CANCER THERAPIES:
REPURPOSED DRUGS & NATURAL SUBSTANCES
Aug 14, 2021 PART Three

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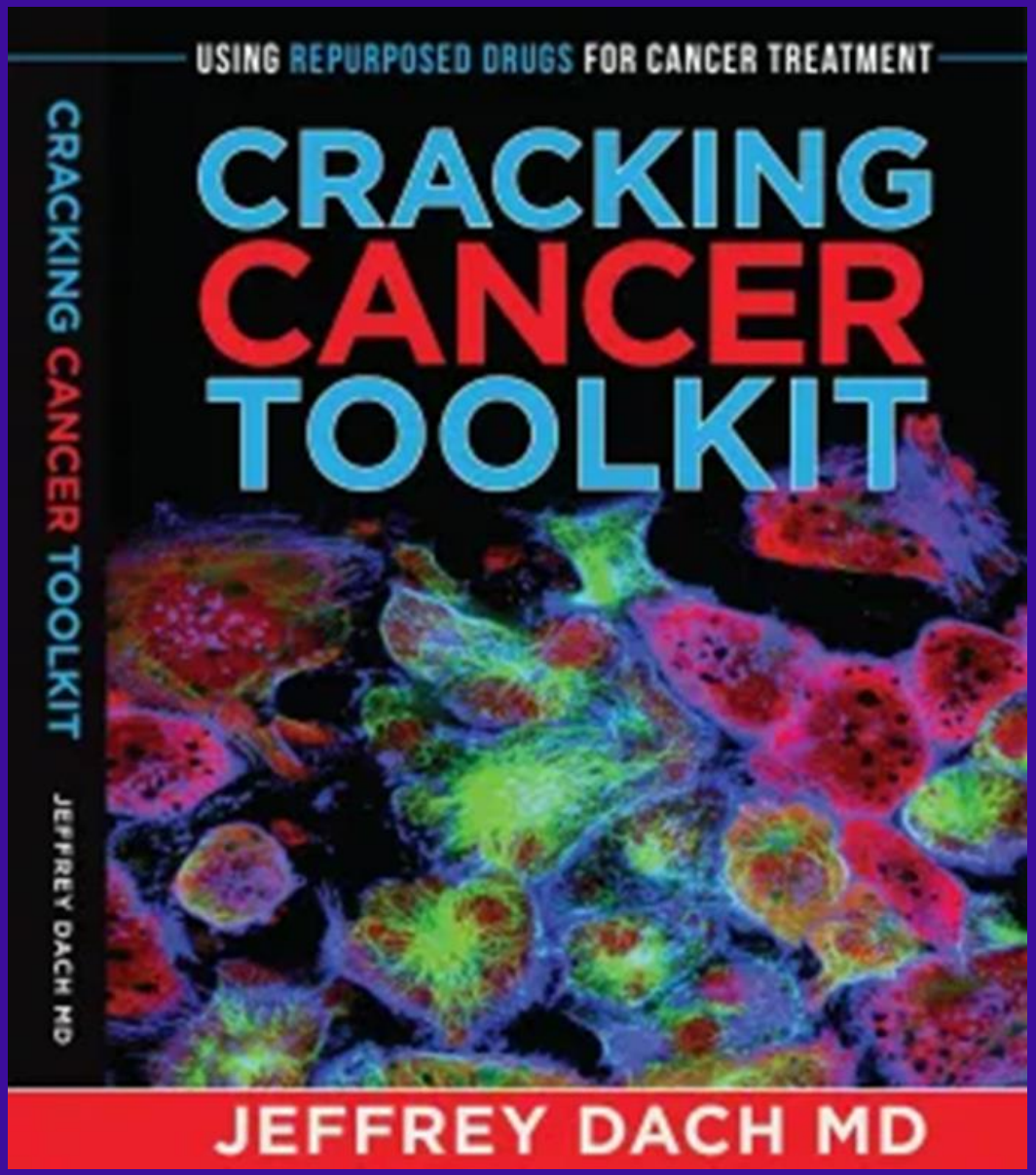
Cancer As a Trophoblastic Disease



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Three Pillars of Cancer Cell Metabolism

GLYCOLYSIS

OXPHOS

Autophagy

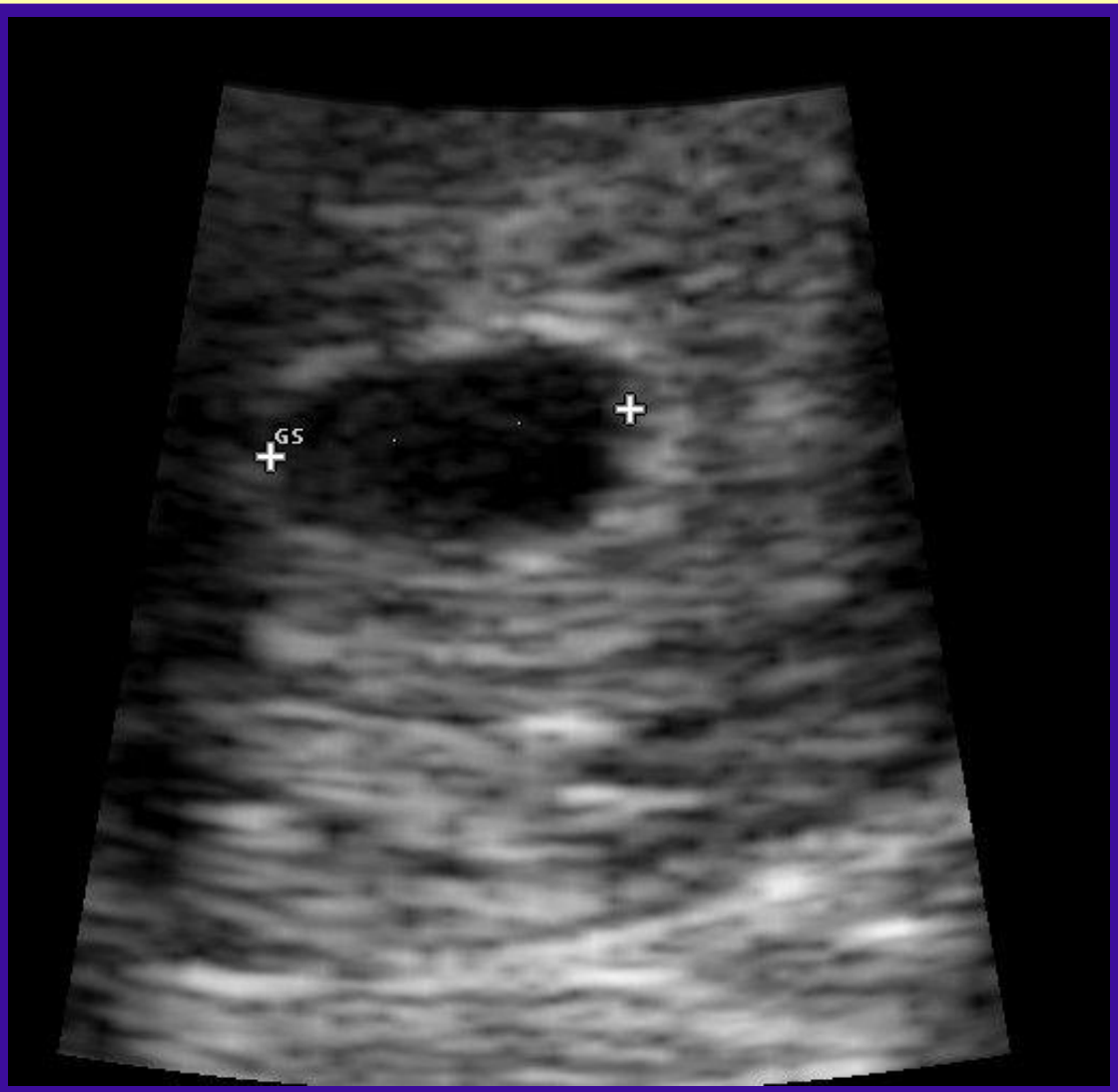
Fourth Pillar

Restore
Host
Immune
Surveillance

Fifth Pillar

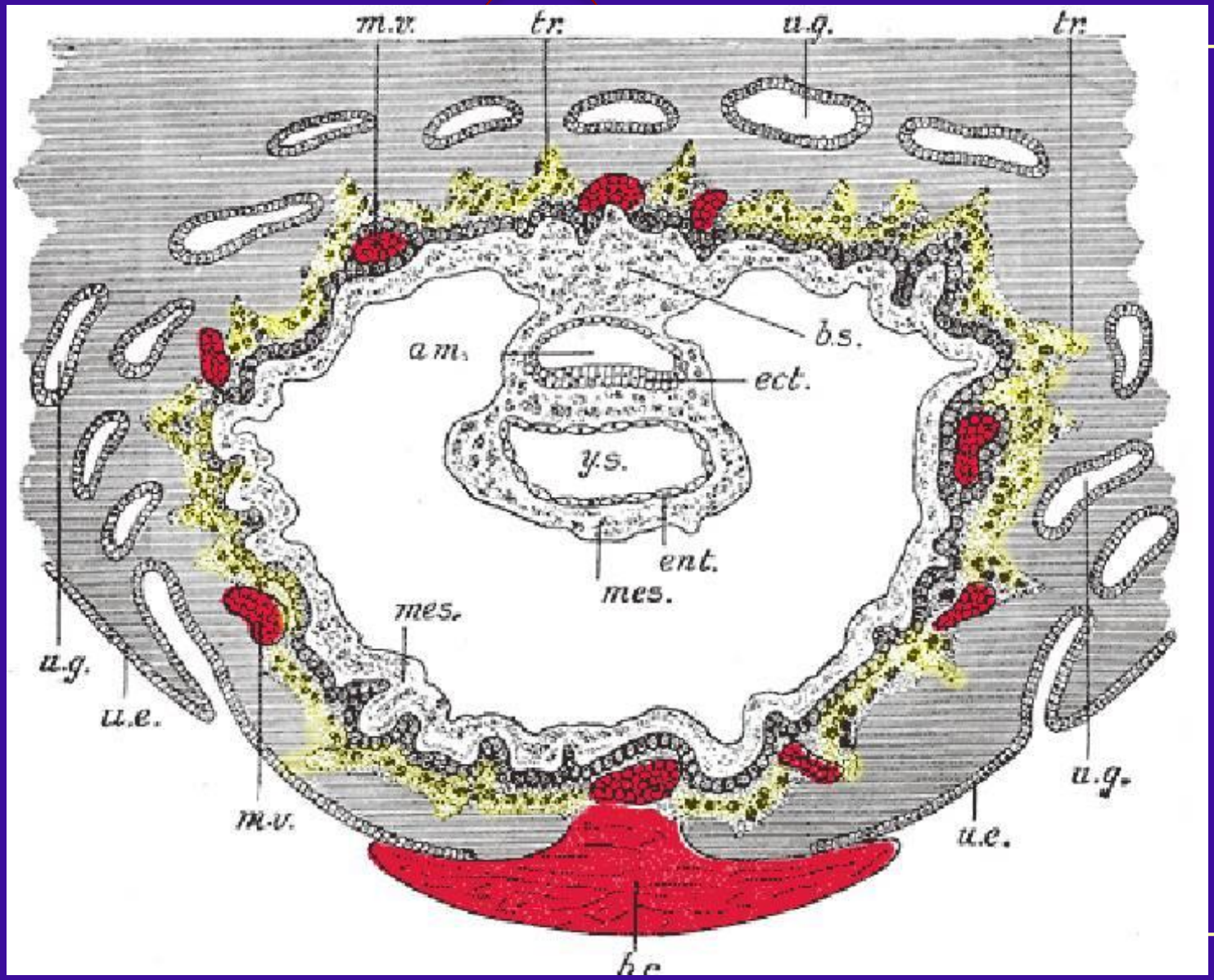
Upregulation Inflammatory Pathways NF-kB, IL-6, COX-2, 5-LOX

US Early Pregnancy



https://commons.wikimedia.org/wiki/File:Pregnancy_ultrasound_110302114249_1145551.jpg

What Is the Trophoblast ?



