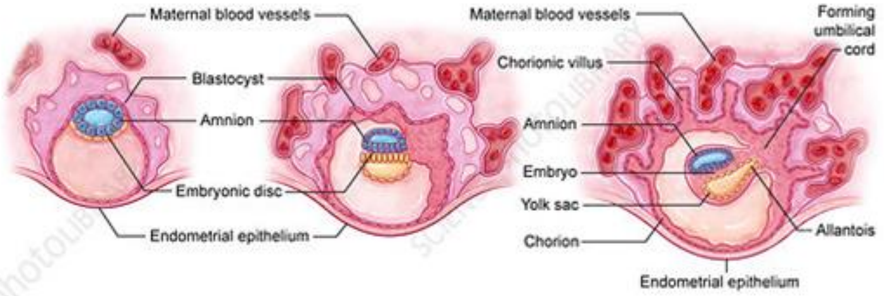

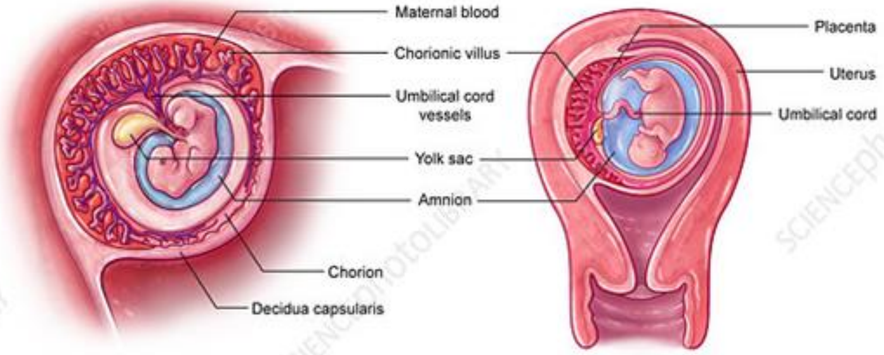

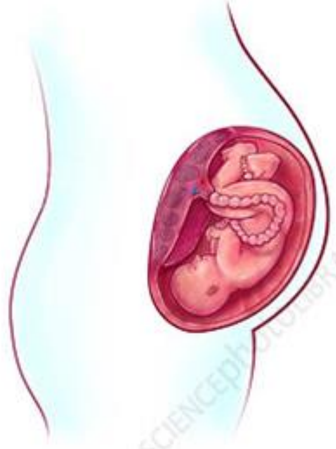

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Healthy stem cells are like super-soldiers

Rogue Stem Cells = Cancer Stem Cells (misinterpretation of a dysfunctional microenvironment?)

So, are all cancers oestrogen / hormone sensitive, not just breast cancer?

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Volume 11 Supplement 1

Approaching complexities in health and environment

Review | Open Access | Published: 28 June 2012

Environmental exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain

Aleksandra Fucic, Marija Gamulin, Zeljko Ferencic, Jelena Katic, Martin Krayer von Krauss, Alena Bartonova & Domenico F Merlo

Environmental Health **11**, Article number: S8 (2012) | Cite this article

11k Accesses | **62** Citations | **53** Altmetric | Metrics

Abstract

The role of steroids in carcinogenesis has become a major concern in environmental protection, biomonitoring, and clinical research. Although historically oestrogen has been related to development of reproductive system, research over the last decade has confirmed its crucial role in the development and homeostasis of other organ systems. As a number of anthropogenic agents are xenoestrogens, environmental health research has focused on oestrogen receptor level disturbances and of aromatase polymorphisms. Oestrogen and xenoestrogens mediate critical points in carcinogenesis by binding to oestrogen receptors,

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POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JULY 01 2018

Abstract 1433: Estrogen-related receptor alpha (ERRα) functions to promote prostate cancer cell stemness via its transcriptional regulation of ZIP1 and ACON2 to enhance oxidative phosphorylation FREE

Taiyang Ma; Zhenyu Xu; Yuliang Wang; Zhu Wang; Weijie Gao; Wenxin You; Leung Franky Chan

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+ Author & Article Information

Cancer Res (2018) 78 (13_Supplement): 1433.

https://doi.org/10.1158/1538-7445.AM2018-1433

Split-Screen Share Tools Versions

PERGAMON Journal of Steroid Biochemistry & Molecular Biology 81 (2002) 281–289

Molecular Biology

www.elsevier.com/locate/jsbmb

Estrogen metabolism in human colorectal cancer cells

G. Fiorelli[a], L. Picariello[a], V. Martineti[a], I. Tognarini[a], F. Tonelli[a], M.L. Brandi[b,*]

[a] *Department of Clinical Physiopathology, University of Florence, Florence, Italy*
[b] *Department of Internal Medicine, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy*

Received 26 October 2001; accepted 15 April 2002

Abstract

Epidemiological and "in vitro" studies support a direct role of estrogens in the pathogenesis and/or progression of colorectal cancer (CRC). Recent observations suggest a local synthesis of 17β-estradiol (E_2). In the present study, the CRC estrogen receptor β (ERβ) positive HCT8, HCT116, DLD-1 and LoVo cell lines were evaluated for expression of functional 17β-hydroxysteroid dehydrogenase (17βHSD) types 1, 2, 3, and 4. RT-PCR analysis revealed that while 17βHSD1 and 17βHSD4 were expressed in all the four cell lines,

frontiers in ENDOCRINOLOGY

MINI REVIEW ARTICLE
published: 25 July 2014
doi: 10.3389/fendo.2014.00124

Estrogens and stem cells in thyroid cancer

Mariangela Zane[1,2†], Veronica Catalano[1†], Emanuela Scavo[1], Marco Bonanno[1], Maria Rosa Pelizzo[2], Matilde Todaro[1] and Giorgio Stassi[1]*

[1] *Department of Surgical and Oncological Sciences, University of Palermo, Palermo, Italy*
[2] *Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Padua, Italy*

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e-mail: giorgio.stassi@unipa.it

Recent discoveries highlight the emerging role of estrogens in the initiation and progression of different malignancies through their interaction with stem cell (SC) compartment. Estrogens play a relevant role especially for those tumors bearing a gender disparity in incidence and aggressiveness, as occurs for most thyroid diseases. Although several experimental lines suggest that estrogens promote thyroid cell proliferation and invasion, their precise contribution in SC compartment still remains unclear. This review underlines the interplay between hormones and thyroid function, which could help to complete the puzzle of gender discrepancy in thyroid malignancies. Defining the association between estrogen receptors' status and signaling pathways by which estrogens exert their effects on thyroid cells is a potential tool that provides important insights in pathogenetic mechanisms of thyroid tumors.

Keywords: thyroid cancer, stem cells, cancer stem cells, estrogens, thyroid hormones, growth factors

POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JULY 01 2018

Abstract 2483: Estrogen receptor beta enhances chemotherapy response in GBM FREE

Mei Zhou; Gangadhara R. Sareddy; Jinyou Liu; Mengxing Li; Suryavathi Viswanadhapalli; Xiaonan Li; Rajeshwar R Tekmal; Andrew Brenner; Ratna K. Vadlamudi

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+ Author & Article Information

Cancer Res (2018) 78 (13_Supplement): 2483.

https://doi.org/10.1158/1538-7445.AM2018-2483

Split-Screen Share Tools Versions

Abstract

Background: The incidence of developing glioblastoma (GBM) is greater in men than in women, and women of reproductive age have a survival advantage over men and postmenopausal women. These

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Common features between cancer cells, trophoblasts and normal cells

Cell Behaviour	Cancer Cells	Trophoblasts (placental cells during implantation)	Somatic Cells (Normal Adult Cells)
Rapid Cell Replication	Y	Y	some cells eg dermis, mucosa
Invasive into surrounding tissues	Y	Y	X
Promotes Angiogenesis	Y	Y	X
Immune Evasion	Y	Y	Y
Driven by Stem Cells	Y	Y	X
Utilises Aerobic Glycolysis	Y	Y	some immune cells
Utilises Glutamine as fuel	Y	Y	X
Grows in Acidic environments	Y	Y	X
Grows in Estrogenic environments	Y	Y	X
High Mutation Rate	Y	Y	X

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So, what changed our internal microenvironment?

- **Environmental Pollution**
  - Persistent Organic Pollutants
  - Xenoestrogens / Endocrine Disruptors
  - Micro / Nano plastics
- **Chronic Infections**
  - Mold exposure / toxicity
  - Chronic Bacterial Infections
  - Chronic Viral Infections

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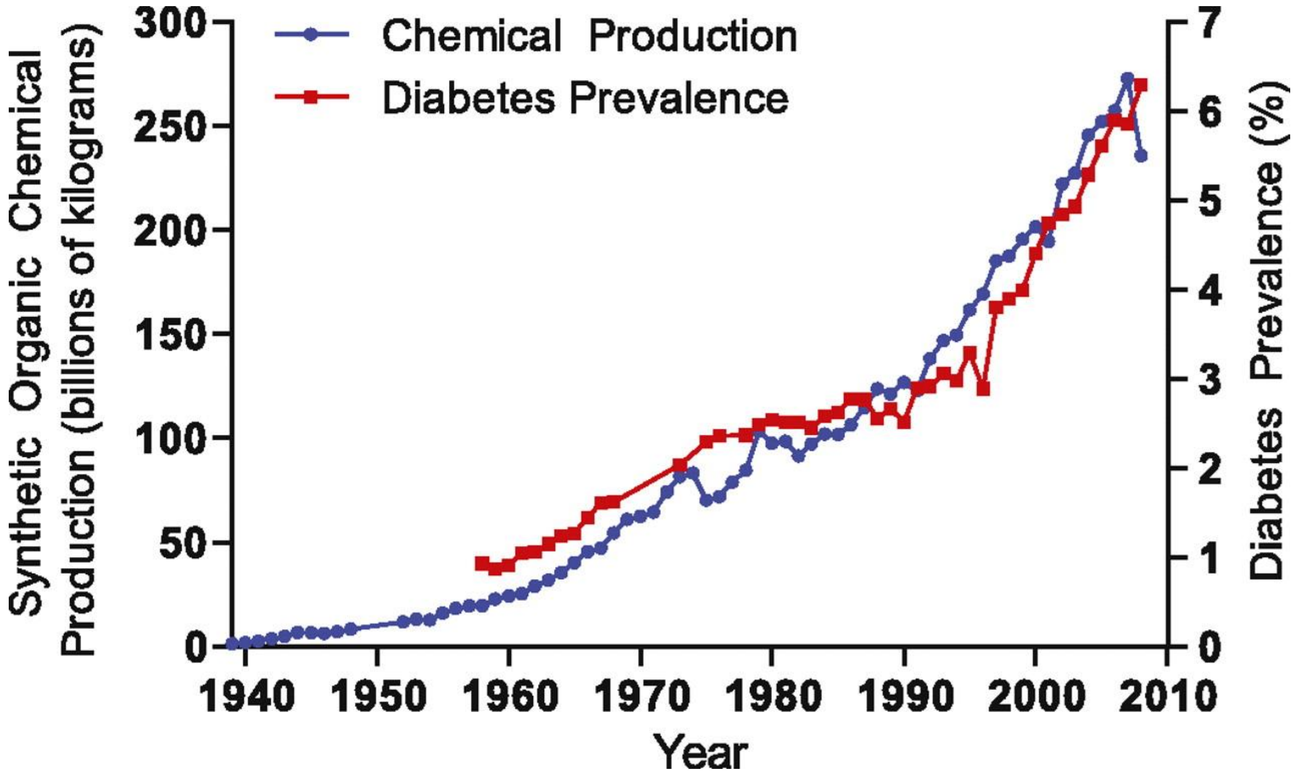
"We are drowning ourselves in XENOESTROGENS"



Neel, Brian A., and Robert M. Sargis. "The paradox of progress: environmental disruption of metabolism and the diabetes epidemic." *Diabetes* 60.7 (2011): 1838-1848.

Table 1. Xenobiotic Compounds in Adipose Tissue of U.S. Citizens. US EPA National Adipose Tissue Survey 1982

Compound	Frequency of Observation (%)	Wet Tissue Concentration (ng/g)
Styrene	100	8-350
1,4-Dichlorobenzene	100	12-500
Xylene	100	18-1,400
Ethylphenol	100	0.4-400
OCDD (dioxin)	100	19-3,700
HxCDD (dioxin)	98	ND-620
1,2,3,4,7,8,9-HpCDD	98	ND-1,300
Benzene	96	ND-97
Chlorobenzene	96	ND-9
Ethylbenzene	96	ND-280
p,p'-DDE	93	ND-6,800
1,2,3,4,6,7,8-HpCDF	93	ND-79
1,2,3,7,8,-PeCDD	91	ND-5,000
Toluene	91	ND-250
2,3,4,7,8-PeCDF	89	ND-90
Beta-BHC	87	ND-570
Total PCBs	83	ND-1,700
Chloroform	76	ND-580
Hexachlorobenzene	76	ND-1,300
2,3,7,8-TCDD	76	ND-14

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Toxicology Letters
Volume 202, Issue 3, 10 May 2011, Pages 161-167

Research paper

Aflatoxin B1 – a potential endocrine disruptor – up-regulates CYP19A1 in JEG-3 cells

Markus Storvik [a, 1], Pasi Huuskonen [a, 1], Taija Kyllönen [a], Sarka Lehtonen [b], Hani El-Nezami [c], Seppo Auriola [a], Markku Pasanen [a]

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https://doi.org/10.1016/j.toxlet.2011.01.028

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Abstract

Previous studies have indicated that aromatase (CYP19A1) is involved in the metabolism of aflatoxin B1 (AFB1). We hypothesized that exposure to AFB1 contaminated food during pregnancy could disrupt the normal production of steroid hormones in placenta. We examined the capability of AFB1 exposure to disrupt CYP19A1 expression as a putative endocrine disrupter, and to investigate the metabolism of AFB1 by CYP19A1. JEG-3 cells, as model for placental cells, were exposed alone and in combination to AFB1 and estrogen receptor ligands for 24–96 h. AFB1 (0.3–1.0 μM) induced the expression of CYP19A1 by 163%–339% compared to control at the 96 h time point, although no induction was observed at 24 h. AFB1 concentrations higher than 1 μM were cytotoxic to JEG-3 cells, and the cytotoxicity was inhibited by the aromatase inhibitor, finrozole. AFB1 was metabolized to aflatoxicol (AFL) by JEG-3 cells and CYP19A1 recombinant protein.

