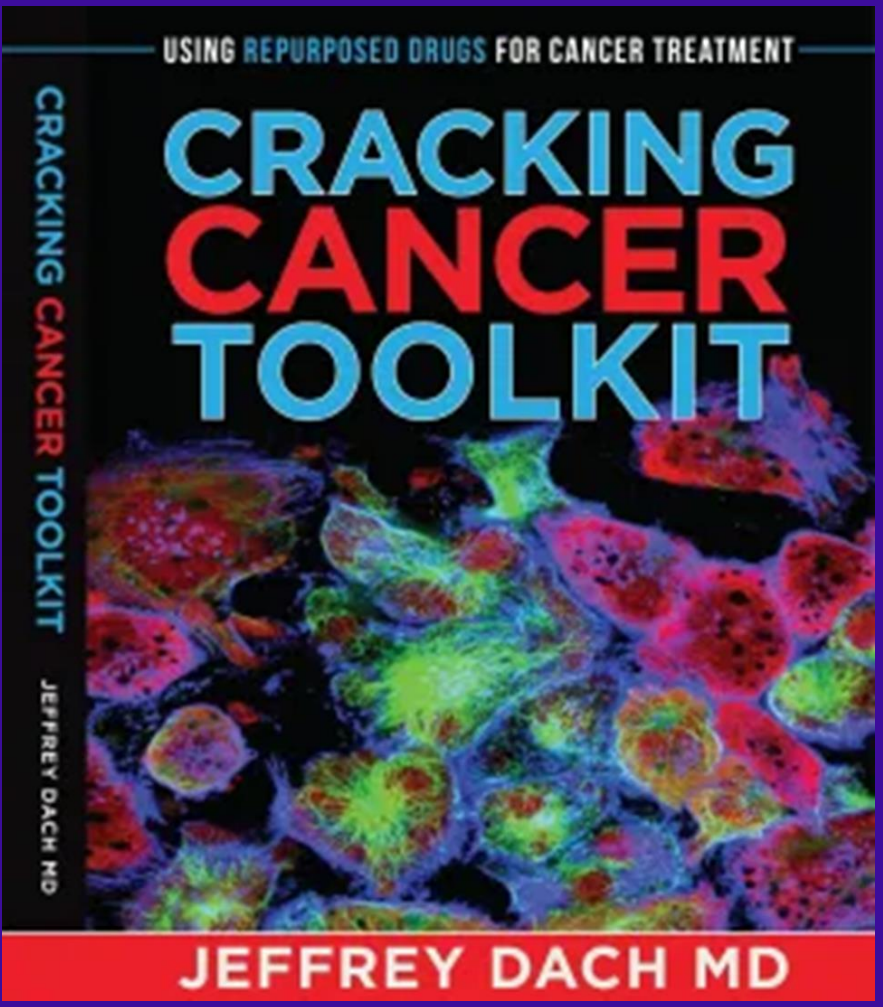
CANCER THERAPIES:
REPURPOSED DRUGS & NATURAL SUBSTANCES
July 19,2021 PART TWO

Jeffrey Dach MD
7450 Griffin Road Suite 190
Davie, FL 33021
954-792-4663

Cancer As a Parasitic Disease



Text Book for Course

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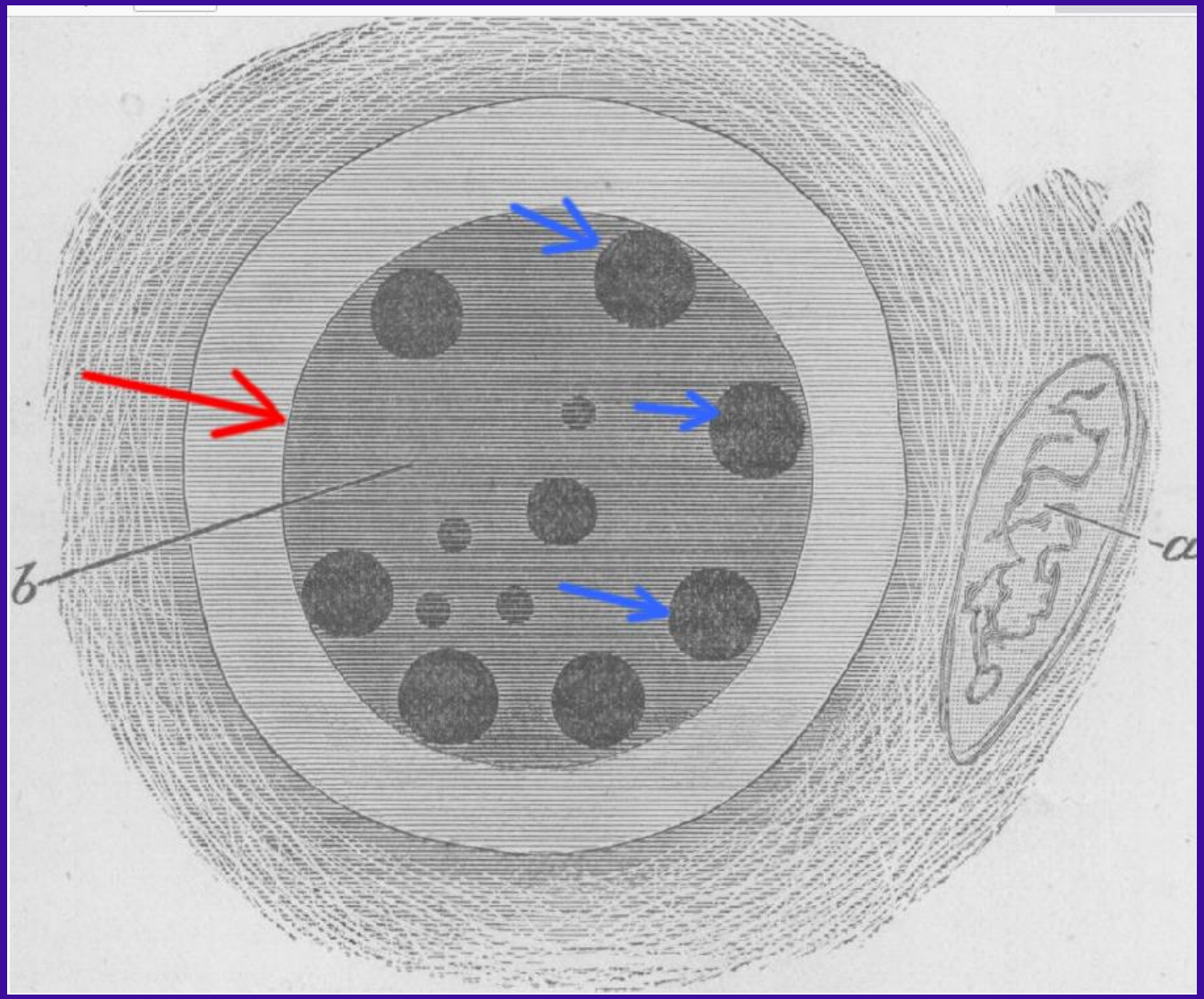
Early Pathologists Thought Cancer was a Parasitic Disease

- December 18,1890 Scottish pathologist William Russell reported a “cancer microbe” seen under his microscope inside cancer cells.
- British Medical Journal: detailed drawings describing parasitic spores within cancer cells.(24)

Russell, William. “An address on a characteristic organism of cancer.” British medical journal 2.1563 (1890): 1356.

Drawings by William Russell 1890



Large Degenerating Organism (Red Arrows) containing Spores (Blue Arrows)
Russell, William. "An address on a characteristic organism of cancer." British medical journal 2.1563 (1890): 1356.

Cancer as a Parasitic Disease

- "The study of parasitic disease affords us an opportunity to better understand cancer biology."

Reference: Cracking Cancer Toolkit by Jeffrey Dach MD Medical Muse Press 2020

Spirochete Parasite Transmitted by Ticks—Resembles Lymphoma

- Theileria is an intracellular parasite transmitted by ticks, resembles Borrelia Lyme parasite in humans.
- T. parva highly pathogenic for cattle and causes a fatal lymphoproliferative disease known as East Coast fever. Treated with buparvaquone.