1918: Grays Anat: Section through ovum imbedded in uterine decidua.

b.s. Body-stalk.
ect. Embryonic ectoderm.
ent. Entoderm.
Mes Mesoderm
m.v. Maternal vessels.
tr. Trophoblast.
u.e. Uterine epithelium. u.g. Uterine glands.
y.s. Yolk-sac.

Hints: Cancer as a Trophoblastic Disease

- A Few Hints from Earlier Presentations:
- Hexokinase II is Embryonic Enzyme, not usually found in somatic cells (a few exceptions).
- Wnt Pathway is Embryonic Stem Cell pathway, usually Dormant in Somatic cells.
- Cancer/Testis Genes-Antigens, PLAC1 , HCG, PIBF
- 4th, 5th Pillar Immune Tolerance, Inflammation.

Old, Lloyd J. "Cancer is a somatic cell pregnancy." (2007)

Kalejs, Martins, and Jekaterina Erenpreisa. "Cancer/testis antigens and gametogenesis: a review and" brain-storming" session." Cancer cell international 5.1 (2005): 1-11.

Ma, JIachi, et al. "PLAC1 Enhances Metastatic Potential and is Associated with PI3K/AKT/NF-κB Signaling Pathway in Colon Cancer." (2019).

Liu, Chunfang, et al. "Abnormal gametogenesis induced by p53 deficiency promotes tumor progression and drug resistance." Cell discovery 4.1 (2018): 1-16.

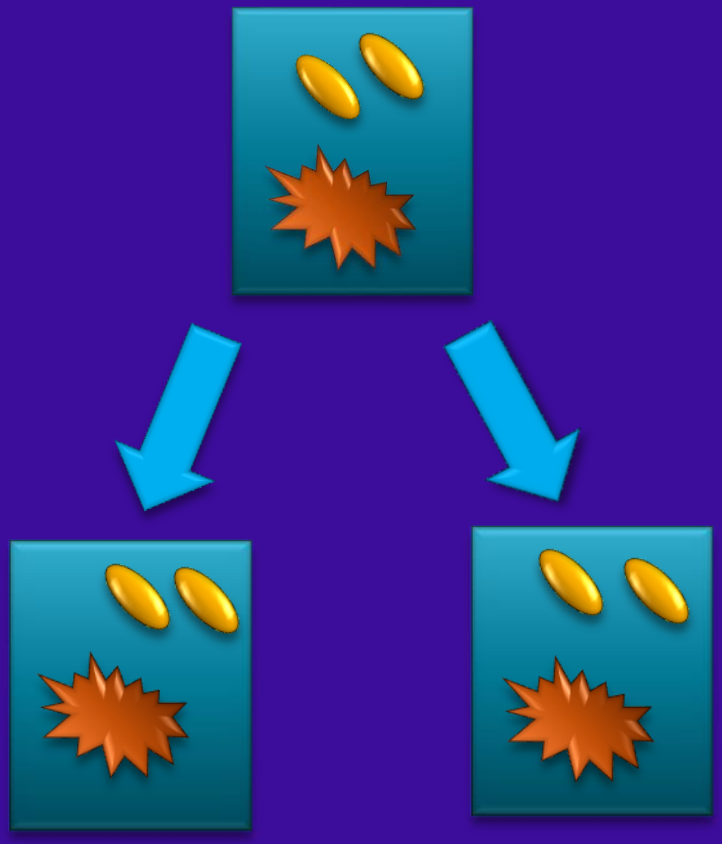
Cancer as a Trophoblastic Disease

- "The trophoblastic program is found in a strictly dormant state in every cell of the body, as evidenced through **reproductive cloning by transfer of the nucleus of a somatic cell into a denucleated oocyte**. It seems to be **reactivated** in cancer cells, endowing them with pro-survival and latent mesenchymal properties, and to play a key functional role in cancer tissue regulation, in particular in expansion of mesenchyme-related myofibroblastic **CAFs**".(Piechowski, 2019)

Piechowski, Jean. "Plausibility of trophoblastic-like regulation of cancer tissue." Cancer management and research 11 (2019): 5033.

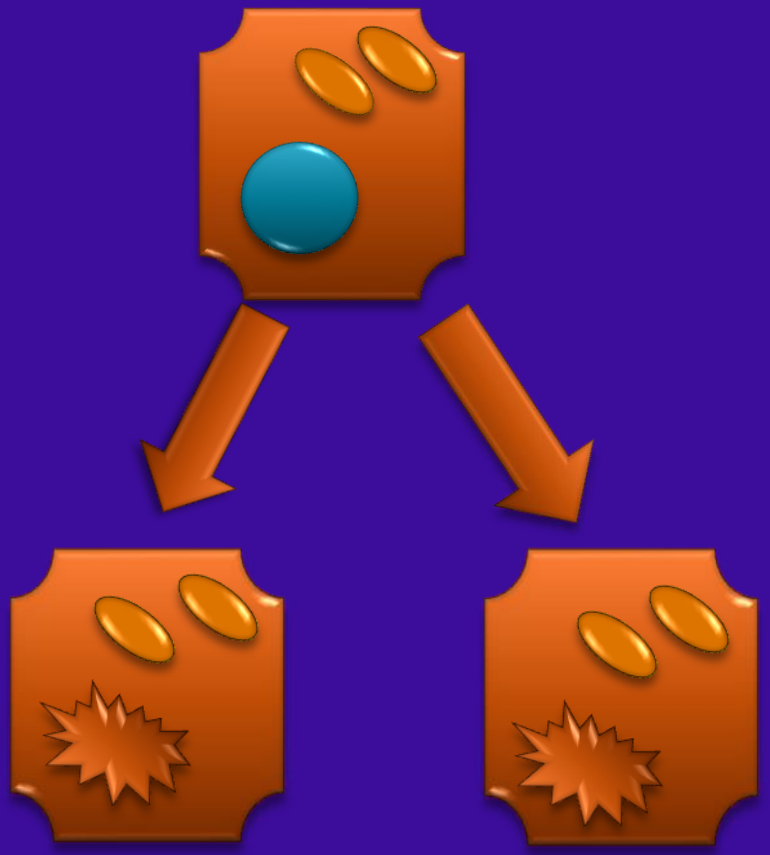
Clone a Normal Nucleus into Tumor Cell

Normal Cytoplasm, Cancer Nucleus



Normal Cells

Tumor Cell, Normal Nucleus



Tumor Cells / Death

Seyfried, Thomas N. "Cancer as a metabolic disease: " Carcinogenesis (2014):

Unified Mechanistic Framework

- "The concept in which the trophoblastic master genes act as master regulators of malignancy, would represent a unified mechanistic framework for the different types of cancer"... (Piechowski, 2019)
- TGF β - A Key Player in Trophoblast Implantation and Cancer Aggressivity

Piechowski, Jean. "Plausibility of trophoblastic-like regulation of cancer tissue." Cancer management and research 11 (2019): 5033.

The Mystery of Maternal-Fetal Tolerance

- 2020, Dr. Nada Al-Khunaizi: the exact mechanism of "maternal-fetal tolerance" is still a **mystery to medical science**:
- "Fetal antigens are allogeneic [foreign] to the mother's immune system and should theoretically elicit an immune response. The fact that this does not occur… without undergoing rejection by her immune system is a **scientific mystery**."

Al-Khunaizi, Nada Is there a Role for HLA-G in the Induction of Regulatory T cells during the Maintenance of a Healthy Pregnancy?." Am J Repro Immuno (2020)
Jørgensen, Nanna,. "The tolerogenic function of regulatory T cells in pregnancy and cancer." Frontiers in immunology 10 (2019): 911.

Cancer/Trophoblast - TGF-β

- "Increase of **TGF-β** also strengthens the **local immune tolerance**, this being true for cancer and trophoblast….Another aspect of malignancy is prometastatic action of **TGF-β** through its active promotion of EMT…a condition conducive to cell migration, just as in the case of the invasive extravillous cytotrophoblast." .(Piechowski, 2019)

Piechowski, Jean. "Plausibility of trophoblastic-like regulation of cancer tissue." Cancer management and research 11 (2019): 5033.

First, Third Trimesters - Inflammatory

- First trimester of pregnancy is a Pro-Inflammatory phase, responsible for “Morning Sickness”.
- 2nd Trimester Anti-Inflammatory.
- 3rd Trimester Pro-Inflammatory, Contraction of Uterus, Rejection of Placenta.

Mor, Gil, et al. "Inflammation and pregnancy: the role of the immune system at the implantation site." Annals of the New York Academy of Sciences 1221.1 (2011): 80.

First Trimester Inflammatory State REF

Chavan, Arun Rajendra, "The inflammation paradox in the evolution of mammalian pregnancy: turning a foe into a friend." Cur Op in Gen & Dev (2017)
Koga, Kaori, and Gil Mor. "Toll-like receptors and pregnancy: trophoblast as modulators of the immune response." J Ob Gyn Res 35.2 (2009): 191-202.
Sargent, I. L., et al. "Trophoblast deportation and the maternal inflammatory response in pre-eclampsia." J of reproductive immunology 59.2 (2003):
Lee, Seung Mi, et al. "Systemic inflammatory stimulation by microparticles derived from hypoxic trophoblast as a model for inflammatory response in preeclampsia." American journal of obstetrics and gynecology 207.4 (2012):
Fest, Stefan, et al. "Trophoblast–macrophage interactions: a regulatory network for the protection of pregnancy." Am j of repro immunology 57.1 (2007): 55-66.
Pijnenborg, Robert. "Implantation and immunology: maternal inflammatory and immune cellular responses to implantation and trophoblast invasion." Reproductive biomedicine online 4 (2002): 14-17.
Hamelin-Morrissette, Jovane, et al. "Leukemia inhibitory factor regulates the activation of inflammatory signals in macrophages and trophoblast cells." Molecular immunology 120 (2020): 32-42.

Early Pathologists Thought Cancer is a Trophoblastic Disease

- William Beard (1858–1924)
- William Donald Kelley, DDS (1926–2005)
- Nicholas Gonzalez, MD (1947, 2015) (68yrs)
  Denver, Boulderfest conference July 17-20 2008, Robert Crayhon: 1961-2010 age 49. colon cancer

5) Gonzales NJ, Isaacs LL. The Trophoblast and the Origins of Cancer: One Solution to the Medical Enigma of Our Time. New York, NY: New Spring Press; 2009.
6) Ross, Colin A. “The trophoblast model of cancer.” Nutrition and cancer 67.1 (2015): 61-67.

Enzyme Treatment of Cancer

- Day 56, Zymogen Granules Appear in Pancreas,
- At which time, Trophoblast Transforms from Aggressive to Benign (could it be the enzymes ?).
- 1906: William Beard Suggested Use of Digestive Enzymes (Trypsin) to Treat Cancer.
- Enzyme Rx Was Never Accepted by Mainstream Medicine.