Toxicology Letters
Volume 217, Issue 3, 13 March 2013, Pages 243-250

Endocrine disrupting effects of ochratoxin A at the level of nuclear receptor activation and steroidogenesis

C. Frizzell [a], S. Verhaegen [b], E. Ropstad [b], C.T. Elliott [a], L. Connolly [a]

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https://doi.org/10.1016/j.toxlet.2012.12.018

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Abstract

Ochratoxin A (OTA) is a mycotoxin and extrolite of fungi which has been reported in a range of foods. This study uses mammalian reporter gene assays (RGAs) with natural steroid receptors and the H295R steroidogenesis assay to assess the endocrine disrupting activity of OTA.

At the hormone production level, H295R cells were used as a steroidogenesis model and exposed to OTA (within a concentration range of 0.1–1000 ng/ml). Treatment of the cells with 1000 ng/ml OTA increased the production of estradiol (117 ± 14 ng/ml) over 3 times that of the solvent control (36 ± 9 pg/ml). Western blotting confirmed an increase in aromatase protein.

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Increased Estradiol levels

- In both studies, exposure to mold toxins, AFLATOXIN and OCHRATOXIN A,
  - Increased aromatase activity by up to **339%**
  - Increased estradiol levels by up to **300%**

- Therefore, mold and mycotoxin exposure, could potentially increase natural estrogen production in both men and women through increased aromatase activity.

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Received: 26 October 2021 | Revised: 16 January 2022 | Accepted: 18 January 2022

DOI: 10.1002/cam4.4646

RESEARCH ARTICLE

Cancer Medicine Open Access WILEY

Tumor marker response to SARS-CoV-2 infection among patients with cancer

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Abstract

Background: Inflammatory responses from benign conditions can cause non-cancer-related elevations in tumor markers. The severe acute respiratory coronavirus 2 (SARS-CoV-2) induces a distinct viral inflammatory response, resulting in coronavirus disease 2019 (COVID-19). Clinical data suggest carcinoembryonic antigen (CEA), carbohydrate antigen 19–9 (CA 19–9), and cancer antigen 125 (CA 125) levels might rise in patients with COVID-19. However, available data excludes cancer patients, so little is known about the effect of COVID-19 on tumor markers among cancer patients.

Methods: We conducted a case series and identified patients with a positive

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What are the hallmarks of ALL cancers again?

- Rapid cell proliferation
- Tissue invasion
- Angiogenesis
- Immune evasion / suppression
- Differing energy metabolism to normal cells (eg. aerobic glycolysis, glutaminolysis)
- Stem-cell driven process

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ALL Cancer Cells have the same behaviour, but misbehaving at different LOCATIONS

So, if ALL cancers - from breast cancer to cardiac myosarcoma (one the rarest form of cancer) have the same cellular behaviour, then I propose that there are **NO different types** of cancer, but just different primary or secondary **LOCATIONS of cancer** eg. a criminal can be of any race, but they are criminals based on their behaviour / actions

The primary cancer being the LOCATION of where the first stem cell changed behaviour to behaving like a TROPHOBLAST (ie Cancer Stem Cell)

Published: 02 October 2014

Physicists' model proposes evolutionary role for cancer

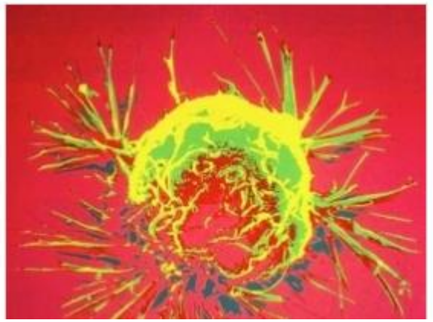
Zeeya Merali

Nature (2014) | Cite this article

446 Accesses | **229** Altmetric | Metrics

Stressed cells could become cancerous as a 'safe mode', pointing to oxygen and immunotherapy are the best ways to beat the disease.

An article by Scientific American.



Could cancer be our cells' way of running in 'safe mode', like a damaged computer operating system trying to preserve itself, when faced with an external threat? That's the conclusion reached by cosmologist Paul Davies at Arizona State University in Tempe and his

The Monthly

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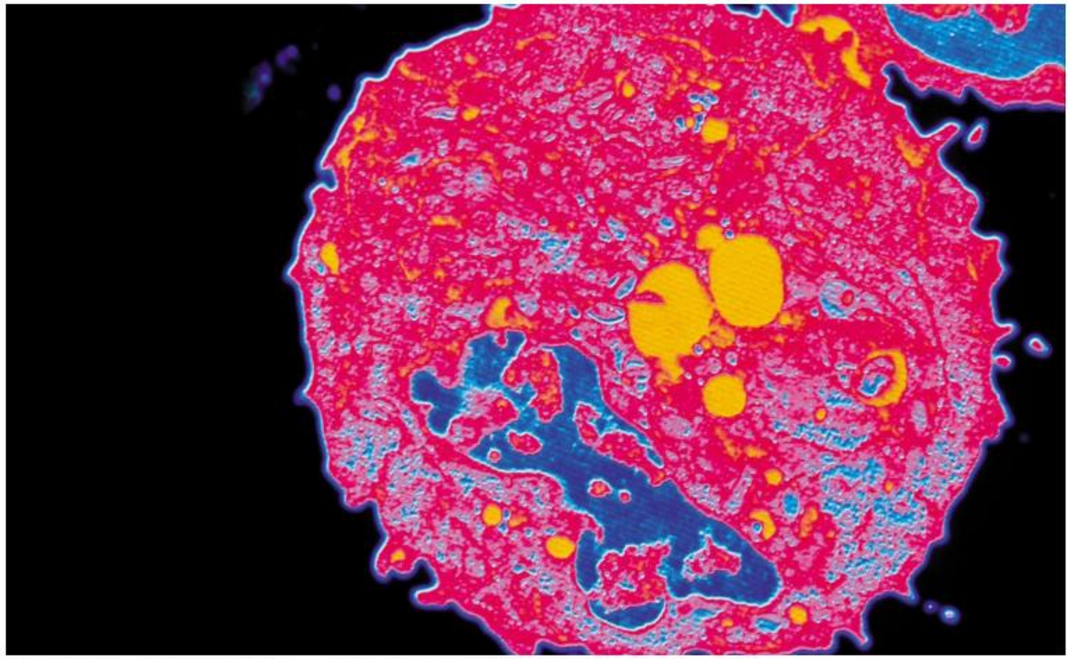
NOVEMBER 2018 ESSAYS

A new theory of cancer

By Paul Davies



Coloured transmission electron micrograph of a cross-section through a cancer cell. © Alfred Pasieka / Science Photo Library / Getty Images

After billions spent for little benefit, it's time to look at the disease in a different way

When President Richard Nixon declared war on cancer in 1971, he set a goal for conquering the disease by 1976. The US National Cancer Institute (NCI) was empowered and expanded by the stroke of the president's pen, and some serious public money injected into a mammoth research effort. In the intervening 47 years, in

Nothing without context. Politics, society, culture.

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Paul Davies, an Astrophysicist, who was recruited by NIH in 2012 to think outside the box and a fresh analysis / model of cancer

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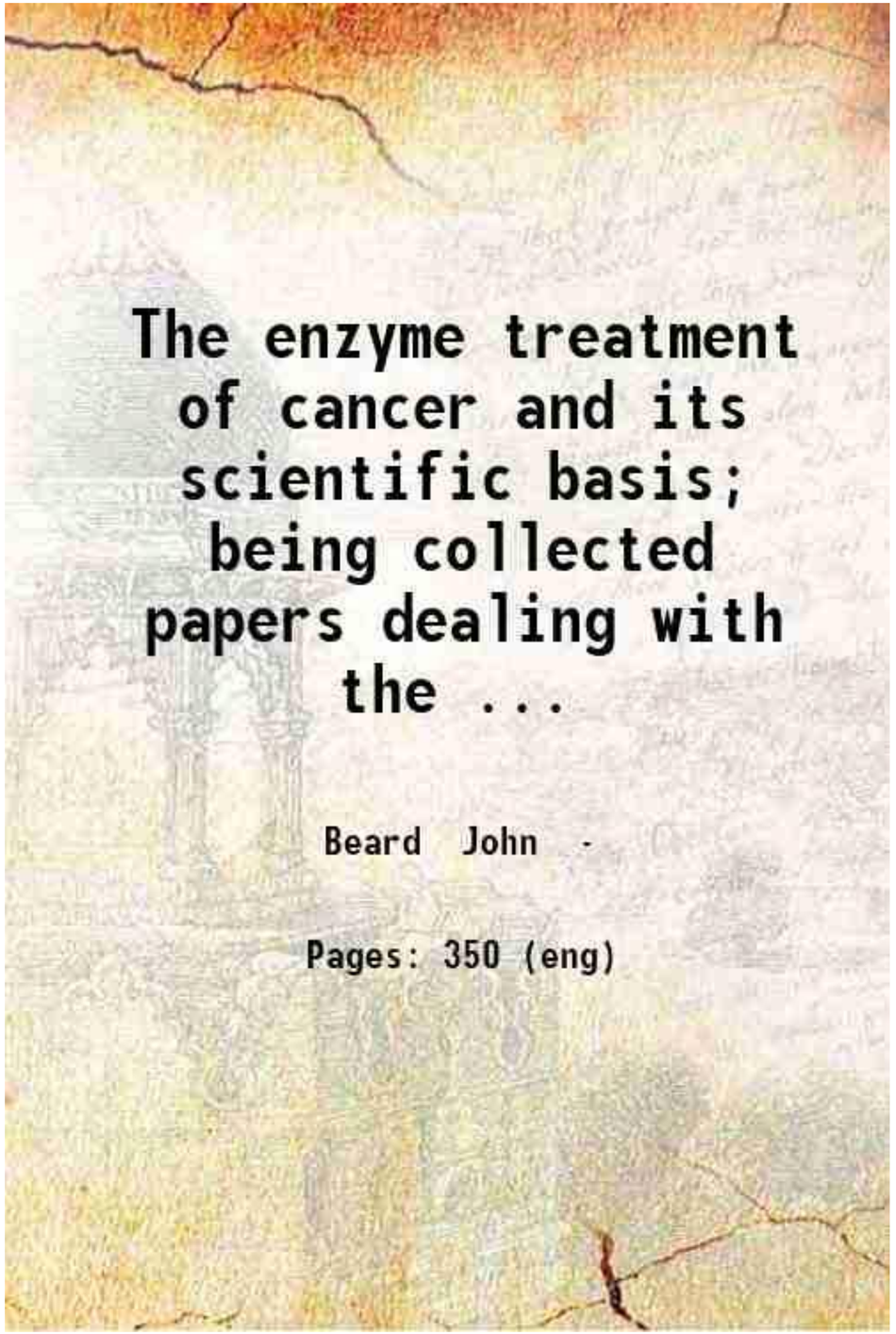

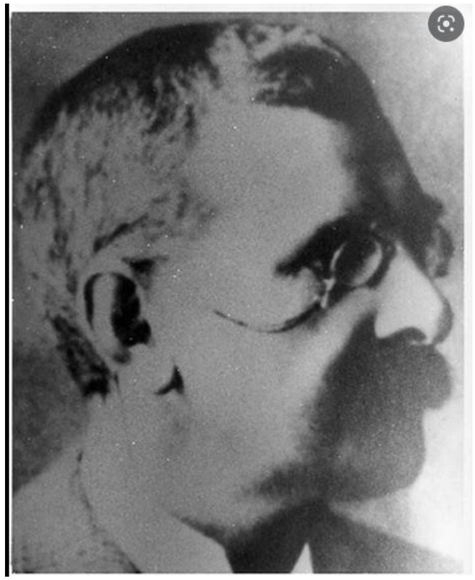

John Beard DSc 1858-1924
Lecturer in Embryology
University of Edinburgh
Nominated for Nobel Prize in Medicine 1906

Trophoblastic Theory published 1902

Enzyme Treatment of Cancer 1911

Oncology

Oncogenesis – Morphogenesis

The Trophoblast Theory of Cancer (*John Beard*, 1857–1924) Revisited

Gurchot C.
Author affiliations

Keywords: Germ cell · Asexual generation – sexual generation · Trophoblast · Repression – derepression of genes · Phorozoon

Oncology 1975;31:310–333
https://doi.org/10.1159/000225037

ABSTRACT | GET ARTICLE | LOGIN / REGISTER

Abstract

Beard's theory can be restated in a modified form in modern terms in the following way. Cancer represents primarily trophoblastic tissue derived either from an aberrant germ cell or from a somatic cell whose normally repressed 'asexual generation' genes are abnormally reactivated ('derepressed'). The variety of tumors, other than teratomas, may be due to a parallel chance derepression of some genes of somatic ('sexual generation') characters. This would be a defensive reaction against intramural parasitization by trophoblast and would result

We have only just covered ‘Hardware’ issues

How about ‘Software’ issues?