9) Beard J. The Enzyme Treatment of Cancer. London: Chatto & Windus, 1911.
10) Beard, John. "The Action of Trypsin upon the Living Cells of Jensen's Mouse-Tumor." British medical journal 1.2351 (1906): 140.

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16) Mullen, Catherine A. “Analogies between trophoblastic and malignant cells.” American Journal of Reproductive Immunology 39.1 (1998): 41-49.
17) Lala, P. K., et al. “Human placental trophoblast as an in vitro model for tumor progression.” Canadian j of physiol and pharm 80.2 (2002):142-149.
18) Koslowski, M. “Placenta-specific gene ectopically activated in many cancers is essentially involved in malignant cell processes.” Can res 67.19 (2007): 95 syngeneic melanoma B16.” Cancer chemo and pharm 47.1 (2001): S16-S22.
Vazquez-Martin, A. "Somatic polyploidy is associated with the upregulation of c-MYC interacting genes and EMT-like signature." Oncotarget 7.46 (2016): 75235.
Erenpreisa, Jekaterina, et al. "The “virgin birth”, polyploidy, and the origin of cancer." Oncoscience 2.1 (2015): 3.
Liu, Jinsong. "The “life code”: A theory that unifies the human life cycle and the origin of human tumors." Sem in cancer biology. Vol. 60. Academic Press, 2020.
26) Cutfield, A: “Trypsin Treatment in Malignant Disease” Br Med J 5, 525, 1907.
27) Wiggin, FH: “Case of Multiple Fibrosarcoma of The Tongue, Use of Trypsin and Amylopsin in the Treatment of Malignant Disease” JAMA 47, 2003-08. 1906.
31) Wald, Martin, et al. “Mixture of trypsin, chymotrypsin and papain reduces formation of metastases and extends survival time of C 57 Bl 6 mice with

Both Cancer and Troph Cells Produce HCG

- Both Cancer and Trophoblast Cells produce HCG (Acevedo, 1995)
- The HCG test is both a pregnancy test and a cancer test.

11) Acevedo HF. Human chorionic gonadotropin-beta subunit gene expression in cultured human fetal and cancer cells. Cancer. 1995 Oct 15;76(8):1467.
13) Acevedo HF. Metastatic phenotype correlates with high expression of membrane-associated beta-HCG in vivo. Cancer. 1996 Dec 1; 78(11):2388
14) Regelson W. Have we found the “definitive cancer biomarker”? The diagnostic and therapeutic implications of HCG-beta expression as a key to malignancy. Cancer. 1995; 76:1299-301.

Both T and C / GLYCOLYSIS (+ Pet Scan)

- Cancer cells Share the Same Metabolic Activities as Trophoblast cells, i.e. the “Warburg Effect.”
- Both have High Glucose utilization, produce Lactate, Shifting from OXPHOS to GLYCOLYSIS. (Warburg Effect).
- Thrive in a low O_2 Environment.

Redel, B.K., **Glycolysis in preimplantation development is partially controlled by the Warburg effect.** Mol. Reprod. Dev. 79, 2012 262–271

Smith, Danielle G., and Roger G. Sturmey. "Parallels between embryo and cancer cell metabolism." Biochemical Society Transactions 41.2 (2013): 664-669.

Sawatzke, Alexander B., et al. "**PET/CT imaging reveals unrivaled placental avidity for glucose** compared to other tissues." Placenta 36.2 (2015): 115-120.

Warburg O. The Metabolism of Carcinoma Cell . J Cancer Res 1925; 9:148-163.

Old, Lloyd J. “Cancer is a Somatic Cell Pregnancy.” (2007): 19.

Bax, Bridget E "Energy metabolism and glycolysis in human placental trophoblast cells during differentiation." Biochimica et Biophysica Acta (1997): 283-292.

Both TR/CA Share Same Molecular Circuitry

- 2006, Dr. C. Ferretti:
- Activation of **PI3K/AKT** axis as **Central Feature**.
- Up-Regulation of Oncogene **C-Myc.**
- Up-Regulation of Growth Factors: **TGF-β**, **PDGF**, **EGFR, VEGF**, (many others).
- Proteolytic Enzymes: Matrix Metalloproteinases, (MMPs).
- Autocrine and Paracrine Loops: (EGFR), hepatocyte (HGFR), (VEGFR).

15) Ferretti, C., et al. "Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts." Human reproduction update 13.2 (2007): 121-141.

PI3K/Akt/mTOR inhibitors – All Activate Protective Autophagy

- Baicalein (Chi Skull)
- Boswellia
- Curcumin
- EGCG
- Ivermectin
- Itraconazole
- Metformin
- Parthenolide (Feverfew)
- Propranolol

- Pterostilbene
- **Quercetin**
- Silybin (milk thistle)
- Solomon's Seal
- Sulforaphane

PI3K/Akt/mTOR inhibitors Refs.

Sui, Xinbing "Baicalin induces apoptosis and suppresses cell cycle progression of lung cancer by downregulating Akt/mTOR signaling." Front in Mole Bio (2021)

Chaudhuri, D "Antiproliferative activity of sulforaphane in Akt-overexpressing ovarian cancer cells." Molecular cancer therapeutics 6.1 (2007): 334-345.

Borges, Gabriel"Curcumin downregulates PI3K–AKT–mTOR pathway and inhibits growth and progression in head and neck cancer cells." Phytother Res (2020)

Issinger, Olaf-Georg "Phytochemicals in cancer and their effect on the PI3K/AKT-mediated cellular signalling." Biomed & Pharm 139 (2021): 111650.

Wang, Wenping. "Itraconazole exerts anti-liver cancer potential through Wnt, PI3K/AKT/mTOR, and ROS pathways." Biomed & Pharma 131 (2020): 110661.

Zhao, Yan. "Metformin is associated with reduced proliferation in endometrial cancer by inhibiting PI3K/AKT/mTOR signaling." Gyne Endo 34.5 (2018): 428

Zhang, Xiaohong,"Ivermectin augments efficacy of cisplatin in epithelial ovarian cancer by suppressing Akt/mTOR signaling." Amer J med sci (2020): 123-129.

Li, Dongfan "Downregulation of miR-382 by propranolol inhibits progression of infantile hemangioma via AKT/mTOR pathway." Int j of molec med 39.3 (2017)

Zhang, Hong, et al. "Lectin PCL inhibits the Warburg effect of PC3 cells by combining with EGFR and inhibiting HK2." Oncology reports 37.3 (2017):

Identical Molecular Circuitry

- "Trophoblastic and cancer cells use comparable mechanisms implemented by **identical molecular circuitries** to achieve their proliferative, migratory and invasive processes." (Ferretti, 2007)

15) Ferretti, C., et al. "Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts." Hum repro upd 13.2 (2007). Carvajal, L "Autophagy Process in Trophoblast Cells Invasion and Differentiation: Similitude and Differences With Cancer Cells." Frontiers in Onc 11 (2021): 916.

PIBF Prevents Immune Rejection of Embryo

- 1985 Dr. Szekeres: **PIBF** was identified as a 34 kDa immunomodulatory molecule secreted by pregnancy lymphocytes.
- 2004: Dr. Lachman**: PIBF: " crucial role in preventing rejection of the embryo by the maternal immune response…**
- mRNA expression analyses revealed that **PIBF mRNA** was **overexpressed in highly proliferating cells** (breast cancer) **independent of the presence of PR…**
- Immunofluorescence microscopy revealed a **centrosomal** localization for the full-length PIBF, while the 35 kDa form showed a diffuse **cytoplasmic staining (microtubules)**."

Lachmann, Margit, et al. "PIBF is overexpressed in highly proliferating cells and associated with the centrosome." International journal of cancer 112.1 (2004): 51-60.
SZEKERES-BARTHO, "The Mechanism of the Inhibitory Effect of Progesterone on Lymphocyte Cytotoxicity: Amer J of Repro Immun and Micro 9.1 (1985): 15-18.

PIBF and Immune Evasion

- Pregnancy Lymphocytes Secrete PIBF, Suppresses the Immune System to Allow Pregnancy to Proceed.
- Cancer cells Secrete PIBF, suppresses NK Killer cells (Immune System), allowing evasion of immune surveillance.
- Blocking the PR (Progesterone Receptors) on lymphocytes with RU-486 (Mifepristone) turns off PIBF production, restores immune competency.

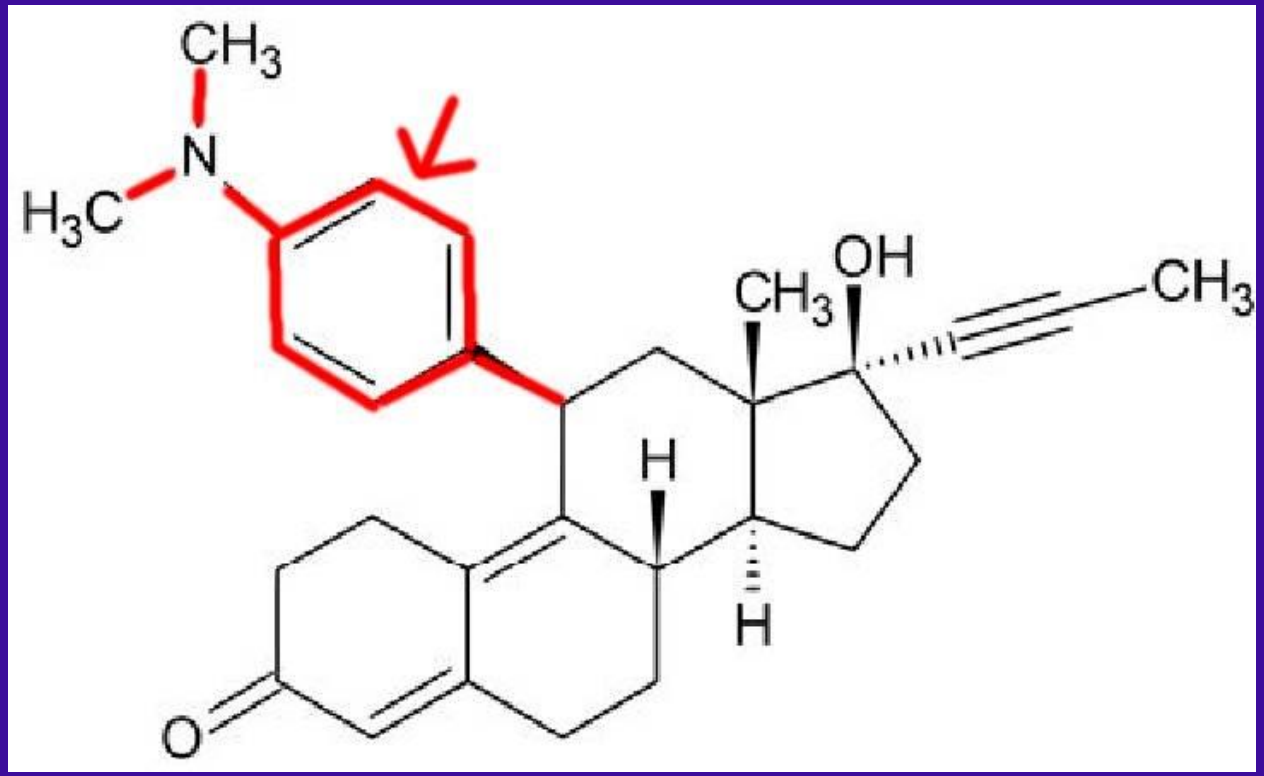
1) Szekeres-Bartho, Julia, and Beata Polgar. "PIBF: the Double Edged Sword. Pregnancy and Tumor." American Journal of Reproductive Immunology 64.2 (2010): 77-86.
2) Halasz, Melinda, et al. "Progesterone-induced blocking factor differentially regulates trophoblast and tumor invasion by altering matrix metalloproteinase activity." Cellular and molecular life sciences 70.23 (2013): 4617-4630.

RU-486 Blocks PIBF

- 1982, Mifepristone Synthesized by Roussel-Uclaff (France) as a Progesterone Receptor Blocker.
- “Abortion Pill,” prescribed (only) at abortion clinics to induce abortion.
- Restricted in the U.S. and Europe , Use requires IND application with FDA or Ongoing Clin Trial.
- Progesterone backbone with dimethyl-amino-benzene added at the 11th position.

3) Chen, Jianzhong, et al. “The unique pharmacological characteristics of mifepristone (RU486): from terminating pregnancy to preventing cancer metastasis.” Medicinal research reviews 34.5 (2014): 979-1000.

Mifepristone Chemical Structure



Progesterone backbone with dimethyl-amino-benzene added at the 11th position.

Chen, Jianzhong, et al. “The unique pharmacological characteristics of mifepristone (RU486): from terminating pregnancy to preventing cancer metastasis.” Med res reviews 34.5 (2014): 979-1000.

Abortion Drug for “Somatic Pregnancy”

- 2021 Dr Liu:
- “…Targeting the key events of somatic pregnancy is likely a better therapeutic strategy for cancer treatment than directly targeting cell mitotic proliferation (chemo), especially for those tumors with p53 inactivation.” (Liu, 2021)
- Abort the “Somatic Pregnancy” !!

Liu, Chunfang, et al. "The Foundational Framework of Tumors: Gametogenesis, p53, and Cancer." Sem in Cancer Biology. 2021.
Old, Lloyd J. "Cancer is a somatic cell pregnancy." (2007).

Complete Remission Leukemia

- 2014: Dr Jerome Check Cooper Inst., IND, Clinical Trial, Case Report:
- Rapidly Advancing Lymphocytic Leukemia in Elderly Female.
- Pt. Declined Chemotherapy.
- Rx: Mifepristone 200 mg daily.
- Achieves 12 month complete remission.

17) Check, Jerome H., et al. “Mifepristone Causing Complete Remission of Rapidly Advancing Leukemia with Measurement of Progesterone-induced Blocking Factor.” Anticancer res (2014) 2413.

Advanced Lung Cancer

- 2016, Dr. Jerome Check Case Report:
- Moribund Woman w/ Untreated Metastatic Lung Cancer, Given Mifepristone.
- Regression of All Lung Lesions.
- Remaining in Remission for Over 5 Years.
- No Adverse Drug Effects. (23)

23) Check, Jerome H., et al. “Long-term high-quality survival with single-agent mifepristone treatment despite advanced cancer.” Anticancer Research 36.12 (2016): 6511-6513.

Pancreatic CA / Osteosarcoma

- 2020, Dr. Check Case Reports:

Check, Jerome H., et al. "Treatment with mifepristone allows a patient with end-stage pancreatic cancer in hospice on a morphine drip to restore a decent quality of life." Anticancer Research 40.12 (2020): 6997-7001.

Check, Jerome H., et al. "Palliative Benefits of Oral Mifepristone for the Treatment of Metastatic Fibroblastic Osteosarcoma." Anticancer Research 41.4 (2021): 2111-2115.

PIBF Breast Cancer Cell Study

- 2004 Dr Lachman: Studied PIBF in highly proliferating MCF-7 (breast cancer) cells.
- PIBF mRNA overexpressed.
- PIBF is associated with the Centrosome and Microtubule system.
- Treatment with Nocodazole [5 µg/ml 4 hr]: "Disappearance of the Perinuclear PIBF dots, which Paralleled Disintegration of the Golgi Apparatus."

24) Lachmann, Margit, et al. "PIBF (progesterone induced blocking factor) is overexpressed in highly proliferating cells and associated with the centrosome." International journal of cancer 112.1 (2004): 51-60.

Mifepristone Unavailable, Try Mebendazole (Fenben)

- Mifepristone Restricted, Unavailable?
- Try Mebendazole (FenBen) (similar to Nocodazole), may also reduce PIBF.
- Both are Microtubule Inhibitors.
- Both Synergize with Autophagy Inhibitors.
- Both Restore Anti-Tumor Immunity.

Lachmann, Margit, et al. “PIBF (progesterone induced blocking factor) is overexpressed in highly proliferating cells and associated with the centrosome.” Int J Cancer 112.1 (2004)

Evasion of Immune Surveillance

- In 2019, Dr. Miao used Squamous Cell Cancer to study how cancer stem cells evade the immune system, finding that cancer stem cells acquire the CD80 surface protein, which directly blocks cytotoxic T cells from killing the cancer cells. (20)

20) Miao, Yuxuan, et al. “Adaptive immune resistance emerges from tumor-initiating stem cells.” Cell 177.5 (2019): 1172-1186.
Olivares, Enrique Ga, et al. "Cultured human decidual stromal cells express B7-1 (**CD80**) and B7-2 (CD86) and stimulate allogeneic T cells." Biology of reproduction 57.3 (1997): 609-615.

Evasion of Immune Surveillance Exosomal FOXP3 protein

- 2019, Dr. A. Dutta, Breast Cancer Stem Cells Generated Their Own Immunosuppressive T-Reg Cells by Secretion of Exosomes into TME containing FOXP3 protein, which binds to a Receptor on the T-Cell, which then Converts the T-Cell into an Immuno-Suppressive T-Reg Cell.(Dutta.2019)

Dutta A. A new insight into tumour immune-evasion: Crosstalk between cancer stem cells and T regulatory cells. Annals of Oncology. 2019 Nov 1;30

Eileen. "**Trophoblast cells** producing HCG promote conversion of CD4+ FOXP3– T cells into CD4+ FOXP3+ regulatory T cells and foster T cell suppressive activity." Biol Repro 94.5 (2016): 106

Evasion of Immune Surveillance Exosomes

- Both Cancer and Trophoblast Cells secrete Exosomes to Modulate T-Cell Signaling.
- "These data suggest that tolerance induction may occur through the generation of exosomes, **as also observed for pregnancy- and cancer-associated exosomes**." (Marleau, 2012)

Marleau, Annette M., et al. "Exosome removal as a therapeutic adjuvant in cancer." J of translational med 10.1 (2012): 1-12.

Evasion of Immune Surveillance Cancer Stem Cells

- 2019, Dr. Alex Miranda studied 21 solid cancers, finding “stemness” to be associated with anti-cancer immunity.
- “molecular pathways involving WNT/B-catenin,c-MYC…..have been implicated in the inhibition of antitumor immunity, yet they also play important roles in stem cell maintenance”

Miranda, Alex, et al. "Cancer stemness, intratumoral heterogeneity, and immune response across cancers." Proceedings of the National Academy of Sciences 116.18 (2019): 9020-9029.

Immune Modulators

AHCC / Beta-Glucans
Artemisinin/ Artesunate
Celecoxib Cox-2 Inhibitor
Coley's Toxins
Cimetidine H2R Antag, Antacid
DCA (All Glycolysis Inhibitors - Reduces Lactate in TME.)
Diclofenac NSAID
Dipyridamole

Iodine (Molecular)
LDN
Mebendazole
Metformin
Mifepristone (RU-486)
Probiotics
Propranolol
Retinoids (Vitamin A, ATRA, Accutane, Vesinoid)
Vitamin D3

Restoring the Host Immune System

- Coley's Toxins (Bacterial)
- RNA Viruses
- The Mouse That Killed Cancer
- Cimetidine
- Beta Glucans
- Others: D3, Iodine, LDN, etc.
- Modern Immunotherapy, Check Point Inhib, Lenalidomide, CAR-T Therapy.

The Father of Immunotherapy

- William Coley (1890–1936) New York Orthopedic Surgeon.
- 1891: Of 90 amputations for Osteosarcoma, only one survivor, pt contracted Erysipelas.
- Coleys Toxins : Heat Killed Streptococcus pyogenes and Serratia marcescens.
- 1000 Pts. Injected, 150 papers.
- 1963 Banned by FDA, IND.

Photo courtesy of : https://www.biologicalmedicineinstitute.com/william-bradley-coley

Wiliam Coley References

30) Coley, William B. “The Treatment of Inoperable Sarcoma with the Mixed Toxins of Erysipelas and Bacillus Prodigiosus: One Hundred and Forty Cases.” Journal of the American Medical Association 31.9 (1898): 456-465.
31) Coley, William B. “The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of the Streptococcus erysipelas and the Bacillus prodigiosus).” Proc Royal Society of Medicine 3.Surg_Sect (1910): 1-48.
Coley, William B. "The Classic: The Treatment of Malignant Tumors by Repeated Inoculations of Erysipelas: With a Report of Ten Original Cases." Clinical Orthopaedics and Related Research (1976-2007) 262 (1991): 3-11.

RNA Viruses with Anti-Cancer Activity

- Mumps
- Newcastle disease virus
- Measles virus
- Vesicular stomatitis virus
- Influenza,
- Reovirus, and
- Poliovirus.

Russell, Stephen J. "RNA viruses as virotherapy agents." Cancer gene ther (2002): 961-966.

Regression of Cancer with Measles Refs

Bluming, AvrumZ,"Regression of Burkitt's lymphoma in association with measles infection." Lancet 298.7715 (1971): 105-106

Grote, Deanna, "Live attenuated measles virus induces regression of human lymphoma xenografts in immunodeficient mice." Blood 97.12 (2001): 3746-3754.

Grote, Deanna"Neutrophils contribute to the measles virus-induced antitumor effect: enhancement by granulocyte macrophage colony-stimulating factor expression." Can res 63.19 (2003):

Peng, Kah-Whye, et al. "Systemic therapy of myeloma xenografts by an attenuated measles virus." Blood, 98.7 (2001): 2002-2007.

Peng, Kah-Whye, et al. "Intraperitoneal therapy of ovarian cancer using an engineered measles virus." Can res 62.16 (2002)

McDonald, Cari J., "A measles virus vaccine strain derivative as a novel oncolytic agent against breast cancer." Breast cancer res and treat 99.2 (2006): 177-184.

The Mouse that Killed Cancer

Mouse Sarcoma S180-Induced Ascites: one of the most aggressive transplantable cancers in experimental mouse models.

https://commons.wikimedia.org/wiki/File:Mouse_in_a_cage.jpg

The SR/CR Mouse

- "The Mouse that Killed Cancer."
- 2003, Wake Forest Med School in N. Carolina.
- Innate T-Cell Immunity to Cancer.
- Genetic Trait.
- Immunity Transferable to Wild Mice by Transfusing T Cells from SR/CR Mouse.