a bit about biophysics

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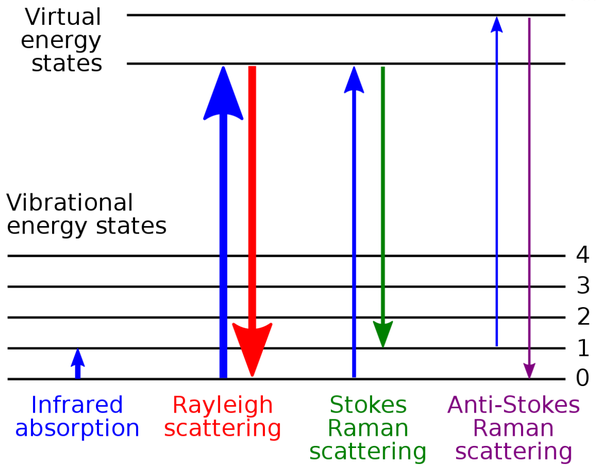
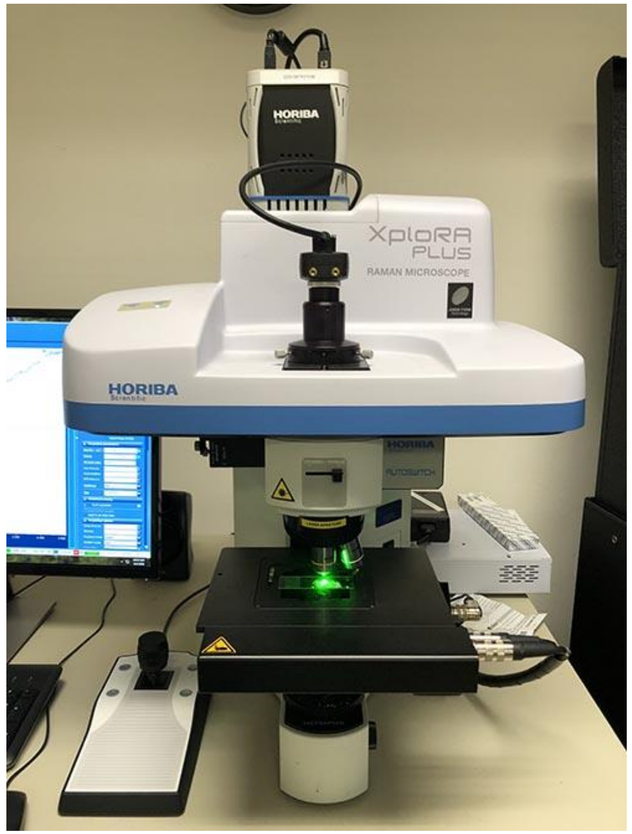
Raman Spectroscopy

- method to determine molecular structures based on VIBRATION of molecules
- based on Raman scattering of lasers / photons
- typically used in chemistry to identify chemical structures / bonds, proteins and DNA
- recently new applications in medicine as a diagnostic tool, based on different VIBRATIONAL (or INFORMATIONAL) differences of cells





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CANCER IMAGING

Intraoperative brain cancer detection with Raman spectroscopy in humans

Michael Jermyn,[1,2]* Kelvin Mok,[3]* Jeanne Mercier,[2] Joannie Desroches,[4] Julien Pichette,[2] Karl Saint-Arnaud,[2] Liane Bernstein,[2] Marie-Christine Guiot,[1,5] Kevin Petrecca,[1]†‡ Frederic Leblond[2]†‡

Cancers are often impossible to visually distinguish from normal tissue. This is critical for brain cancer where residual invasive cancer cells frequently remain after surgery, leading to disease recurrence and a negative impact on overall survival. No preoperative or intraoperative technology exists to identify all cancer cells that have invaded normal brain. To address this problem, we developed a handheld contact Raman spectroscopy probe technique for live, local detection of cancer cells in the human brain. Using this probe intraoperatively, we were able to accurately differentiate normal brain from dense cancer and normal brain invaded by cancer cells, with a sensitivity of 93% and a specificity of 91%. This Raman-based probe enabled detection of the previously undetectable diffusely invasive brain cancer cells at cellular resolution in patients with grade 2 to 4 gliomas. This intraoperative technology may therefore be able to classify cell populations in real time, making it an ideal guide for surgical resection and decision-making.

Jermyn, Michael, et al. "Intraoperative brain cancer detection with Raman spectroscopy in humans." *Science translational medicine* 7.274 (2015): 274ra19-274ra19.

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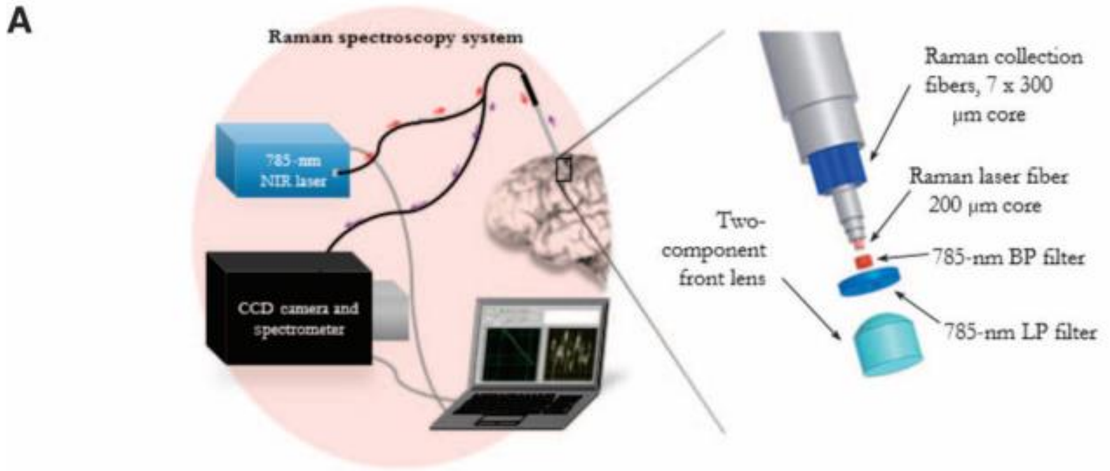

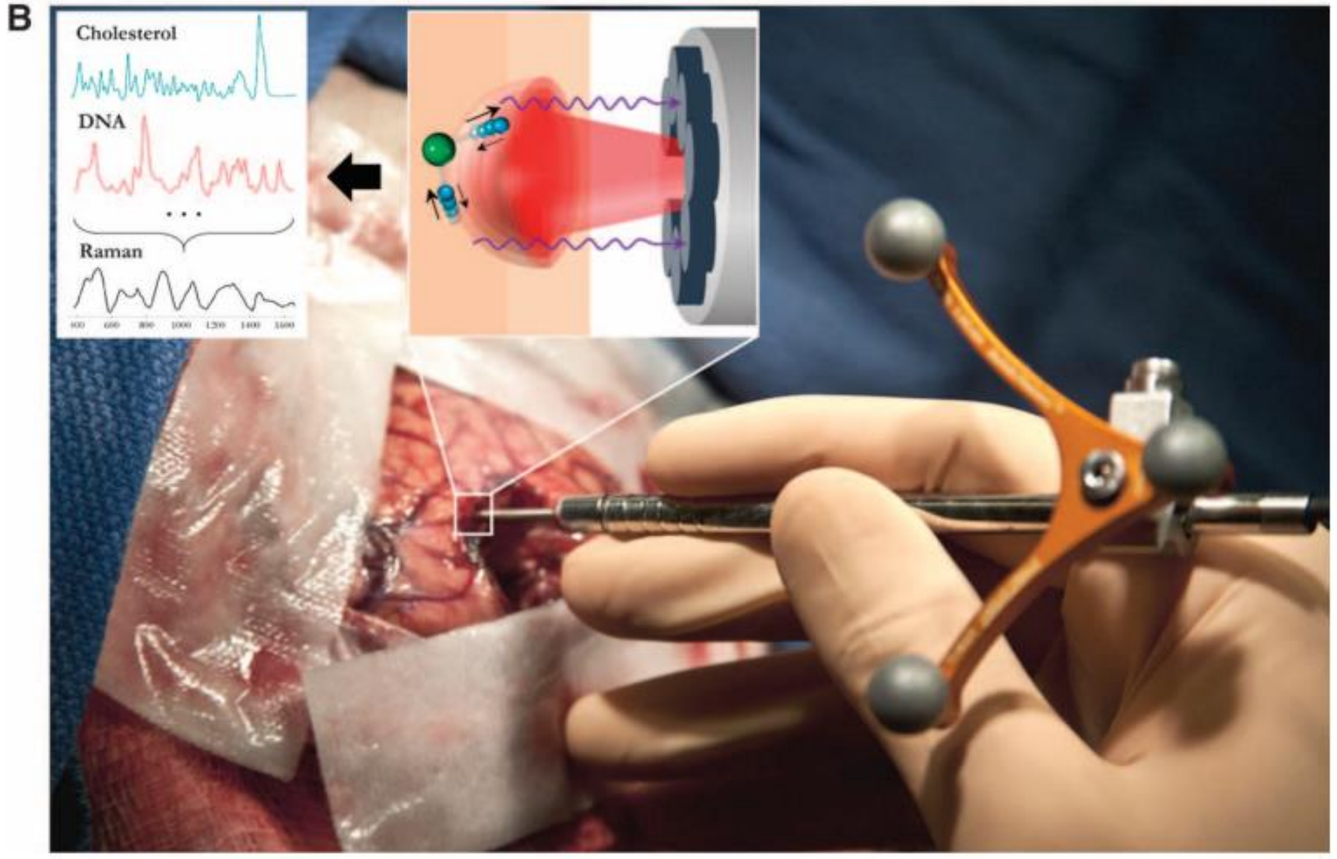

Fig. 1. The handheld contact fiber optic probe for Raman spectroscopy. (**A**) Experimental

samples corresponding to normal brain (*33*). Using this technique, we were able to distinguish normal brain from tissue with the presence of cancer cells (including both invasive and dense cancers) with an accuracy of 92%, sensitivity of 93%, and specificity of 91% (Table 2, Eqs. 1 to 3). For

obtained a ROC curve with AUC of 0.96 (Fig. 3B). In comparison, the sample labels (either normal brain or cancer) given by the surgeon after visual inspection using a bright-field microscope and MR guidance produced an accuracy of 73%, sensitivity of 67%, and specificity of 86%.

Jermyn, Michael, et al. "Intraoperative brain cancer detection with Raman spectroscopy in humans." *Science translational medicine* 7.274 (2015): 274ra19-274ra19.

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Discrimination between Oral Cancer and Healthy Tissue Based on Water Content Determined by Raman Spectroscopy

E. M. Barroso[†], R. W. H. Smits[‡], T. C. Bakker Schut[*§], I. ten Hove[†], J. A. Hardillo[‡], E. B. Wolvius[†], R. J. Baatenburg de Jong[‡], S. Koljenović[∥], and G. J. Puppels[§]

View Author Information

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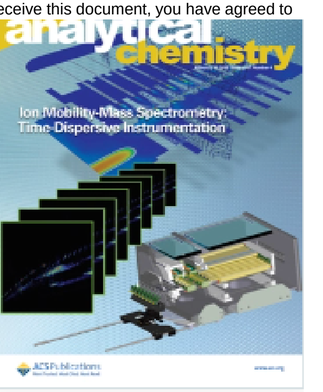

Analytical Chemistry

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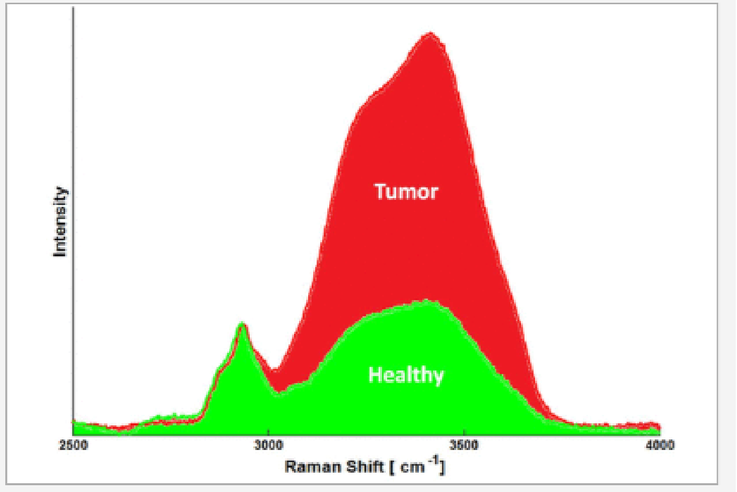
SUBJECTS: Anatomy, Cancer, Oscillation, Raman spectroscopy, Tumors

Abstract

Tumor-positive resection margins are a major problem in oral cancer surgery. High-wavenumber Raman spectroscopy is a reliable technique to determine the water content of tissues, which may contribute to differentiate between tumor and healthy tissue. The aim of this study was to examine the use of Raman spectroscopy to differentiate tumor from surrounding healthy tissue in oral squamous cell carcinoma. From 14 patients undergoing tongue resection for squamous cell carcinoma, the water content was determined at 170 locations on freshly excised tongue specimens using the Raman bands of the OH-stretching vibrations (3350–3550 cm^{-1}) and of the CH-stretching vibrations (2910–2965 cm^{-1}). The results were correlated with histopathological assessment of hematoxylin and eosin stained thin tissue sections obtained from the Raman measurement locations. The water content values from squamous cell carcinoma measurements were significantly higher than from surrounding healthy tissue (p-value < 0.0001). Tumor tissue could be detected with a sensitivity of 99% and a specificity of 92% using a cutoff water content value of 69%. Because the Raman measurements are fast and can be carried out on freshly excised tissue without any tissue preparation, this finding signifies an important step toward the development of an intraoperative tool for tumor resection guidance with the aim of enabling oncological radical surgery and improvement of patient outcome.



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Imaging Cancer and Healthy Cell Sounds in Water by Cymascope, Followed by Quantitative Analysis by Planck-Shannon Classifier

John S. Reid[1], Beum Jun Park[2], and Sungchul Ji[3]

[1]Sonic Age, Ltd., St. John's-in-the-Vale, Cumbria, England; [2]Pharm D/MD candidate, Ernest Mario School of Pharmacy and The Robert Wood Johnson Medical School, Rutgers University, Piscataway, N.J; and [3]Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, N.J.

Keywords: Cymascope instrument, Cymascopic, Faraday Waves, Hydrodynamics, Planck-Shannon Classifier, Planckian Distribution Equation, Planckian information of the second kind, Shannon entropy, Raman Spectroscopy, sonified Raman spectral features of cancer cells and healthy cells, tumorectomy.

Submitted: September 30, 2019; Revised: November 6, 2019; Accepted: December 3, 2019;
Published: December 24, 2019; Available Online: December 24, 2019.

10.14294/WATER.2019.6

Abstract

In controlled conditions water can be used as a means of transforming sonic periodicities to water wavelet periodicities, a process that results in the production of Faraonly to quantum mechanics but also to macrophysics. The new classification method referred to as the Planck-Shannon Classifier, which is formulated based on PDE is

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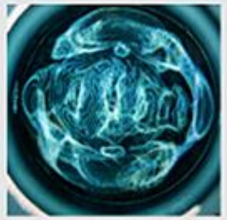
Time Point	Cancer Cells in Brain Tissues						Healthy Cells in Brain Tissues					
	1		2		3		5		6		7	
	Image #	I_{PS}/H	#	I_{PS}/H	#	I_{PS}/H	#	I_{PS}/H	#	I_{PS}/H	#	I_{PS}/H
1												
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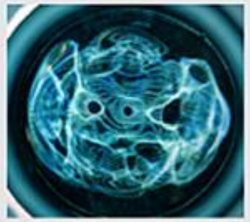
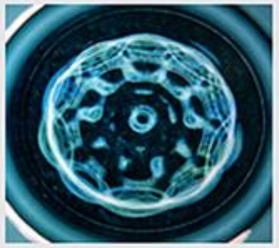
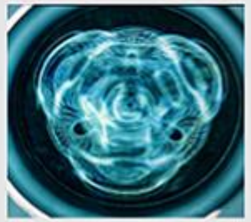
2												
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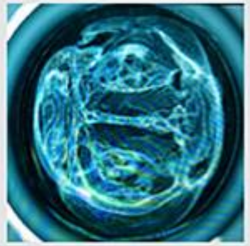
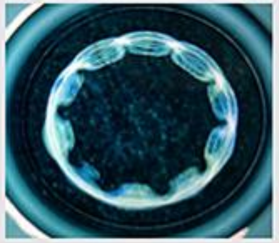
3												
	82	6.277 2.868	82	6.173 3.381	82	6.116 2.594	59	7.144 1.715	29	7.331 1.728	90	7.690 1.438

Cymatics - Standing / Faraday Wave of water at 50Hz

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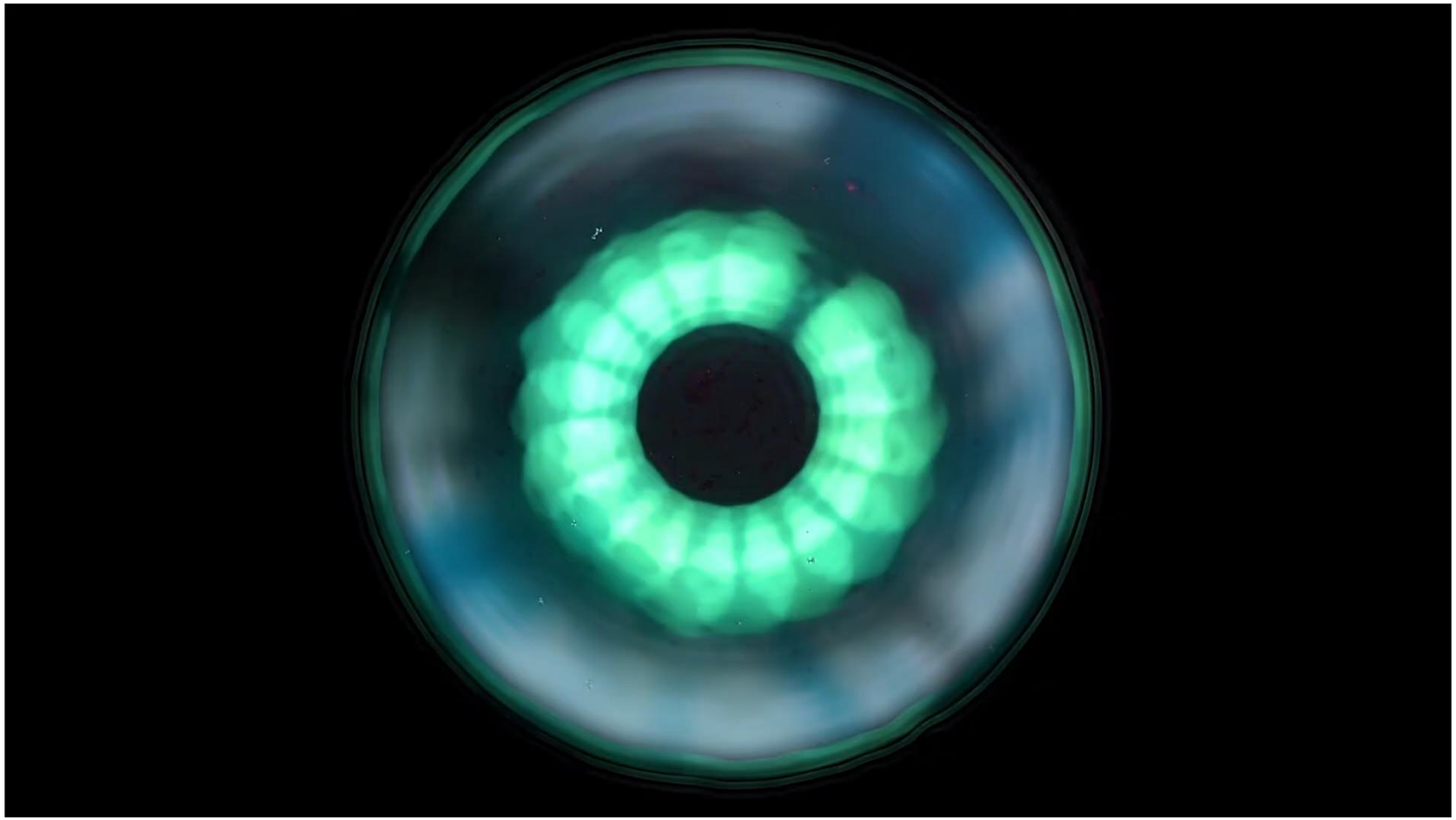

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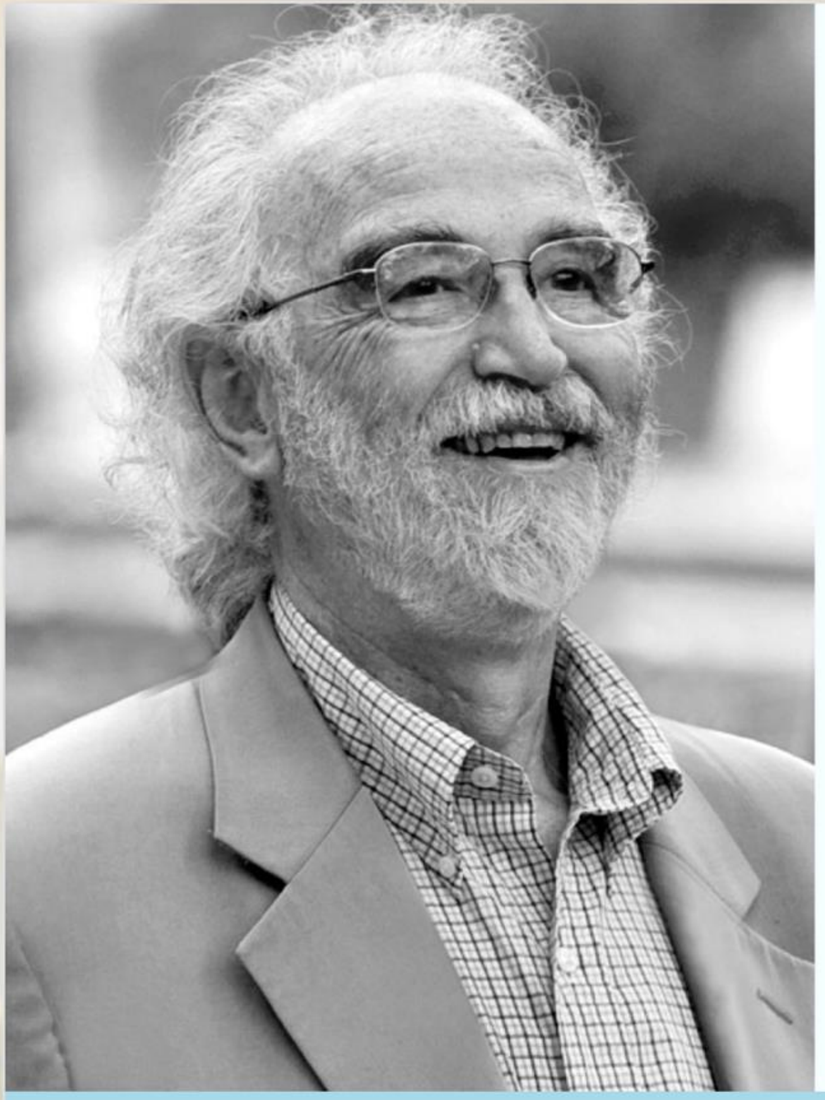
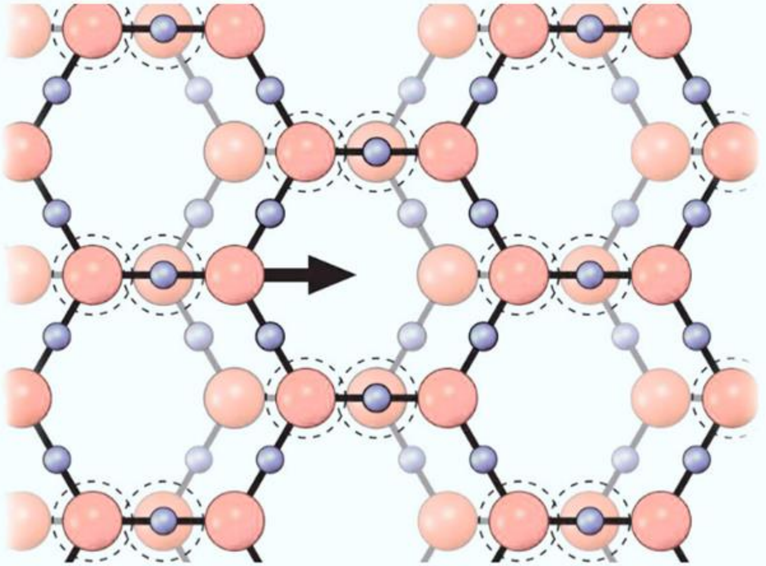


Gerald H Pollack



EZ WATER H_3O_2

The Fourth Phase of Water and Effects on Health

We all know that water is essential for life and that it can exist in three phases – solid, liquid, and vapor; however, have you heard about the fourth phase? For several years Professor Gerald Pollack from the

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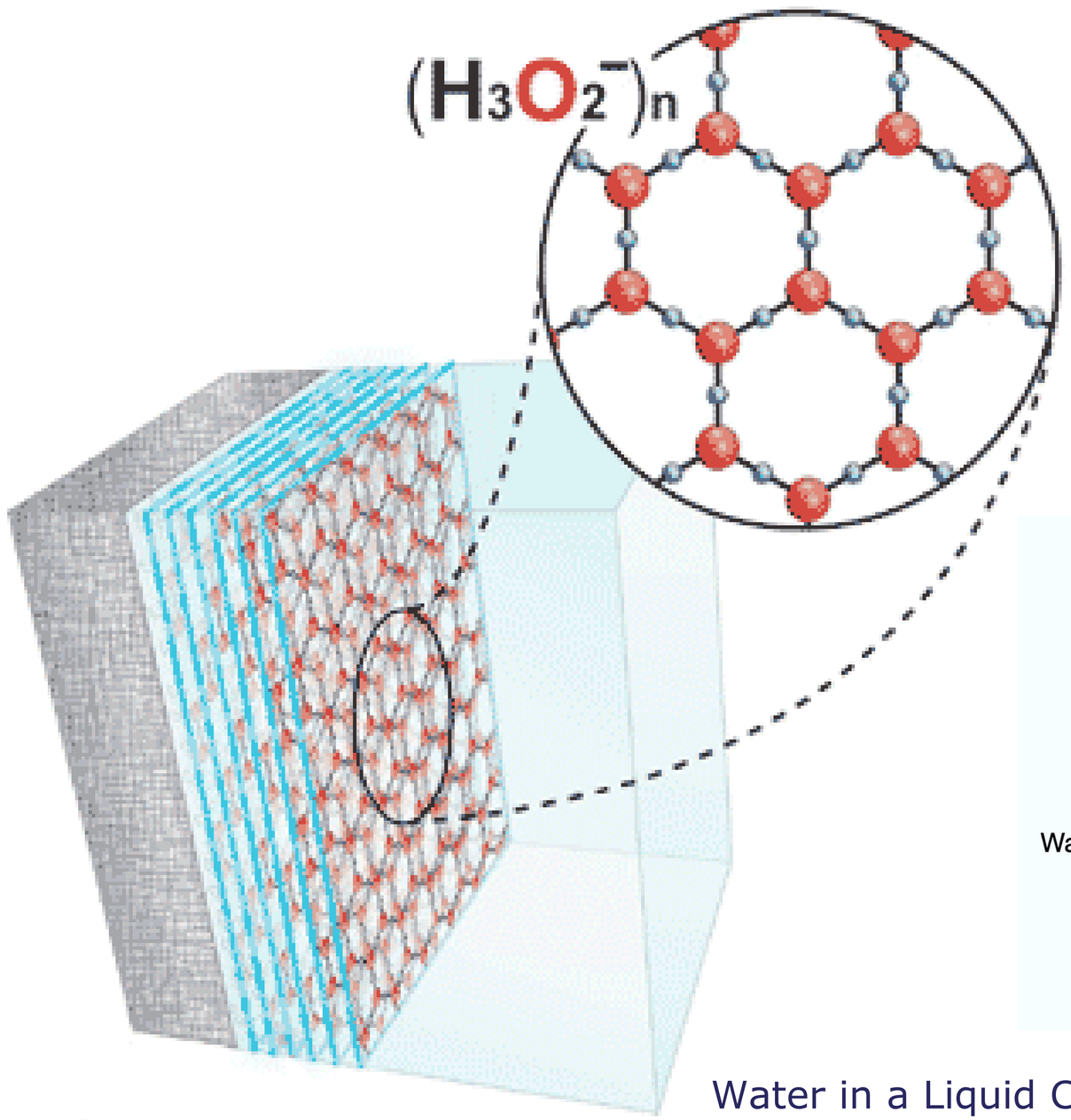