SR/CR Mouse References

1) Cui, Zheng, “Spontaneous regression of advanced cancer: a genetically determined, age-dependent trait in mice.” Proc Nat Acad Sci 100.11 (2003): 6682-6687.
2) Hicks, Amy M., et al. “Effector mechanisms of the anti-cancer immune responses of macrophages in SR/ CR mice.” Cancer Immunity Archive 6.1 (2006): 11.
3) Hicks, Amy M.“Transferable anticancer innate immunity in spontaneous regression/complete resistance mice.” Proc Nat Acad of Sci 103.20 (2006): 7753-7758.
4) Stehle, John R.“Impact of sex, MHC, and age on the therapeutic effect of transferred leukocytes from cancer-resistant SR/CR mice.” BMC cancer 9.1 (2009): 328.

Cimetidine H2 R Blocker

- 1970 Discovered by Smith Kline & French.
- 1979 Tagamet © FDA approved for Heartburn and Gastric Ulcer.
- Binds to H2 Receptors in Parietal Cells of Stomach, Blocks Gastric Acid Secretion.
- 1989 World No. 1 Drug, 1 Billion in sales.
- Now OTC, replaced by PPI's.
- Unexpectedly Found to Stimulate Host Immune Cell Expansion, and Reverse Tumor Immune Evasion.
- Case Reports of Cancer Remission (G Lymphoma)

Cimetidine (Tagamet) MOA

- In 2006, Dr. Takahashi :PBMC 10 volunteers.
- via H2R, CIM induces IL-18 Production in Monocytes.
- Interleukin-18 (IL-18) is an Immuno-Stimulatory Cytokine with Anti-Cancer Activity. (Takahashi, 2006)(Xiong, 2019)

Takahashi, Hideo “Cimetidine induces interleukin-18 production through H2-agonist activity in monocytes.” Molec pharm 70.2 (2006): 450-453.
Xiong, Donglan, et al. "Antitumor activity of interleukin-18 on A549 human lung cancer cell line." J of cancer research and therapeutics 15.7 (2019): 1635.

Cimetidine Anti-Histamine Anti-Cancer Effects

- 2014, Dr. Pan Pantziarka Review:
- Immuno-Modulatory. Increased NK Cells, Reduced T Reg. Shift T2 to T1.
- Anti-Proliferative.
- Anti-Angiogenic Effects.
- Inhibition of Tumor Cell Adhesion.

24) Pantziarka, Pan,"Cimetidine as an anti-cancer agent."(2014).
25) Kubecova, M "Cimetidine: An anticancer drug?" Euro J Pharm Sci 42.5 (2011): 439-444.
26) Lefranc, F Cimetidine for glioblastoma. Int j onc 28.5 2006 ,1021.

Cimetidine Cancer Cell Types Studied

- Remission in Gastric Lymphoma Case Reports (Strauchen, 1987)
- Remission in Leukemia CR (Ankerst, 1984)
- Renal Cell Cancer 2 Complete Remissions lasting 26 and 33+ months, 38 pts treated.(Inhorn, 1992)
- Lung Cancer (Zheng, 2013)
- Ovarian Cancer (Kikuchi,1985) Mouse Xeno.
- Many Clin Trials: Gastric CA, Colon CA, Melanoma, Metastatic renal CA (Lefranc, 2006)
- Glioblastoma (In vivo in vitro) (Lefranc, 2006)

Cimetidine References

1) Strauchen, James A., et al. “Spontaneous regression of gastric lymphoma.” Cancer 60.8 (1987): 1872-1875.
2) Ankerst, Jaro, et al. “Complete remission in patient with acute myelogenous leukemia treated with leukocyte α-interferon and cimetidine.” Cancer Imm, Immunotherapy 17.1 (1984): 69-71.
3) Inhorn, L., et al. “High-dose cimetidine for the treatment of metastatic renal cell carcinoma. A Hoosier Oncology Group study.” American journal of clinical oncology 15.2 (1992): 157-159.
6) Lefranc, Florence “Cimetidine, unexpected anti-tumor agent, for the treatment of glioblastoma.” Int j of onc 28.5 (2006): 1021-1030.
7) Zheng, Yisheng, et al. “Cimetidine suppresses lung tumor growth in mice through proapoptosis of myeloid-derived suppressor cells.” Molecular immunology 54.1 (2013): 74-83.
12) Kikuchi, Yoshihiro, et al. “Effects of cimetidine on tumor growth and immune function in nude mice bearing human ovarian carcinoma.” J of Nat Cancer Inst 74.2 (1985): 495-498.

Cimetidine for Cutaneous Warts (HPV)—Enhancing Cell-Mediated Immunity

- 2018, Das: 8 Pediatric Heart Transplant Pts Multiple Cutaneous Warts (HPV).
- All Immunosuppressed with Tacrolimus, (Mycophenolate or AZT).
- 7 of 8 Had Complete Remission with CIM.
- Safe to use High Dose Cimetidine (30–40 mg/kg/day) in 2 divided doses for 5–6 months.

Das, B "Cimetidine for cutaneous warts in pediatric heart transplant recipients." Med Sci 6.2 (2018): 30.

Cimetidine for Herpes Viruses

29) Kapińska-Mrowiecka, M. Efficacy of cimetidine in treatment of Herpes zoster in the first 5 days Polski tygodnik lekarski (1996
30) Komlos, Luise, et al. “In vitro cell-mediated immune reactions in herpes zoster patients treated with cimetidine.” Asian Pacific journal of allergy and immunology 12 (1994): 51-51.
33) Hayne, S. T.“Herpes zoster: treatment w cimetidine.” Can Medical Association Journal 129.12 (1983): 1284.
34) Cohen, Philip “Herpes simplex virus infections and cimetidine therapy.” J of the Amer Acadof Derm 19.4 (1988): 762-763.
35) Kurzrock, R “Cimetidine therapy of herpes simplex virus infections in immunocompromised patients.” Clinical and experimental dermatology 12.5 (1987): 326-331.
36) Levy, D. W., “Cimetidine in the treatmentof herpes virus infections.” South African medical journal 58.3 (1980): 112-116.
37) Wakefield, Denis. “Cimetidine in recurrent genital herpes simplex infection.” Ann of internal med 101.6 (1984): 882

Cimetidine Adverse Effects

- Inhibitor of Cytochrome P450.
- Most common AEs: headache, dizziness, diarrhea, and rash.
- Rare (at high doses): Gynecomastia, Reversible Impotence. Leukopenia.
- Malabsorption of B12, Fe and Ca+2 from Prolonged Suppression of Gastric Acid.

Pantziarka, P "(ReDO)—Cimetidine as an anti-cancer agent.“ Ecancermedicalscience 8 (2014).

Cimetidine / Mebendazole

- 1987, Dr. Bekhti: 3 pts w/ Hepatic Echinococcal cyst.
- Mebendazole (1.5 Grams TID x 30 Days)
- CIM (1200 mg/day x 30 Days),
- 1 Hr Serum Conc. of MB Doubled.
- Complete Resolution of the previously unresponsive liver cysts.

38) Bekhti, A., Cimetidine increases serum mebendazole concentrations in treatment of hepatic hydatid cysts." Brit j clin pharm 24.3 (1987): 390-392.

Dietary Beta Glucans

- Edible Mushrooms, Reishi, Maitake, and Shiitake.
- Baker's Yeast and Cereals .
- PAMPS- Pathogen Associated Molecular Patterns (Long Chains of Polysaccharides).
- Immune Stimulating Effects.
- Replacement for Coley's Toxins ?

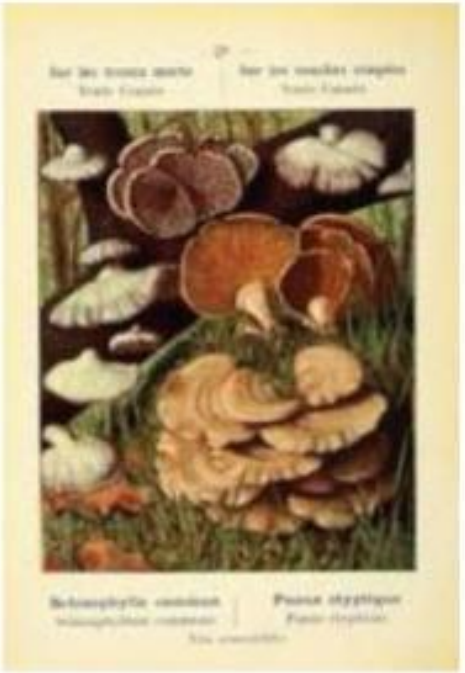
Del Cornò, "Shaping the Innate Immune Response by Dietary Glucans Any Role in Control of Cancer?. Cancers 12.1 (2020) 155.

Mushrooms Containing β-glucans

Pleurotus ostreatus
(Oyster mushroom)
Pleuran

Grifola frondosa
(Maitake)
Grifolan

Schizophyllum commune
(Split Gill mushroom)
Schizophyllan



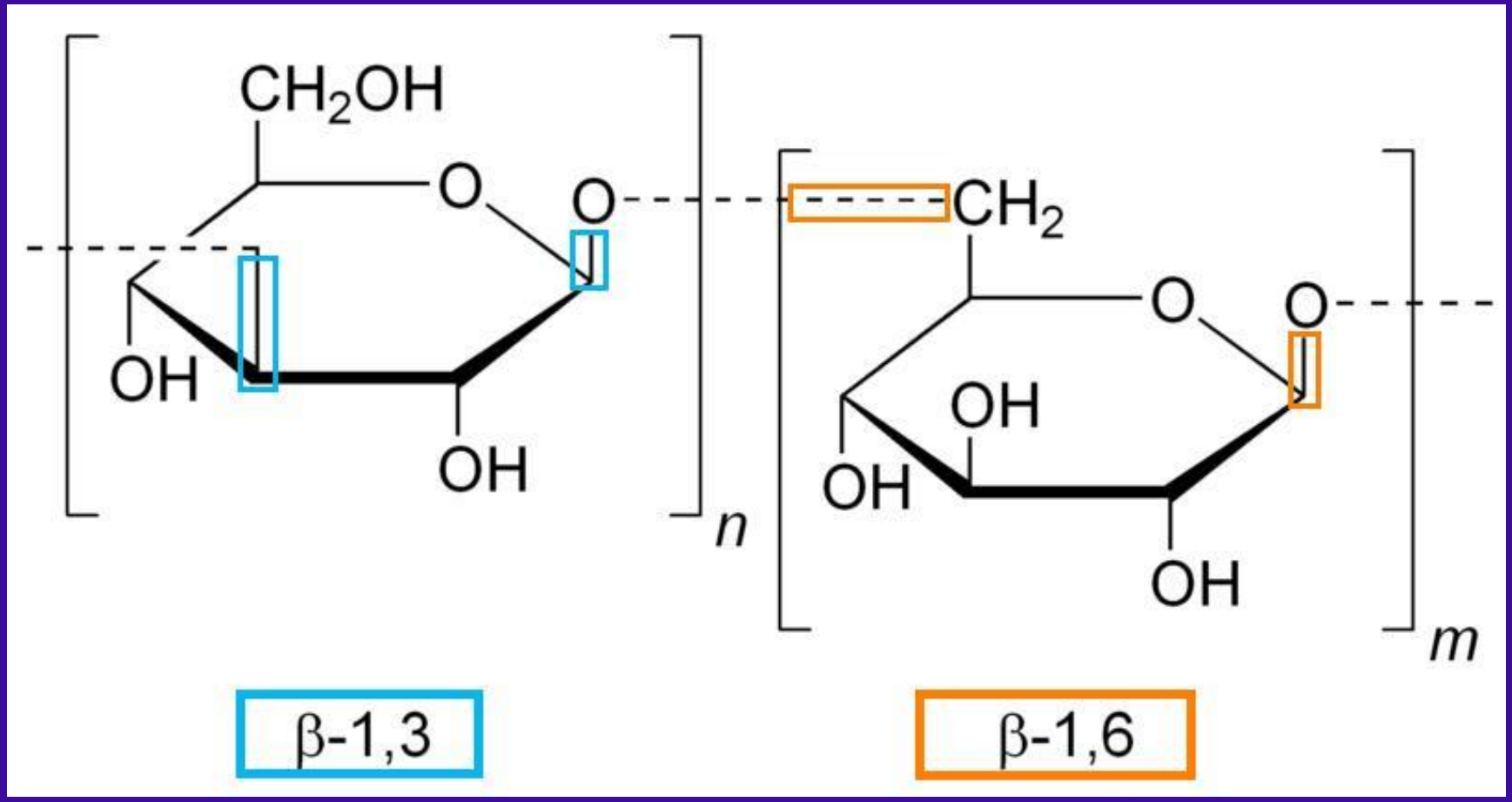
Sclerotium rolfsii
Scleroglucan

Lentinus edodes
(Shitake mushroom)
Lentinan

Ganoderma lucidum
(Reishi)
GI - 1

Hericium erinaceus
Lion's Mane

β-Glucans – Polysaccharide Chains



https://commons.wikimedia.org/wiki/Category:Beta-glucans#/media/File:BetaGlucanGuide.jpg

AHCC Prostate CA Case Report

- 2009, Dr. Jeffrey Turner: 66-year-old Male with Metastatic Prostate Cancer.
- PSA 2,000 w/ Blastic Mets to LS Spine, L Hip Pain
- Rx Androgen Blockade , after 4 Mo., PSA =4
- Rx DC'd, then after 10 Mo, PSA = 69.
- AHCC started by pt., PSA dropped to 1.5, Stable disease, improved ambulation.

Turner, J Dramatic PSA response with activated hemicellulose compound in metastatic castration-resistant prostate cancer." Anti-cancer drugs 20.3 (2009)

Fifth Pillar

Upregulation Inflammatory Pathways NF-kB, IL-6, COX-2, 5-LOX

NF-kB Inhibitors

- Artemisinin/Artesunate
- Aspirin
- Azithromycin
- Baicalein Chinese Skullcap
- Berberine
- Boswellia (Frankincense)
- CBD Cannabidiol
- Clarithromycin
- Curcumin
- Doxycycline Potent Inhibitor
- Fenofibrate
- Ivermectin
- Mefloquine
- Niclosamide
- Parthenolide (Feverfew)
- Pterostilbene
- Statin Drugs
- Sulfasalazine
- Sulforaphane
- Thymoquinone

COX-2 Inhibitors

- Regulation of COX-2 Protein Expression is Downstream to the Nuclear Factor Kappa B pathway.
- Aspirin Irreversible Inhibitor of COX-1 and COX-2
- Celecoxib COX-2 Inhibitor
- Diclofenac Nonspec COX Inhib, c-Myc and Glycolysis)
- Dipyridamole (Inhib NF-kB, and then COX2)
- Sulindac Nonspecific COX Inhibitor, suppresses 5-LOX.

Park, Mi Hee, "Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches." Cells 5.2 (2016): 15.
St-Germain, Marie-Eve “Regulation of COX-2 protein expression by Akt in endometrial cancer cells is mediated through NF-κB/IκB pathway.” Molecular Cancer 3.1 (2004): 7.

Celecoxib COX-2 Inhibitor

- 1998 FDA-approved for rheumatoid arthritis and osteo-arthritis.
- 1999 for prevention of FAP (familial adenomatous polyposis) precursor for colon cancer.
- 2005 for ankylosing spondylosis
- 2006 for juvenile rheumatoid arthritis.

Hashemi Goradel, Nasser, et al. “Cyclooxygenase-2 in cancer: A review.” Journal of cellular physiology 234.5 (2019): 5683-5699.

Celecoxib COX-2 Inhibitor

- Very Useful as Adjuvant with Chemotherapy and/or Radiotherapy. (Hashemi, 2019)
- Very Useful in Hematologic Cancers which Upregulate COX2. Bernard 2008
- Useful in Breast Cancer (Shaashua, 2017)

Hashemi Goradel, Nasser, et al. “Cyclooxygenase-2 in cancer: A review.” Journal of cellular physiology 234.5 (2019): 5683-5699.
Bernard, M. P., et al. “Targeting cyclooxygenase-2 in hematological malignancies: rationale and promise.” Current pharmaceutical design 14.21 (2008): 2051-2060.
Shaashua, Lee, et al. "Perioperative COX-2 and β-adrenergic blockade improves metastatic biomarkers in breast cancer patients in ph-II randomized trial." Clin Can Res (2017): 4651-4661.

Celecoxib Anti-Cancer Effects

- 1) Inhibition of Angiogenesis by reducing VEGF [Vascular Endothelial Growth Factor]
- 2) Reduces invasion by reduction in MMP [Matrix Metallo-Proteinase]
- 3) Inhibition of proliferation by reduction in NF-kB, STAT3, MEK and Cyclins, Upregulation of p27 [tumor suppressor gene].

Bernard, M. P., et al. “Targeting COX-2 in hematological malignancies.” Curr pharm design 14.21 (2008): 2051-2060.

Celecoxib Anti-Cancer Effects

- 4) Impairs survival by Downregulating BCL-2 [anti-apoptotic protein], NF-kB, Glutathione, AKT, increasing reactive oxygen species (ROS), Caspase Activity.
- 5) Significantly Attenuates Glutathione Levels.
- 6) Enhances Host Immune Function.
- 7) Reduced T-Reg Cells [immunosuppressive cells]. (Bernard, 2008)

Bernard, M. P "Targeting cyclooxygenase-2 in hematological malignancies (2008): 2051-2060.

Celecoxib COX2 Inhibitor

- Dr Sareddy 2013: Glioblastoma Cells:
- Celecoxib Targets Cancer Stem Cells, Wnt/Beta Catenin/TCF Pathway.

Sareddy, Gangadhara Reddy, et al. “Nonsteroidal anti-inflammatory drugs diclofenac and celecoxib attenuates Wnt/β-catenin/Tcf signaling pathway in human glioblastoma cells.” Neurochemical research 38.11 (2013): 2313-2322.

21) Maier, Thorsten Jürgen, et al. “Targeting the Beta-Catenin/APC pathway: a novel mechanism to explain the cyclooxygenase-2-independent anticarcinogenic effects of celecoxib in human colon carcinoma cells.” The FASEB journal 19.10 (2005): 1353-1355.

Celecoxib PI3K/Akt/mTOR

- Celecoxib Blocks the phospho-inositol-kinase-Akt/mTOR (PI3K/Akt/mTOR) pathway, a “master regulator” for cancer cell survival, growth, and proliferation,
- Also a CSC pathway.
- Note: All OXPHOS Inhibitors are Wnt/CSC pathway inhibitors. All OXPHOS inhibitors also Inhibit mTOR, Inducing “Protective Autophagy.”

Celecoxib PI3K/Akt/mTOR REF.

34) Hsu, Ao-Lin, “The COX-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2.” J Biol Chem (2000):
35) Liu, Min,“Celecoxib regulates apoptosis and autophagy via PI3K/Akt signaling pathway in gastric cancer cells.” Int j mol med 33.6 (2014): 1451-1458.
36) Leng, Jing, et al. “COX-2 promotes hepatocellular carcinoma cell growth through Akt activation: evidence for Akt inhibition in celecoxib induced apoptosis.” Hepatology 38.3 (2003): 756-768.
37) Glynn, Sharon A.,“COX-2 activation is associated with Akt phosphorylation and poor survival in ER-neg, HER2-pos breast cancer.” BMC cancer 10.1 (2010)
Setia, Shruti. "The PI3K/Akt pathway in colitis associated colon cancer and its chemoprevention with celecoxib, a Cox-2 selective inhibitor." Biomed & Pharm 68.6 (2014): 721-727.

Quercetin - Natural PI3K/Akt/mTOR Inhibitor

Granato, Marisa, "Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways." The J nut biochem 41 (2017): 124-136.
Jia, Lijun, et al. "Quercetin suppresses the mobility of breast cancer by suppressing glycolysis through Akt-mTOR pathway mediated autophagy induction." Life sciences 208 (2018): 123-130.
Song, Jing, et al. "Effects of Quercetin on Autophagy and Phosphatidylinositol 3-kinase/Protein Kinase B/Mammalian Target of Rapamycin Signaling Pathway in Human Prostate Cancer PC-3 Cells." Acta Academiae Medicinae Sinicae 42.5 (2020): 578-584.
Li, Xiuli, et al. "Quercetin suppresses breast cancer stem cells (CD44+/CD24−) by inhibiting the PI3K/Akt/mTOR-signaling pathway." Life sciences 196 (2018): 56-62.
Granato, Marisa “Reduction of c-Myc expression and PI3K /AKT/mTOR signaling by Quercetin induces strong cytotoxic effect against Burkitt’s lymphoma." Int j biochem cell biology (2016): 393

Celecoxib Synergies w/

- Atorvastatin
- Auranofin
- Curcumin
- Metformin
- Quercetin
- Tocotrienol

Celecoxib Synergies refs

Yu, C.-P. Celecoxib and quercetin induce apoptosis in human hepatocarcinoma. Biomed. Res. 2017, 28, 3465–3470

Shirode, Amit B. "Synergistic anticancer effects of combined γ-tocotrienol and celecoxib associated with suppression in Akt and NFκB signaling." Biomed & Pharmacother 64.5 (2010): 327-332.

Hu, Jun-Wen, et al. "Novel combination of celecoxib and metformin improves the antitumor effect by inhibiting the growth of Hepatocellular Carcinoma." Journal of Cancer 11.21 (2020): 6437.

Han, Yi, et al. "Synergy between auranofin and celecoxib against colon cancer in vitro and in vivo through a novel redox-mediated mechanism." Cancers 11.7 (2019): 931.

Xiao, Hang, "Combination of atorvastatin and celecoxib synergistically induces cell cycle arrest and apoptosis in colon cancer cells." Int j cancer 122.9 (2008)

Lev-Ari, Shahar, et al. "Celecoxib and curcumin synergistically inhibit the growth of colorectal cancer cells." Clinical Cancer Research 11.18 (2005): 6738-6744.

Alqahtani, A. M., "Curcumin-Celecoxib: a synergistic and rationale combination chemotherapy for breast cancer." Europ rev med and pharma sci 25.4 (2021

Celecoxib w/ Chemo: Curative Efficacy

- 2011 Dr Jin, and 2016, Dr. Lisa Pang:
- COX-2 plays an important role in CSC survival and repopulation of CSCs after chemotherapy.
- Inhibition of COX-2 prevents this chemotherapy induced cancer stem cell survival and repopulation, potentially leading to “Curative Efficacy”.