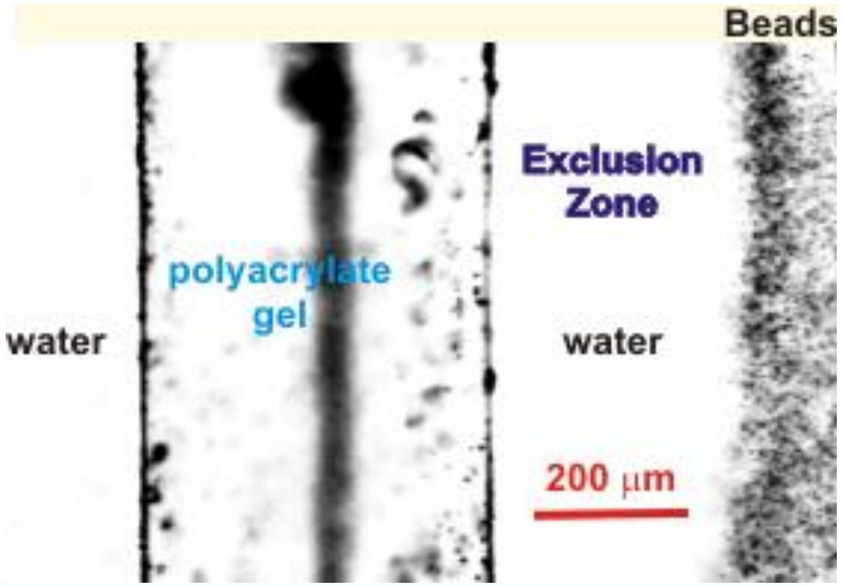

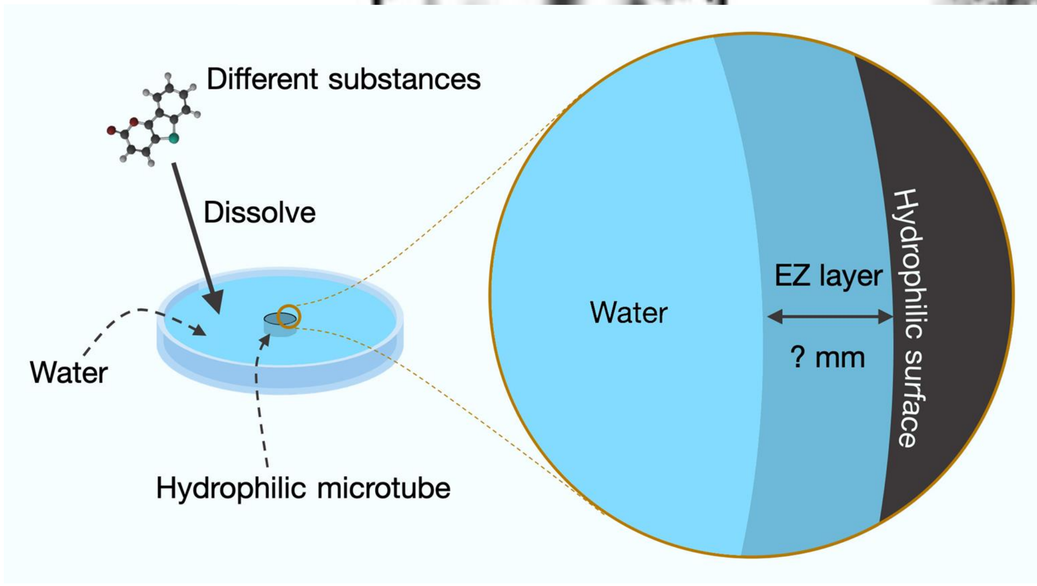

Water in a Liquid Crystal State = memory or data storage

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BioSystems 178 (2019) 16–24

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Quantum biology and human carcinogenesis

Michael Bordonaro

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ARTICLE INFO

Keywords:
Cancer
Quantum mechanics
Density matrix
Decoherence
Adaptive mutation
Wnt signaling

ABSTRACT

Quantum-mediated effects have been observed in biological systems. We have previously discussed basis-dependent quantum selection as a mechanism for directed adaptive mutation, a process in which selective pressure specifically induces mutation in those genes involved in the adaptive response. Tumor progression in cancer easily lends itself to the adaptive evolutionary perspective, as the Darwinian combination of heritable variations together with selection of the better proliferating variants are believed to play a major role in multistep carcinogenesis. Adaptive mutation may play a role in carcinogenesis; accordingly, we propose that the principles of quantum biology are involved in directed adaptive mutation processes that promote tumor formation. In this paper, we discuss the intersection between quantum mechanics, biology, adaptive evolution, and cancer, and present general models by which adaptive mutation may influence neoplastic initiation and progression. As a potential theoretical and experimental model, we use colorectal cancer. Our model of "quantum cancer" suggests experiments to evaluate directed adaptive mutation in tumorigenesis, and may have important implications for cancer therapeutics.

Coherent Information
is an entropy measure used in quantum information theory.

or

‘Corrupted’ or ‘Uncorrupted’ data stored in intracellular (4th phase) water
predict location of primary cancer and metastasis
- trauma based events

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That's it for the Origin Story

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Dr Binjemain's Total Cancer Management v1.2

Areas	Hallmarks	Suggested Management
Tumour Microenvironment	Acidic (Lactic)	Alkalising salts / Mg / Potassium / CAI
	Inflammation / Cytokine storms	NSAIDs / Curcumin / IVC / DMSO
	Estrogenic (Natural and Xeno)	Est blockers / Aromatase inhibitors / Genistein / DIM + CDG / I3C / IR Sauna
	Toxins / Dead cell debris / Tumour lysis (*)	IR Sauna / IV Glutathione / Selenium
Cancer cells	Rapid replication	Chemo / Radiation / Targeted therapy
	Cancer-specific metabolism	Off label drugs / supps
	Angiogenesis	MAB against VEGF / Apigenin / Angiostop / Lycopene
	Immune evasion	Checkpoint inhibitors / other MABs
	Invasion	CAI / Alkalising salts
	Loss of apoptosis	THC / Ferroptosis inducing agents / CAI
	Rapid DNA repair	PARP-i / Quercetin / Niacinamide
	Stem cell-driven	Pancreatic proenzymes / Vit A analogues / PB / IP6
Psychology (*)	Stress	EFT / Matrix / Biofield / CBD
	Fear	EFT / Matrix / Biofield / CBD
	Trauma	EFT / Matrix / Biofield / CBD
	Self-limiting beliefs	EFT / Matrix / Biofield
	Increasing joy	
	Strong reason to live	

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Metabolic / Energy Blockade

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BMB Rep. 2018 Jul; 51(7): 319–326.
Published online 2018 Jul 31. doi: 10.5483/BMBRep.2018.51.7.112
PMCID: PMC6089865
PMID: 29764565

Cancer stem cell metabolism: target for cancer therapy

Young Chan Chae[1] and Jae Ho Kim[2,3,*]

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Abstract

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Increasing evidence suggests that cancer stem cell (CSC) theory represents an important mechanism underlying the observed failure of existing therapeutic modalities to fully eradicate cancers. In addition to their more established role in maintaining minimal residual disease after treatment and forming the new bulk of the tumor, CSCs might also critically contribute to tumor recurrence and metastasis. For this reason, specific elimination of CSCs may thus represent one of the most important treatment strategies. Emerging evidence has shown that CSCs have a different metabolic phenotype to that of differentiated bulk tumor cells, and these specific metabolic activities directly participate in the process of CSC transformation or support the biological processes that enable tumor progression. Exploring the role of CSC metabolism and the mechanism of the metabolic plasticity of CSCs has become a major focus in current cancer research. The targeting of CSC metabolism may provide new effective therapies to reduce the risk of recurrence and metastasis. In this review, we summarize the most significant discoveries regarding the metabolism of CSCs and highlight recent approaches in targeting CSC metabolism.

Keywords: Cancer Metabolism, Cancer Stem Cell, Glycolysis, Mitochondria, OXPHOS

- Cancer stem cells are **METABOLICALLY FLEXIBLE**
- CSCs' **mitochondria are functioning well** - assuming that their mitochondria is not functioning due to the presence of aerobic glycolysis is erroneous
- Switch between glycolysis, OXPHOS, fatty acid oxidation, Glutamine, Amino Acids etc

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Journal List > Ecancermedicalscience > v.8; 2014 > PMC4096030

ecancermedicalscience
The open access cancer journal focused on under-resourced communities

Ecancermedicalscience. 2014; 8: 442.
Published online 2014 Jul 10. doi: 10.3332/ecancer.2014.442

PMCID: PMC4096030
PMID: 25075216

The Repurposing Drugs in Oncology (ReDO) Project

Pan Pantziarka,[1,2] Gauthier Bouche,[1] Lydie Meheus,[1] Vidula Sukhatme,[3] Vikas P. Sukhatme,[3] and P. Vikas[3,4]

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Abstract

Go to: ▸

The Repurposing Drugs in Oncology (ReDO) Project seeks to repurpose well-known and well-characterised non-cancer drugs for new uses in oncology. The rationale for this project is presented, examining current issues in oncological drug development, challenges for health systems, and existing and future patient needs. In addition to discussing the advantages of repurposing, the paper

ecancermedicalscience

ReDO Project

Repurposing Drugs In Oncology

ReDO Repurposing Drugs In Oncology

Home | Who We Are | Drug Candidates | ReDO Database | Covid19db | Clinical Trials | Publications | Press | Contact

Clinical Trials

A number of clinical trials are being supported by the Anticancer Fund making use of repurposed drugs.

Propranolol in Angiosarcoma (PROPAN). Neo-adjuvant beta-blocker (propranolol) in angiosarcoma patients. This is a single-arm neoadjuvant window of opportunity phase II study to explore the activity of propranolol in cutaneous angiosarcoma. Propranolol will be administered as monotherapy in a dose of 40-80 mg 2-3 times a day, if tolerated. 14 patients with newly diagnosed, recurrent or metastatic cutaneous angiosarcoma (including angiosarcoma of the breast) will be recruited.

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OFF LABEL USE OF DRUGS FOR THE PURPOSE OF BLOCKING CANCER METABOLIC PATHWAYS
TO BE USED IN CONJUNCTION WITH STANDARD OF CARE TREATMENTS (STARVE AND KILL)
SLOWS THEM DOWN SO CYTOTOXIC THERAPY (CHEMO/RAD) CAN KILL THEM EASIER
HAVE TO LOOK OUT FOR TUMOUR LYSIS SYNDROME

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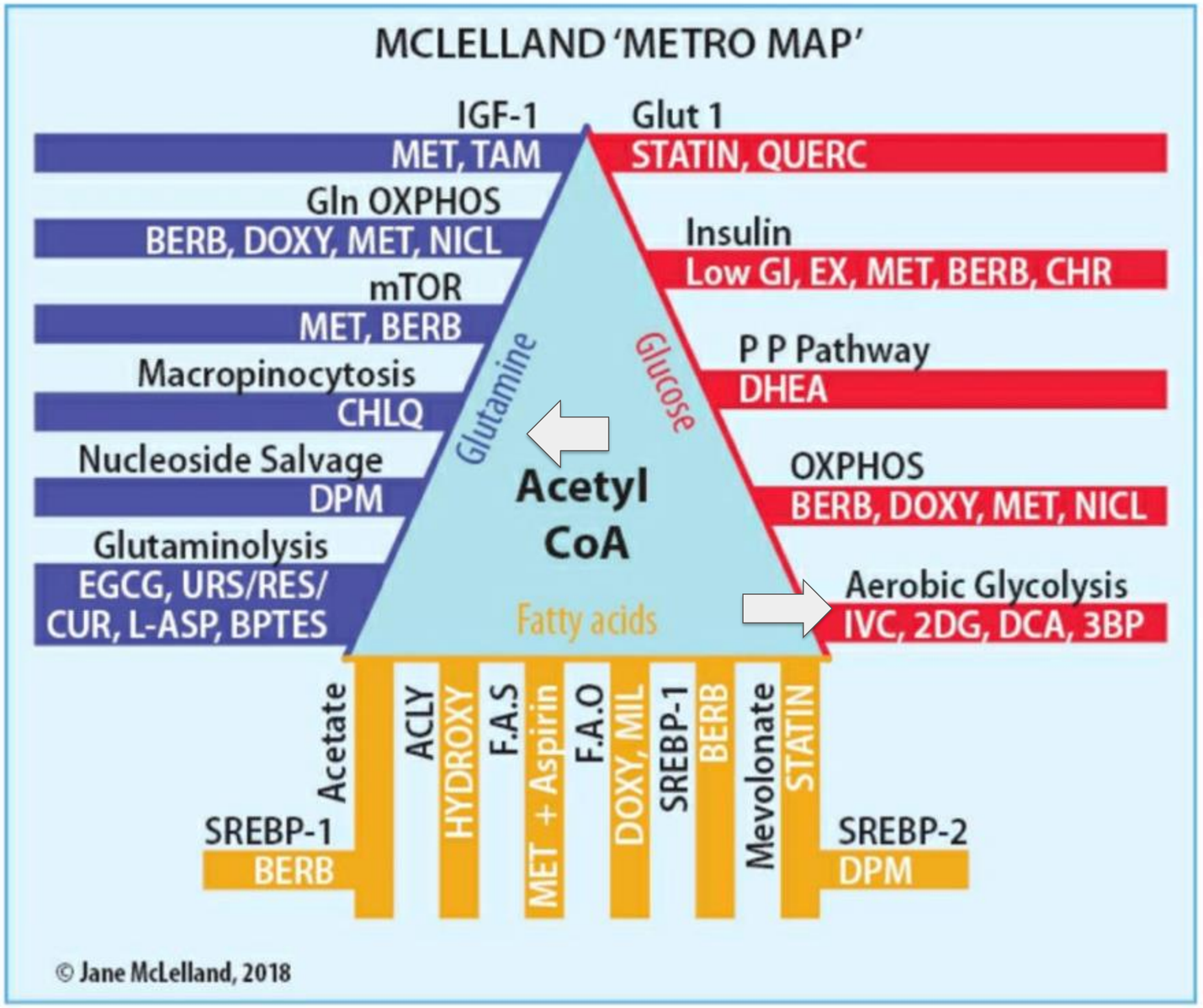
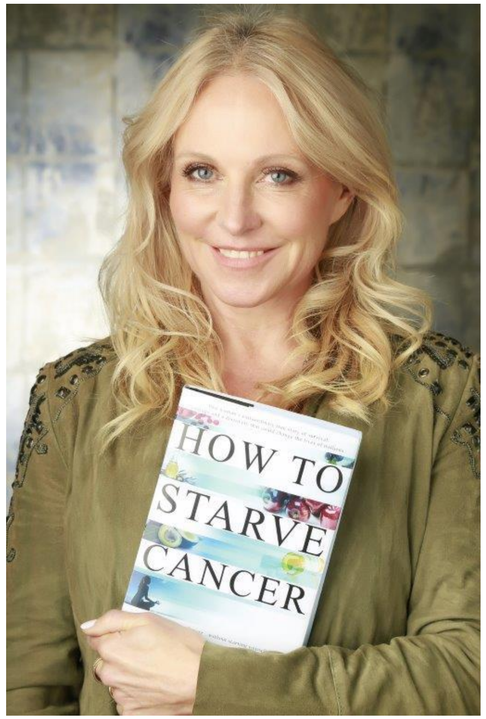