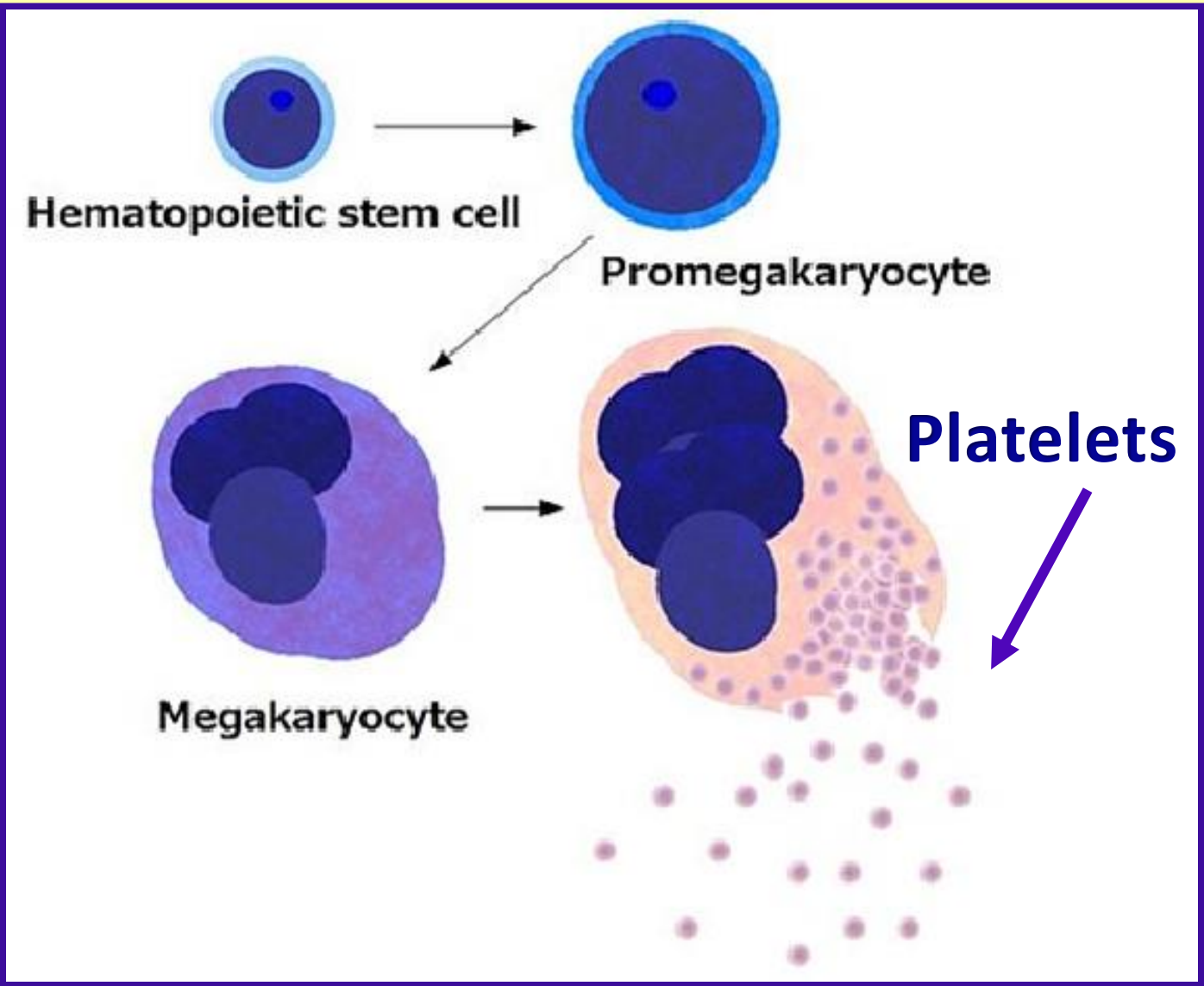
Jin, C. H. "Observation of curative efficacy following combination chemotherapy with celecoxib in advanced colorectal cancer." J of Int Med Res 39.6 (2011
Pang, Lisa Y., “Cyclooxygenase-2: a role in cancer stem cell survival and repopulation of cancer cells during therapy.” Stem cells int (2016).

Celecoxib Adverse Effects

- CardioVascular: Increased risk of myocardial infarction and stroke.
- GI Bleeding. (All NSAIDS)
- Reduces serum testosterone by reducing prostaglandin synthesis in testicular Leydig cells.

Pang, Lisa Y., “Cyclooxygenase-2: a role in cancer stem cell survival and repopulation of cancer cells during therapy.” Stem cells international 2016 (2016).

Platelets Budding Off Megakaryocytes



Platelets by budding off from megakaryocytes.jpg

Platelets are Functional Players in Cancer

- Thrombocytosis >400,000 (poor prognosis).
- Cancer secretes IL-6, Stimulates Liver to make TPO (Thrombopoetin), Increases platelet count.
- "Platelets are … **functional players** in primary tumor growth and in all steps of the metastatic process. They infiltrate into the TME to directly interact with cancer cells. In the circulation, platelets protect CTCs from the deadly attack of the immune system…" (Haemmerle, 2018)

10) Haemmerle, Monika, et al. "The platelet lifeline to cancer: challenges and opportunities." Cancer Cell (2018): 965-983.

Platelets Facilitate Cancer

- Sports Medicine: PRP for Sports Injuries.
- Oncology Ignores the Role of Platelets
- Cancer Uses Platelets for Growth Factors.
- PDGF= platelet-derived growth factor,
- VEGF= vascular endothelial growth factor
- TGF-β = Transforming Growth Factor Beta.
- Platelet Inhibitors = Dipyridamole , ASA

5) Carrillo-Mora, Paul, et al. “Platelets-rich plasma: a versatile tool for regenerative medicine.” Cir Cir 81.1 (2013): 74-82.
6) Mishra, Allan, et al. “Sports medicine applications of platelet rich plasma.” Current pharmaceutical biotechnology 13.7 (2012): 1185-1195.

Natural Anti-Platelet Agents
Pt Must be Off x 1 Wk before Surgery

- Baicalein (Chinese Skullcap)
- Berberine
- Boswellia (Frankincense)
- Cordyceps
- Curcumin
- EGCG
- Garlic (Allicin)
- Oregano (carvacrol/thymol)
- Pterostilbene (Methylated Resveratrol)
- Quercetin
- Sulforaphane
- Thymoquinone
- Others (Fish Oil, Vit E)

Elisa Hirsch, Gabriela, et al. "Natural products with antiplatelet action." Current pharmaceutical design 23.8 (2017): 1228-1246.

Platelets Facilitate Cancer Refs

21) Takehara, Kazuhiko, Atsuyuki Igarashi, and Yasumasa Ishibashi. “Dipyridamole specifically decreases platelet-derived growth factor release from platelets.” Pharmacology 40.3 (1990): 150-156.

22) Takehara, Kazuhiko, et al. “Dipyridamole decreases platelet-derived growth factor levels in human serum.” Arteriosclerosis: An Official Journal of the American Heart Association, Inc. 7.2 (1987): 152-158.

30) Menter, David G., et al. “Platelets and cancer: a casual or causal relationship: revisited.” Cancer and Metastasis Reviews 33.1 (2014): 231-269.

31) Amo, Laura, et al. “Involvement of Platelet–Tumor Cell Interaction in Immune Evasion. Potential Role of Podocalyxin-Like Protein 1.” Frontiers in oncology 4 (2014): 245.

32) Nieswandt, Bernhard, et al. “Lysis of tumor cells by natural killer cells in mice is impeded by platelets.” Cancer research 59.6 (1999): 1295-1300.

34) Catani, Maria Valeria, et al. “The “Janus face” of platelets in Cancer.” International Journal of Molecular Sciences 21.3 (2020): 788.

35) Tzanakakis, George N“Prevention of human pancreatic cancer cell-induced hepatic metastasis in nude mice by dipyridamole and its analog RA-233.” Cancer 71.8 (1993

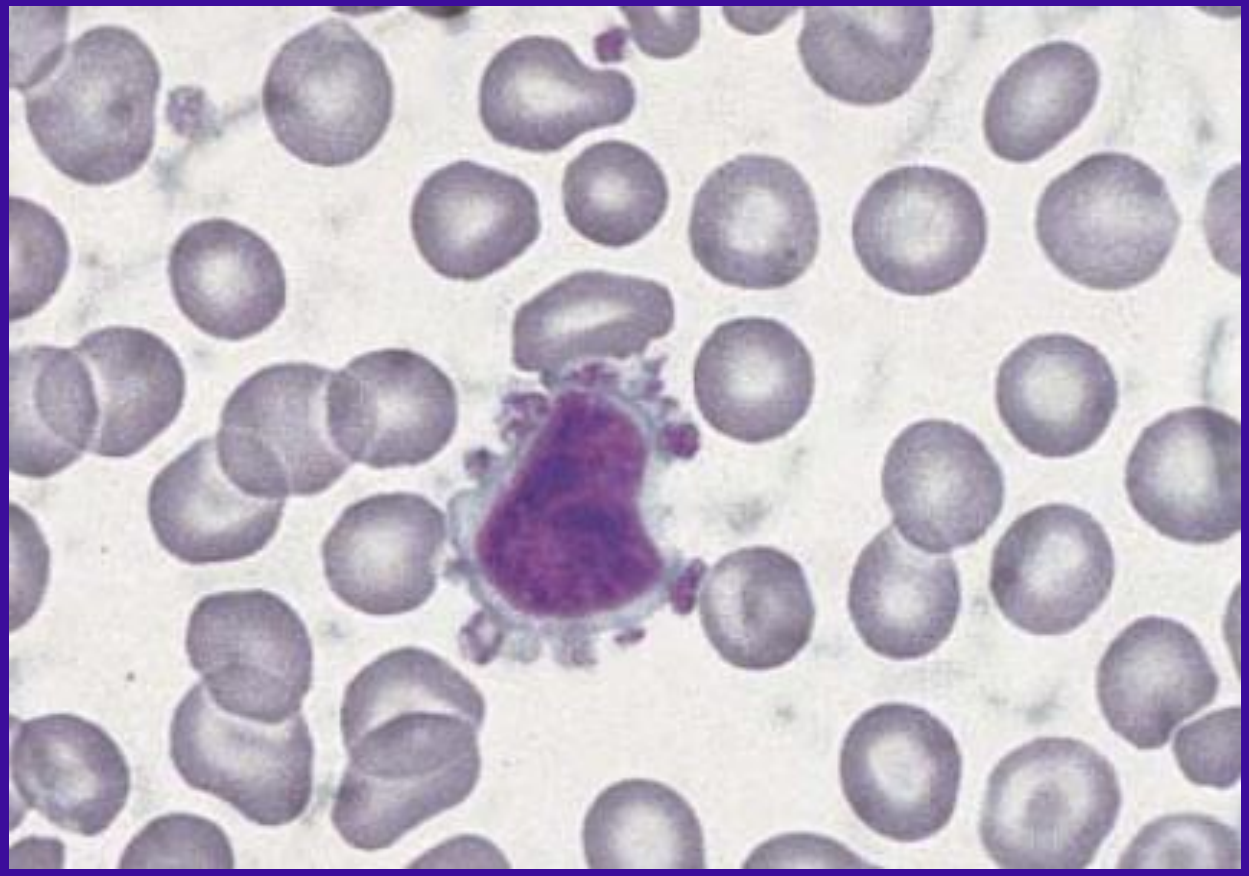
58) Thomé, Marcos P., et al. “Dipyridamole impairs autophagic flux and exerts antiproliferative activity on prostate cancer cells.” Experimental cell research 382.1 (2019): 111456

Platelets/ Metastatic Disease

- In 2017, Dr. Omar Elaskalani:
- “Cancer cell adhesion to platelets is vital for successful metastasis…. within the blood circulation, platelet-cloaked tumour cells can bypass natural killer cell-mediated cytotoxicity.” (2)

2) Elaskalani, Omar, et al. “Targeting Platelets for the Treatment of Cancer.” Cancers 9.7 (2017): 94.