Figure 21.2. My Stem Cell 'Metro Map'



COCKTAIL OF PRESCRIPTION MEDICATIONS AND SUPPLEMENTS TO BLOCK ALL KNOWN METABOLIC PATHWAYS IN CONJUNCTION WITH STANDARD OF CARE TREATMENTS (STARVE N KILL)

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Metformin

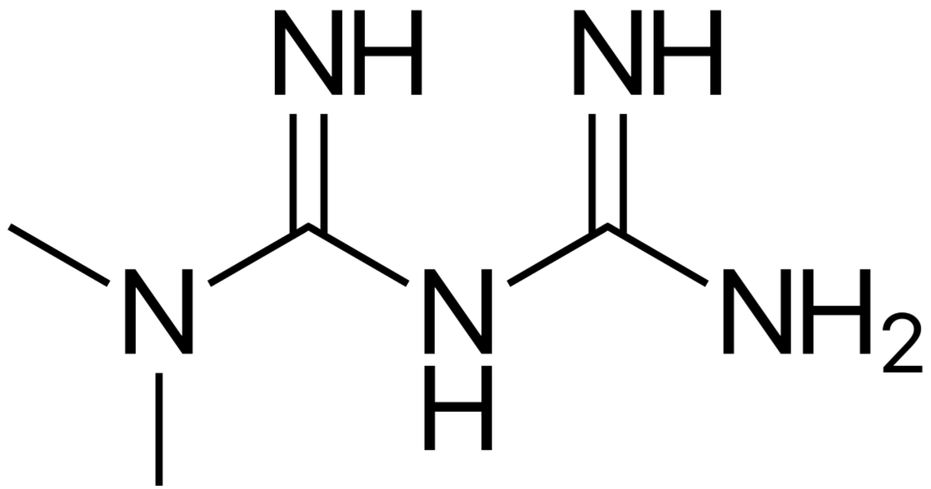

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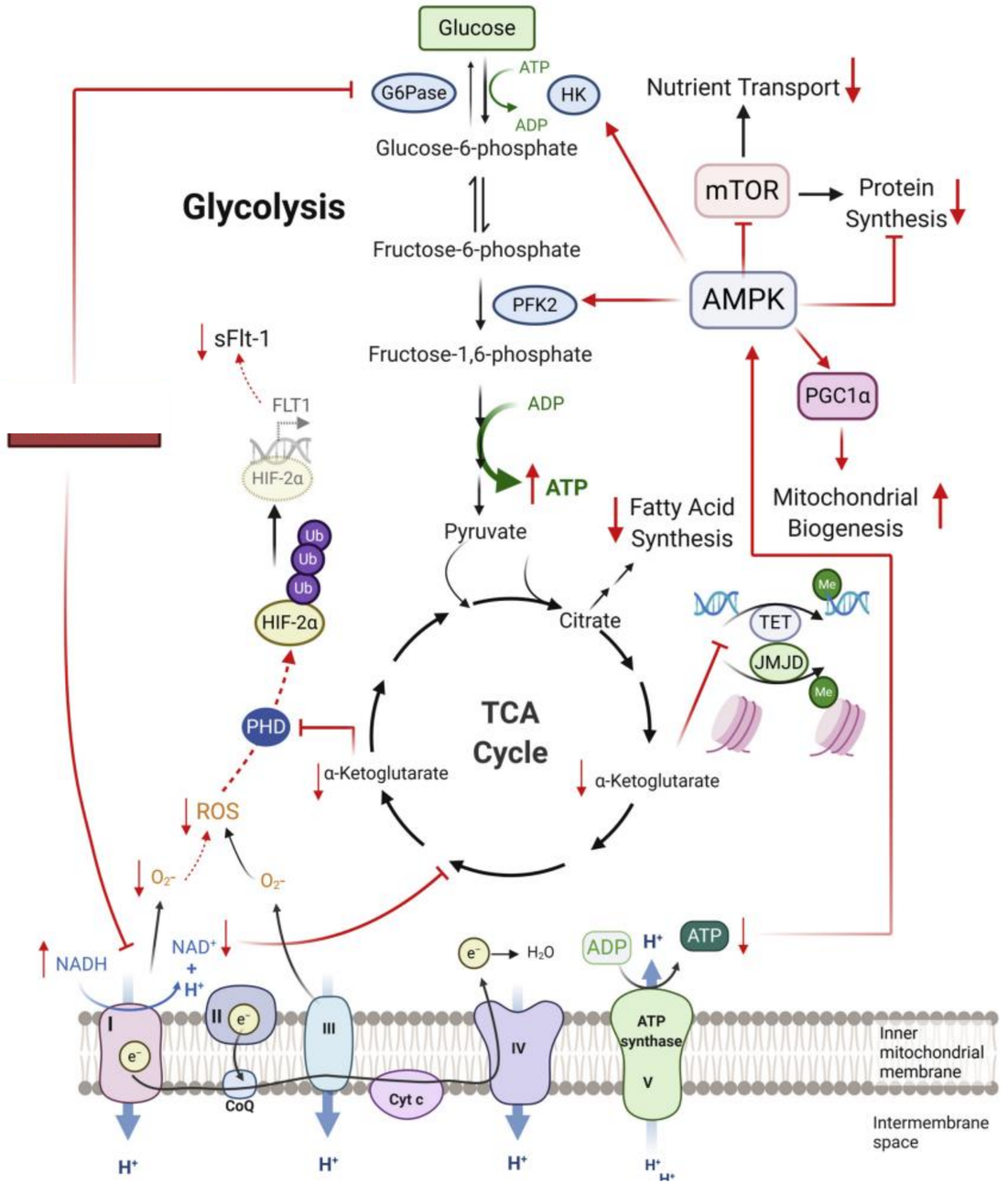
FIGURE 6

targets multiple pathways in energy metabolism



Irving L.M.H. Aye, Catherine E. Aiken, D. Stephen Charnock-Jones, Gordon C.S. Smith, **Placental energy metabolism in health and disease—significance of development and implications for preeclampsia, American Journal of Obstetrics and Gynecology**, Volume 226, Issue 2, Supplement, **2022**, Pages S928-S944

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Metformin

- Inhibits IGF1-R pathways
- Inhibits mTOR pathways
- Inhibits cancer oxidative phosphorylation
- Inhibits fatty acid synthetase
- Reduces insulin resistance, hence lower insulin
- Typical dose 500mg BD - same precautions when starting the medication in any patient

Li, L., Wang, Y., Peng, T., Zhang, K., Lin, C., Han, R., Lu, C., & He, Y. (2016). Metformin restores crizotinib sensitivity in crizotinib-resistant human lung cancer cells through inhibition of IGF1-R signaling pathway. Oncotarget, 7(23), 34442–34452. https://doi.org/10.18632/oncotarget.9120
Amin, S., Lux, A., & O'Callaghan, F. (2019). The journey of metformin from glycaemic control to mTOR inhibition and the suppression of tumour growth. British journal of clinical pharmacology, 85(1), 37-46.
Ashton, T. M., McKenna, W. G., Kunz-Schughart, L. A., & Higgins, G. S. (2018). Oxidative phosphorylation as an emerging target in cancer therapy. Clinical Cancer Research, 24(11), 2482-2490.
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Metformin is an AMP kinase–dependent growth inhibitor for breast cancer cells M Zakikhani, R Dowling, IG Fantus, N Sonenberg… - Cancer research, 2006 - AACR
Metformin inhibits mammalian target of rapamycin–dependent translation initiation in breast cancer cells, RJO Dowling, M Zakikhani, IG Fantus, M Pollak… - Cancer research, 2007 - AACR
Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission, HA Hirsch, D Iliopoulos, PN Tsichlis, K Struhl - Cancer research, 2009 - AACR

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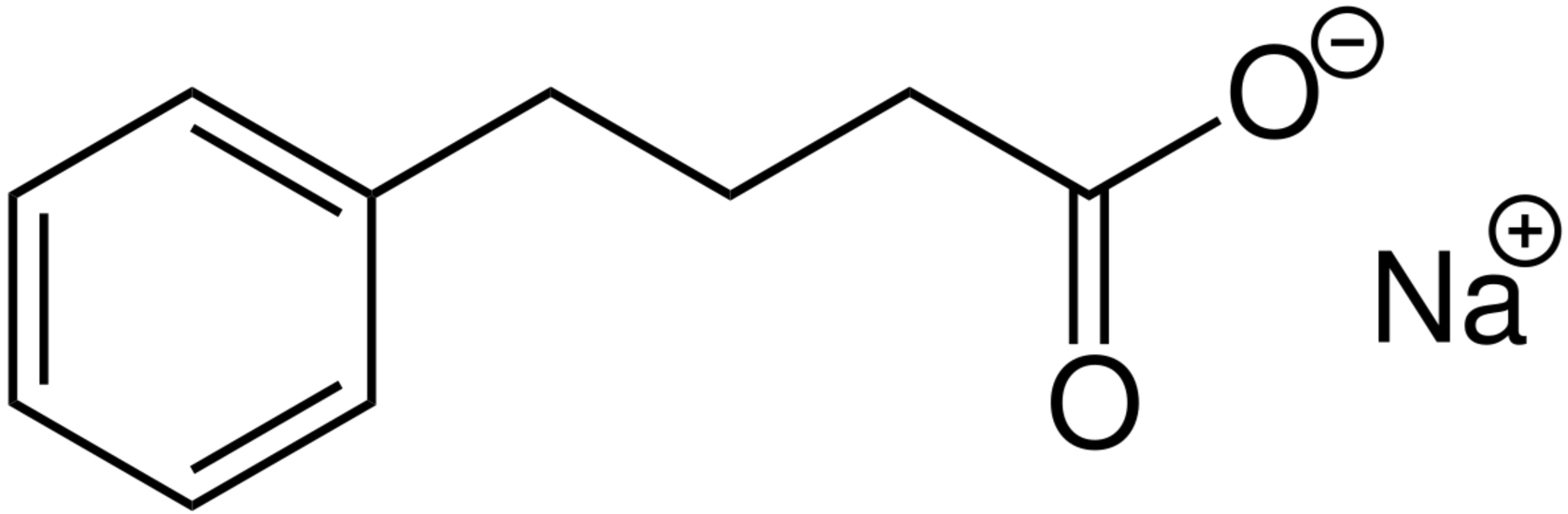
Phenylbutyrate



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Phenylbutyrate

- TGA approved for urea cycle disorders (paediatric)
- Excessive levels of ammonia leads to encephalopathy (check serum ammonia)
- Nitrogen binding agent is rapidly metabolised to phenylacetate.
- Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine which is then excreted by the kidneys.
- As a consequence, nitrogen binding agent reduces elevated plasma ammonia and glutamine levels in patients with urea cycle disorders (and cancer patients)

TGA Product Information

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Phenylbutyrate

- Histone Deacetylase Inhibitor (HDAC-I)
- The histone deacetylation by HDACs is responsible for transcriptional repression through chromatin condensation.
- Hypoacetylated histones are generally associated with transcriptionally silent loci.
- Histones are spools where DNA can wind themselves around.
- For DNA to be active, they have to be unwind after the histones have been acetylated (activated)

Iannitti, T., Palmieri, B. Clinical and Experimental Applications of Sodium Phenylbutyrate. Drugs R D 11, 227–249 (2011). https://doi.org/10.2165/11591280-000000000-00000