Platelet Satellitism



- Peripheral blood smear showing platelet satellitism around a neoplastic lymphoid cell

Cesca, Christine "Platelet satellitism as presenting finding in mantle cell lymphoma: case report." Am j clin path 115.4 (2001): 567-570.

TGFβ1 Platelets Major Storage Site

- In 2017, Dr. Omar Elaskalani et al. write: "Platelets are the **major storage site** for **TGFβ1** [transforming growth factor beta1] within the blood circulation, which is released from α-granules [platelet-derived granules] upon activation…. "
- "Soluble platelet-derived factors **[mainly TGFβ1]** and direct physical contact with tumour cells activating **NF-κB pathway** work synergistically to induce **EMT** and subsequent migration and metastasis." (2)

2) Elaskalani, Omar, et al. "Targeting Platelets for the Treatment of Cancer." Cancers 9.7 (2017): 94

Platelet Derived TGFβ1 Immune Modulator

- Platelet-Derived TGF-Beta Is an Immune Modulator by Enhancing Differentiation of T cells toward T-reg cells. (35)
- In 2018, Dr. Min Soon Cho et al. studied a murine model of ovarian cancer, finding platelet inhibition restores anti-tumor immune response and could be used as adjunct to checkpoint inhibitors and other immunotherapies. (36)

35) Rachidi, Saleh, et al. "Platelets subvert T cell immunity against cancer via GARP-TGFβ axis." Science immunology 2.11 (2017).
36) Cho, Min Soon, et al. “The Inhibition of Platelets Restore Anti-Tumor Immune Response to Ovarian Cancer and Its Therapeutic Implication.” Blood 132. Supplement 1 (2018): 3698-3698.

TGF-β - Pregnancy and Cancer

- "We Can Understand Implantation in Early Pregnancy by Studying Tumor Progression" (Latifi 2019)

Latifi, Zeinab, et al. "Dual role of **TGF-β** in early pregnancy: clues from tumor progression." Biology of Reproduction 100.6 (2019): 1417-1430.

TGFβ - Pregnancy and Cancer

- 2019 Dr. Latifi : "During embryo implantation, both apoptosis and proliferation of endometrial cells happen at the same time **and it seems TGF-β is the factor that controls both of these processes."**
- As shown in **cancer cells**…this cytokine **(TGF-β)** can have a dual effect and switch the action from apoptosis to proliferation.
- **"Owing to the similarity between embryo implantation and cancer development"**… we suggest the existence of such a switching in endometrium during the early pregnancy.

Latifi, Zeinab, et al. "Dual role of TGF-β in early pregnancy: clues from tumor progression." Biology of Reproduction 100.6 (2019): 1417-1430.

Platelet Inhibition -Dipyridamole

- 1960's Boehringer Ingelheim DP as an antithrombotic agent, coronary vasodilator.
- Phosphodiesterase inhibitor.
- Prevents Platelet Activation.
- Prevents Release of Platelet Growth Factors such as TGF-β, PDGF etc.
- ASA/ Dipyridamole.

Born, Gustav, and Carlo Patrono. "Antiplatelet drugs." Briti j pharm 147. (2006): S241.
Sierko, E"Inhibition of platelet function: better cancer control?." Sem Thromb hemo 2007.

Dipyridamole for Melanoma

- 1985 Dr. Rhodes in Lancet.
- 30 Melanoma Pts Rx DP, 300 mg a day. 11 Year F/U.
- 26 pts presented with Distant Metastatic Disease.
- On DP: 77% 5 year survival.
- Off DP 20-30% 5 year survival.

14) Rhodes, E. L., et al. “Dipyridamole for treatment of melanoma.” The Lancet 325.8430 (1985): 693.

Dipyridamole for Breast Cancer Mouse Xenografts

- 2013 Dr. Daniela Spano, Mouse Xenograft Model for Breast Cancer.
- DP Prevents Progression of TNBC

15) Spano, Daniela, et al. “Dipyridamole prevents TNBC progression.” Clin exper metastasis 30.1 (2013): 47-68..

Dipyridamole for Breast Cancer

- "Low dose DP significantly reduced primary tumor growth and metastasis…while high dose resulted in almost total reduction in primary tumor"…
- "Dipyridamole had significant effects on Wnt (CSCs), MAPK/ERK (Kinases, Growth Signals) and NF-kB (Inflam) pathways in both animal models"...
- "DP significantly decreased infiltration of TAMs and MDSC in primary tumors, and the inflammatory cytokines." (Spano, 2013)

15) Spano, Daniela, et al. "Dipyridamole prevents TNBC progression." Clin exper metastasis 30.1 (2013): 47-68..

Dipyridamole MOA

- Prevents platelet activation, which prevents release of Growth Factors VEGF, PDGF and TGF-β, COX2 into TME.
- Restores Anti-Tumor Immune Response. (Adjunct to Checkpt Inhibs).
- Inhibits cellular uptake of adenosine.
- Inhibits the phosphodiesterase enzymes (PDE) that normally break down cAMP, thus increasing cellular cAMP levels in cells.

2) Elaskalani, Omar, et al. “Targeting Platelets for the Treatment of Cancer.” Cancers 9.7 (2017): 94

Dipyridamole Synergy w Statins

- 2014 Dr Pandrya Screened 100 drugs (antimicrobials and metabolic regulators) for synergy with Atorvastatin in MM and AML cells.
- "The combination of statins and dipyridamole is synergistically antiproliferative and induces apoptosis in AML and MM cell lines and primary patient cells." (Pandrya 2014)
- DP Inhibits Feedback loop, prevents compensatory upregulation of Mevalonate pathway after statin.

Pandyra, Aleksandra, et al. "Immediate utility of two approved agents to target both the metabolic mevalonate pathway and its restorative feedback loop." Cancer research 74.17 (2014): 4772-4782.

Dipyridamole References

Elaskalani, Omar, et al. “Targeting Platelets for Treatment of Cancer.” Cancers 9.7 (2017): 94

Gamboa, Alfredo, et al. “Role of adenosine and nitric oxide on the mechanisms of action of dipyridamole.” Stroke 36.10 (2005): 2170

Takehara, K “Dipyridamole specifically decreases platelet-derived growth factor release from platelets.” Pharm 40.3 (1990): 150-156

Tzanakakis, “Prevention of human pancreatic cancer cell-induced hepatic metastasis in nude mice by dipyridamole and its analog RA-233.” Cancer 71.8 (1993): 2466-2471.

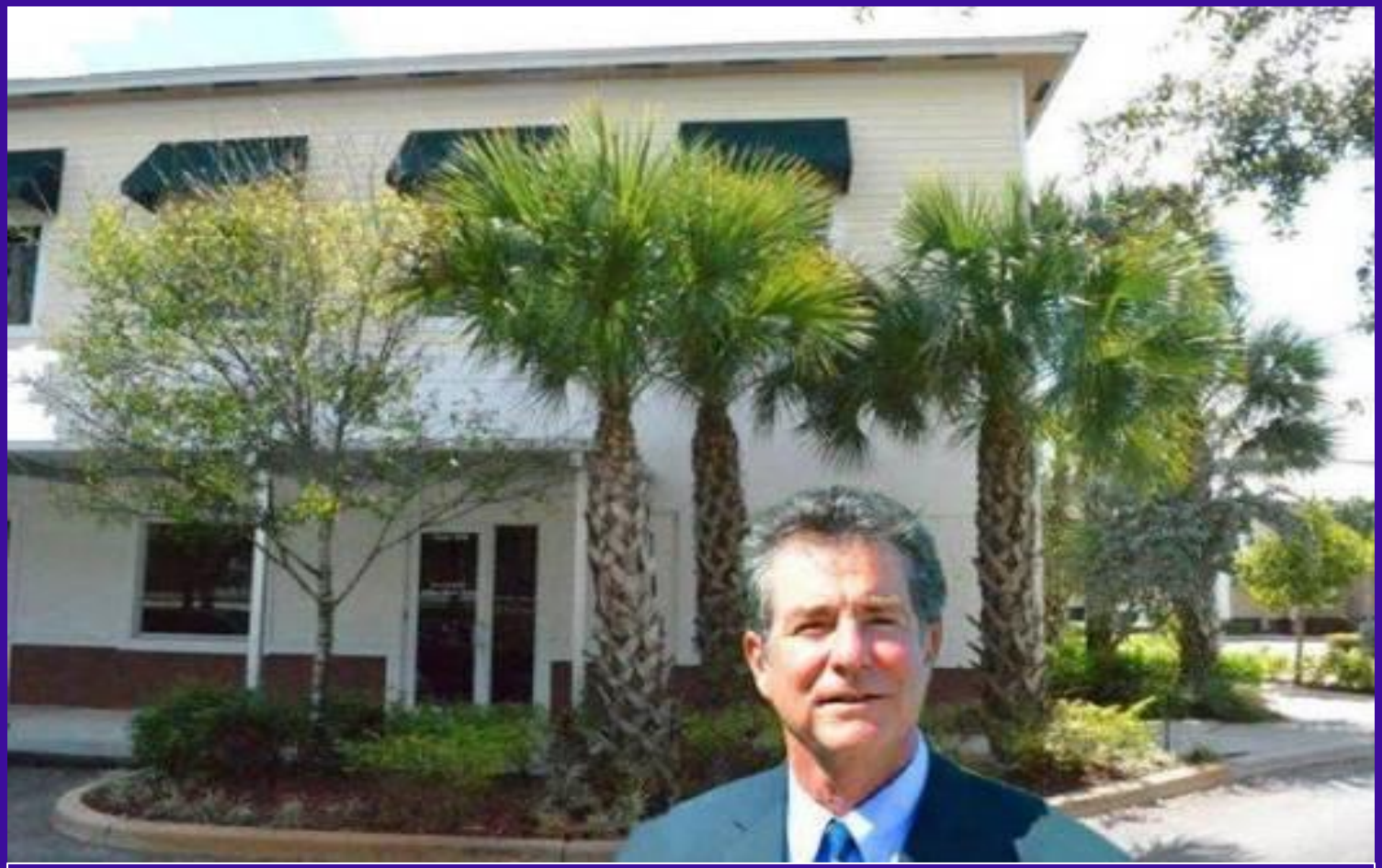
36) Cho, Min Soon, et al. “The Inhibition of Platelets Restore Anti-Tumor Immune Response to Ovarian Cancer and Its Therapeutic Implication.” Blood 132. Supplement 1 (2018): 3698-3698

Rachidi, Saleh, et al. “Platelets subvert T cell immunity against cancer via GARP-TGFβ axis.” Science immunology 2.11 (2017).

Cancer as a Trophoblastic Disease Summary Slide

- Similarity in molecular circuitry, immune evasion, inflammation - Trophoblasts - Cancer.
- PIBF, Mifepristone AntiCancer Effects
- William Coley – The Father of Immunotherapy.
- SR/CR Mouse/The Mouse that Killed Cancer.
- Cimetidine Immune Stimulator.
- Beta Glucans Immune Stimulator.
- Celecoxib, COX-2 Inhibitors .
- Dipyridamole Prevents Platelet Activation, Prevents Release of TGF-β, PDGF.

Thank You – Any Questions?



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