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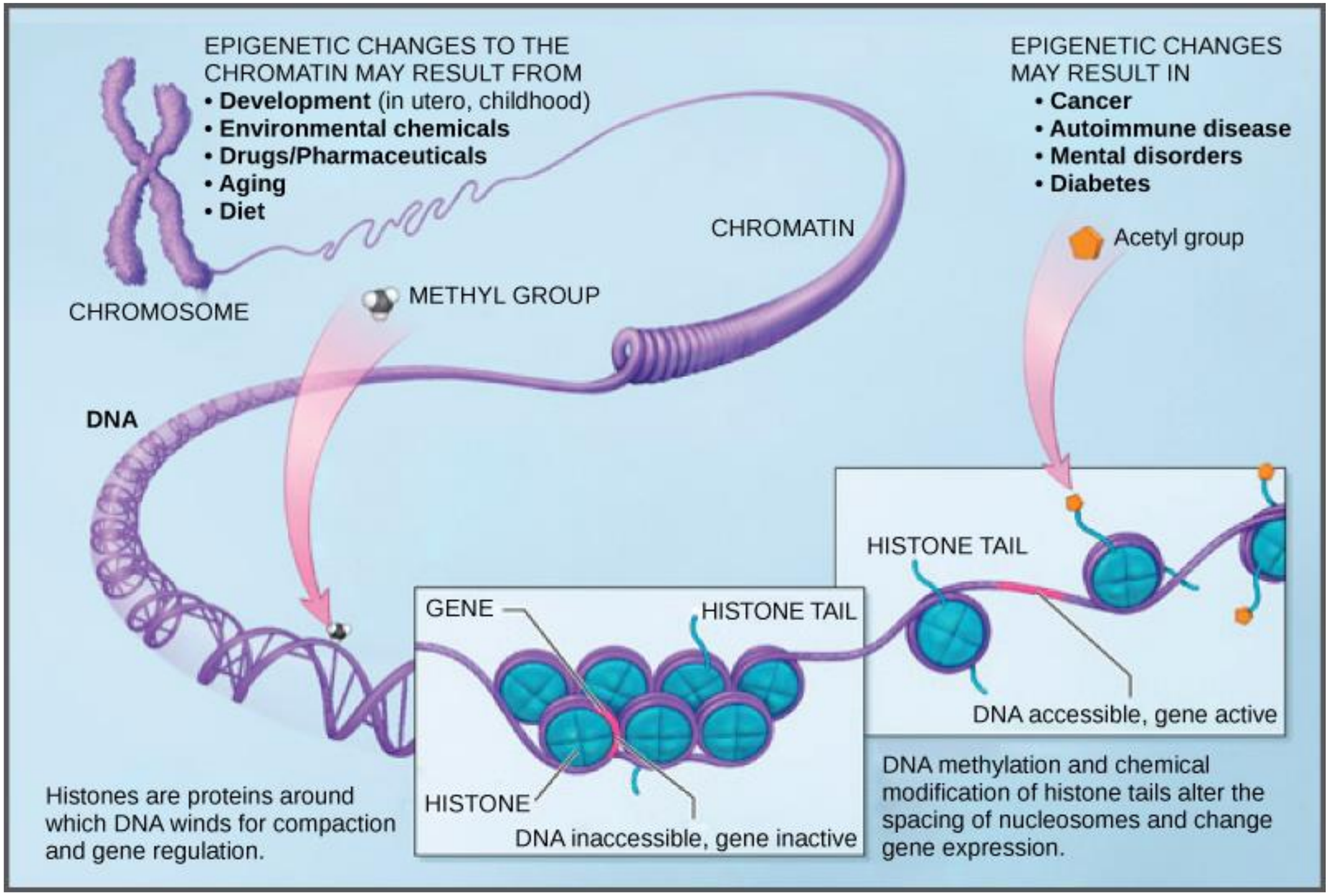

Source: https://courses.lumenlearning.com/wm-biology1/chapter/reading-eukaryotic-epigenetic-gene-regulation/

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Phenylbutyrate (PB)

- Induces cell differentiation (CD)
- Cancer stem cells to non-cancer stem cells (1)
- "Demoting 5-star Generals to foot soldiers"
- Less aggressive phenotype, less resistant to cytotoxic therapies
- CD as been demonstrated in many cancer cell lines using PB - leukaemia, lymphoma, prostate, breast, glioblastoma and others (2)
- Differentiation therapy is a non-toxic way of treating cancer, and a treatment aim for better long term outcomes eg. Acute Promyelocytic Leukemia and Retinoic Acid (3)

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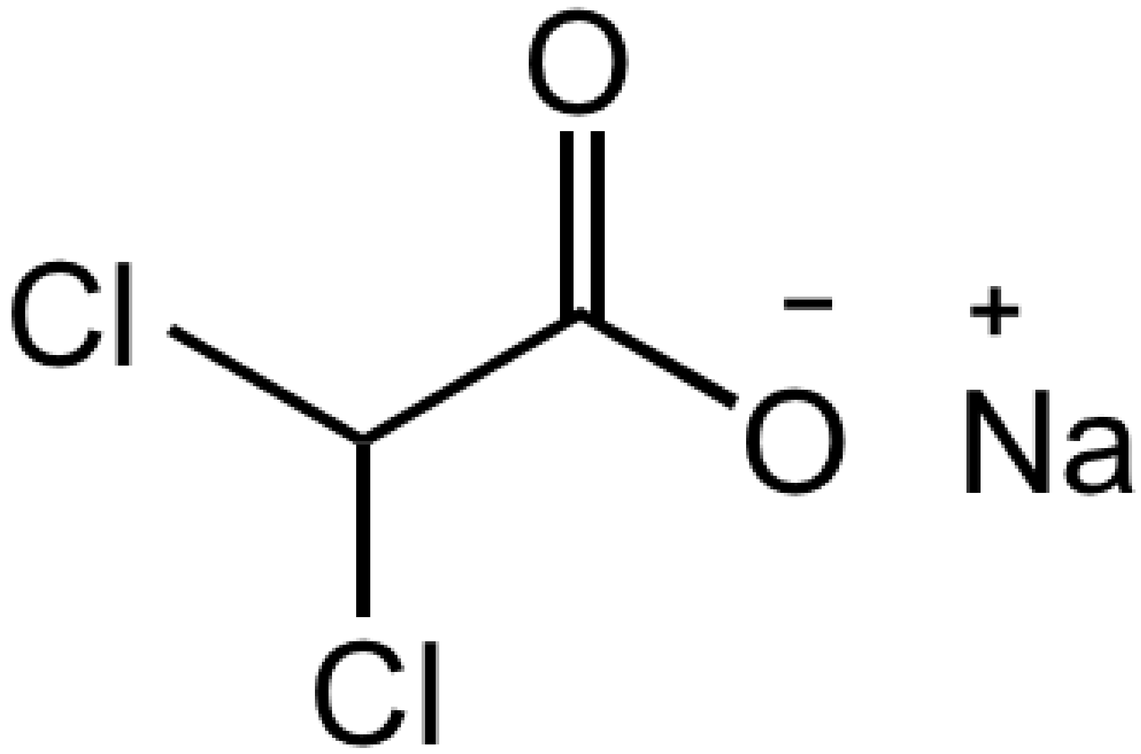
Dichloroacetate



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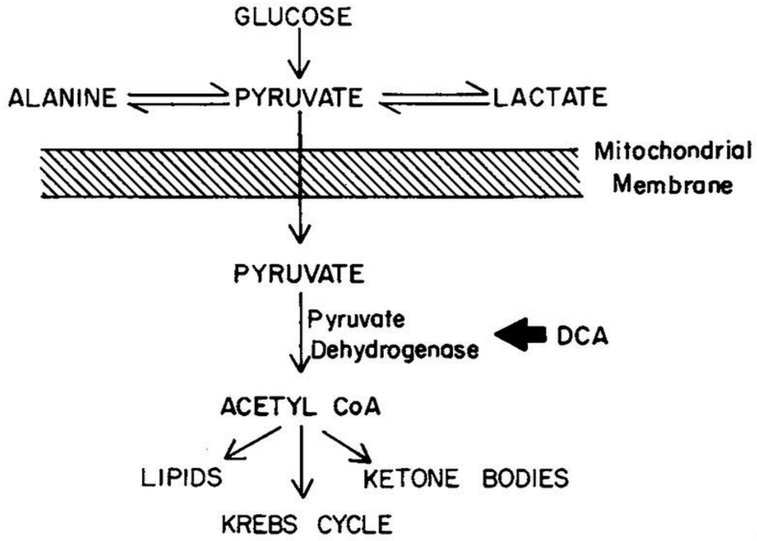
Dichloroacetate

- Orphan drug (rare diseases), mainly investigational use in metabolic disorders (1)
- Inhibit pyruvate dehydrogenase kinase / complex (1)
- Therefore, allows pyruvate into mitochondria
- Reduces lactate
- Clinically proven to reduce lactic acidosis (2)
- Recent studies in cancer, mostly cell / animal studies and clinical phase 1 trials and case reports (3-6)
- Reduces glycolysis and hence building blocks
- Main side effect - peripheral neuropathy in some



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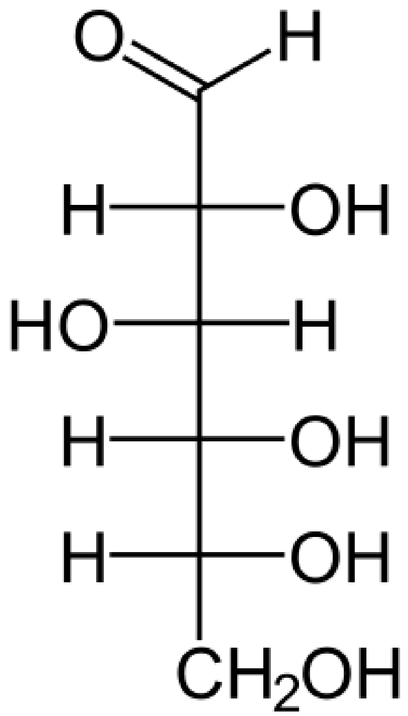
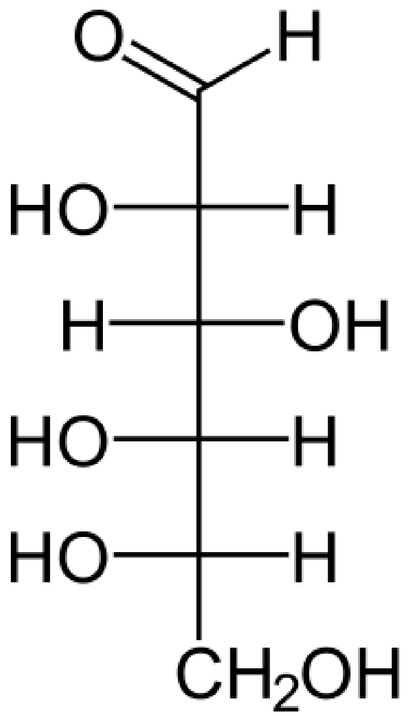
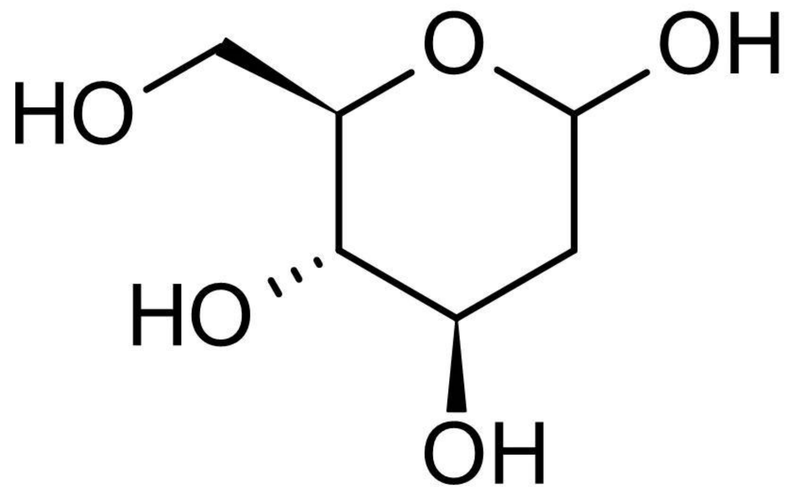
2-Deoxy-D-Glucose (2DG)



D-Glucose



L-Glucose



2DG

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2DG

- Glucose analogue, not biologically active as it is in the 'D' form (1)
- Inhibits glycolysis (1)
- Increases oxidative stress within cancer cells (1)
- Inhibits N-linked glycosylation (1)
- Induces autophagy (1)
- More effective against aggressive CSCs phenotype (2)
- Works well as a chemo or radiation sensitising agent (3,4)

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4.Raez, L.E., Papadopoulos, K., Ricart, A.D. et al. A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol 71, 523–530 (2013)

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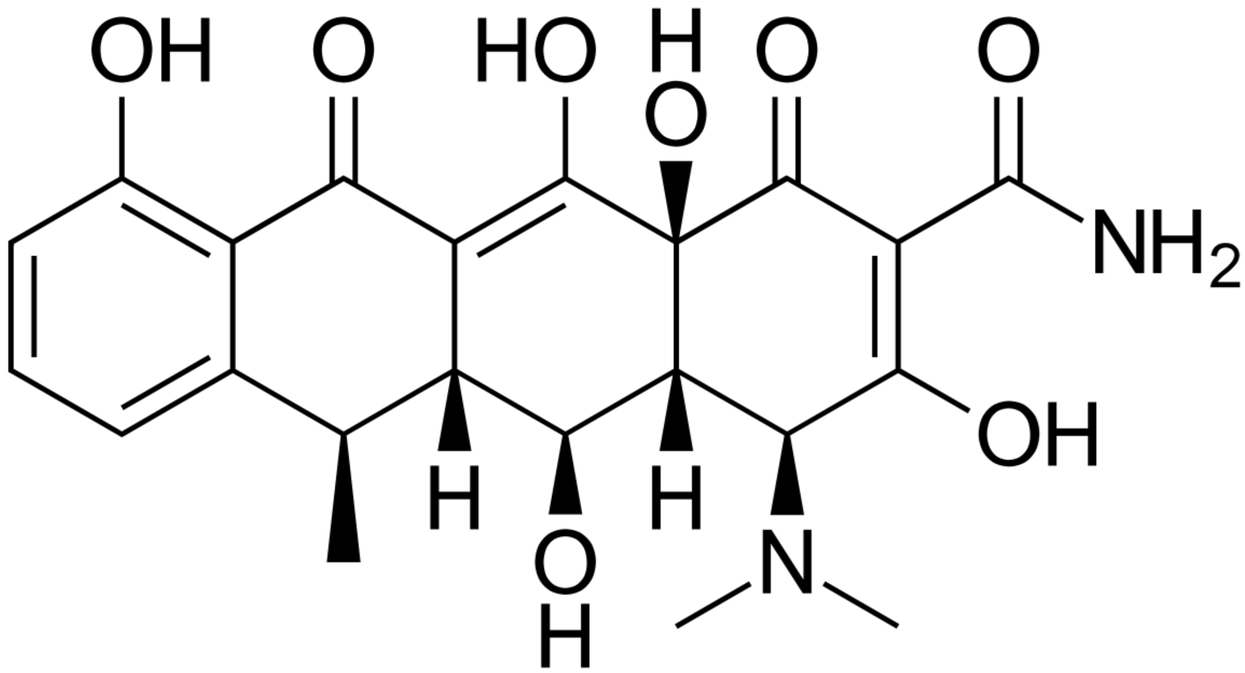
Doxycycline



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Doxycycline

- Bacteriostatic. It works by preventing bacteria from reproducing through the inhibition of protein synthesis.
- Highly lipophilic so can easily enter cells.
- Induces mitochondrial mediated pathway of apoptosis (1) - affects OXPHOS
- Synergises with Gemcitabine to induce mito-mediated apoptosis (2)
- Inhibits cancer stem cells and epithelial-to-mesenchymal transition. "Expression of stem cell factors Oct4, Sox2, Nanog and CD44* were also significantly downregulated after doxycycline treatment"(3)
- Potent MMP inhibitors and are highly osteotropic - esp for bone mets (4)
- Blocks Fatty Acid Oxidation as a source of energy, indirectly (5)

Ref
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2. Dijk, S.N., et al. Mitochondria as target to inhibit proliferation and induce apoptosis of cancer cells: the effects of doxycycline and gemcitabine. Sci Rep 10, 4363 (2020)
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* refer to RGCC lecture
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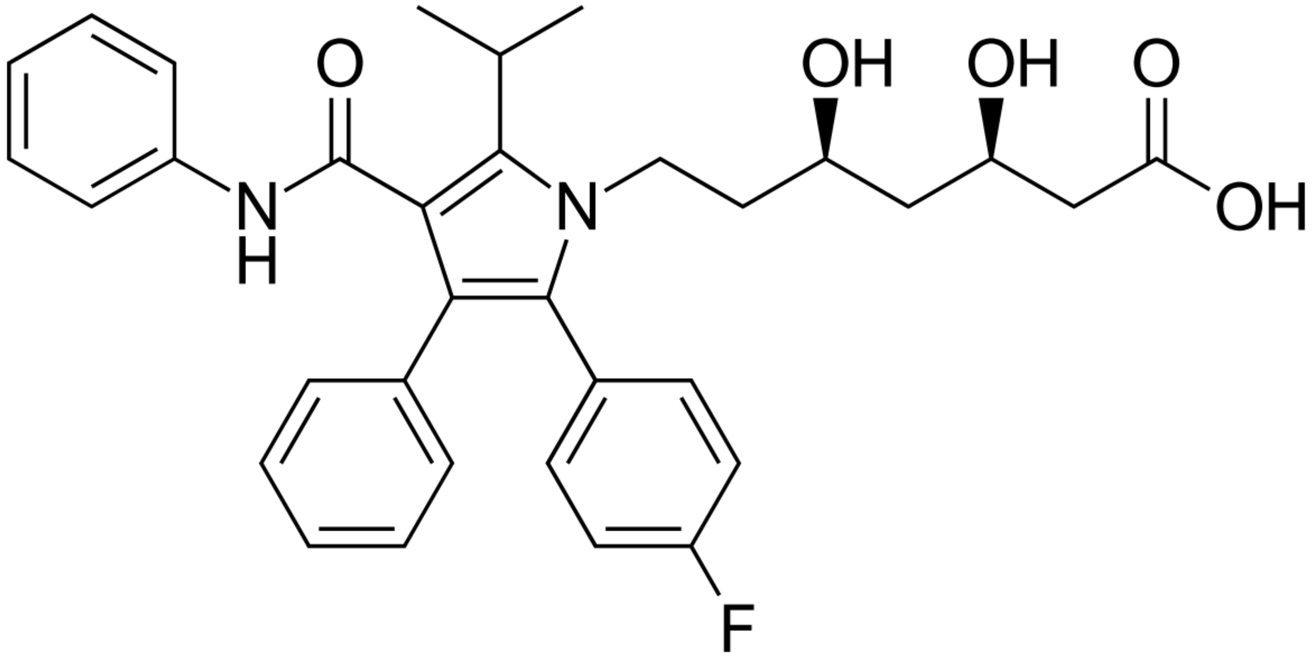
Atorvastatin



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Atorvastatin

- Inhibitors of HMG-CoA reductase in cholesterol biosynthesis
- Lipophilic
- Its action directly blocks the Mevalonate pathway
- Cancer cells utilises the Mevalonate pathway to access lipids for membrane synthesis
- Inhibition of the active form of oncoproteins such as Rho and Ras and their downstream pathway regulating proliferation, migration, invasion, survival and stemness.(1)
- Also inhibit GLUT-mediated glucose uptake in cancer cells (2)

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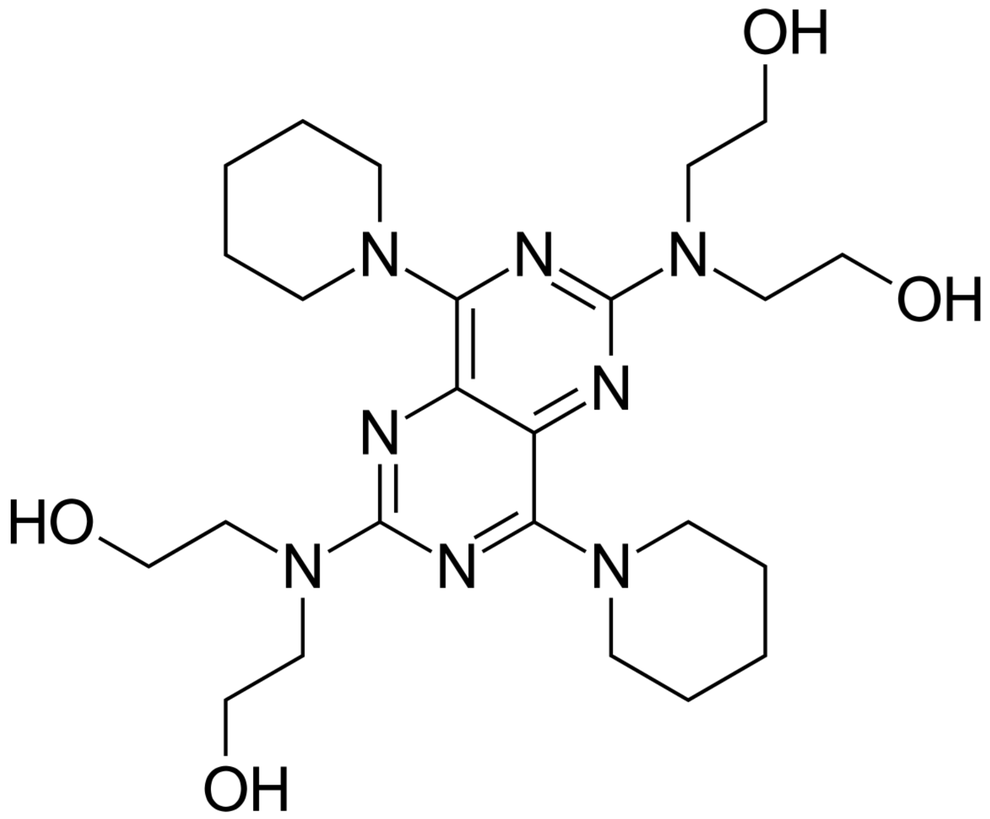
Dipyridamole



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Dipyridamole

- Inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP, an inhibitor of platelet function.
- Nucleoside transport inhibitor (ENT1) - blocks the nucleoside Adenosine from entering endothelial cells.
- Hence blocks nucleoside salvage (recycling of DNA building materials from dead cancer cells)(1)
- Significant effects on Wnt, ERK1/2-MAPK and NF-kB pathways in vivo (2)
- Significantly decreased infiltration of tumor-associated macrophages and myeloid-derived suppressor cells in primary tumors ($p < 0.005$), and inflammatory cytokines in vivo (2)
- Synergises with chemotherapy (5FU, Mitomycin) in locally advanced pancreatic cancer (3)

Ref
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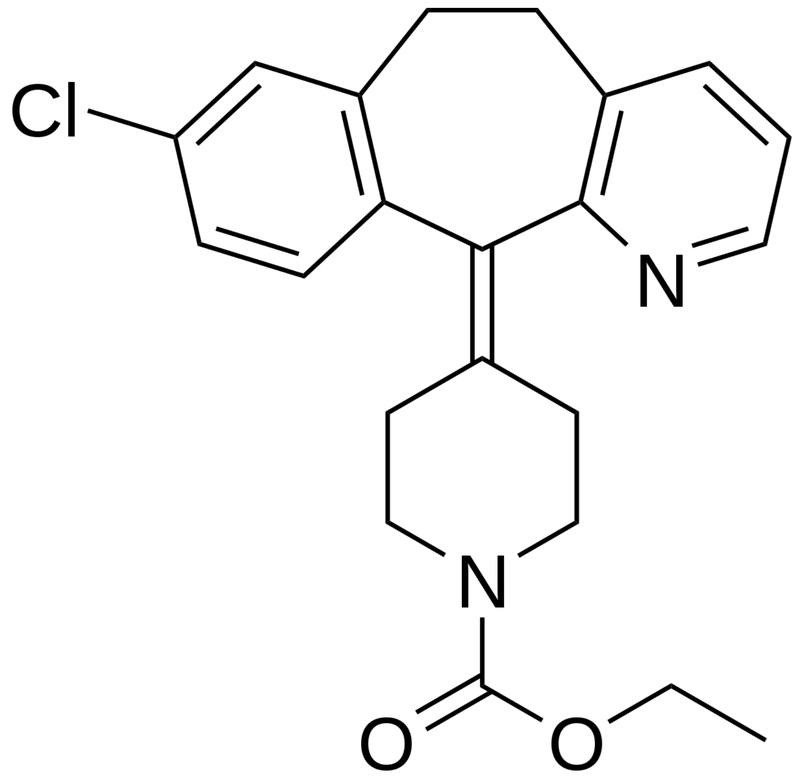
Loratadine



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Loratadine

- Binds to H1 histamine receptors - epithelial cells, endothelial cells, eosinophils, neutrophils, airway cells, and vascular smooth muscle cells among others.(1)
- Targets cancer lysosomes or macropinocytosis (intracellular packets) through their cationic amphiphilic nature - breaks down lysosomes which are used as signaling packets, cell nutrition and pH modulation (2)
- Has been shown to improve survival in population studies - breast cancer and melanoma patients (3,4)

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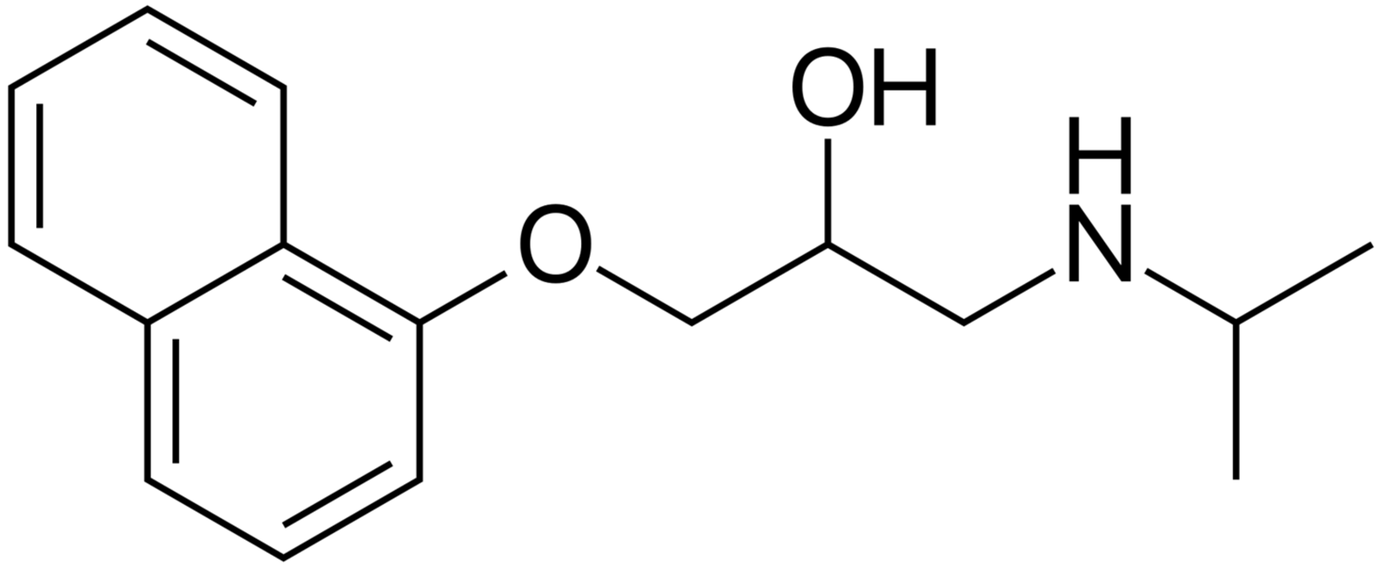
Propranolol



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Propranolol

- cancer cells are metabolically flexible - glucose / glutamine / fatty acids / amino acids
- Propranolol promotes glucose dependence and hence reduces its metabolic flexibility(1)
- used in conjunction with a glycolytic inhibitor eg DCA / 2DG / metformin(1)(2)
- prevents cachexia and weight loss in cancer patients by reducing basal metabolic rate and reduces sympathetic tone(3)
- reduces anxiety and multiple other cancer pathways(4)
- warn regarding blood pressure

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Summary (sample plan)

- Cocktail of medications / supplements
- Metformin 500mg BD
- Atorvastatin 20mg BD
- Propranolol 40mg BD
- Sodium Phenylbutyrate 2g morning 4g before bed
- DCA 500mg BD or 2DG 1g in 500mls water in small sips from evening to bed
- Doxycycline 50mg BD 1month on 1month off
- Dipyridamole 200mg BD
- other supplements including EGCG / Berberine / D-mannose / Hydroxycitrate
- use at your own discretion

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Summary

- Study placental / trophoblast bioenergetic and biosynthetic metabolic pathways
- Virtually identical metabolic pathways with cancer cells
- Different from metabolic activity in normal cells, which makes it a good target (eg glutamine addiction, aerobic glycolysis)
- Both placenta and cancer are highly adapted for survival - metabolically flexible
- Fast growing, highly aggressive cancer cells are more energy dependent - can escape replication blocking therapy (chemo / radiation) but more vulnerable to metabolic blocking therapy - hence synergy with SOC
- Need to block as many cancer metabolic pathways as possible to reduce chance of escape
- Need a cocktail of off-label common medications and natural extracts to block pathways in conjunction with SOC therapies
- Practical tip - introduce metabolic blocks one at a time