- Dr. Vishvanath Nene (2016) writes: "Infected cells acquire a metastatic, cancer-like phenotype and are the primary cause of pathology." (18)

18) Nene, Vishvanath, et al. "The biology of Theileria parva and control of East Coast fever–Current status and future trends." Ticks and tick-borne diseases (2016).

Cryptosporidium Mouse Model of Colon Cancer

- Dr. Sadia Benamrouz et al. (2014)
- Mice inoculated with crytosporidium develop colon cancer.
- Upregulated Wnt signalling.

22) Benamrouz, Sadia, et al. “Cryptosporidium parvum-induced ileo-caecal adenocarcinoma and Wnt signaling in a mouse model.” Disease Models and Mechanisms 7.6 (2014): 693-700.

Cancer Arising from Tapeworm Infection

- In 2015, Dr. Atis Muehlenbachs Case Report:
- Immunosuppressed patient with enlarged lymph nodes invaded by cancer cells.
- Genomic analysis of lymph node biopsy: Tapeworm DNA (Hymenolepis nana) in the cancer cells, indicating:
- "Malignant transformation of a tapeworm parasite," apparently indicating the parasitic origin of this patient's cancer." (Muehlenbachs, 2015)

106) Muehlenbachs, Atis, et al. "Malignant Transformation of Hymenolepis nana in a Human Host." New England Journal of Medicine 373.19 (2015): 1845-1852.

Anti-Parasitic Drugs – Repurposed as Anti Cancer Drugs

- Anti-Malarials – Artemisinin, Mefloquine, HCQ CQ
- Ivermectin
- Mebendazole (Vermox), Fenbendazole
- Niclosamide
- Nitazoxanide (Alinia)
- Pyrvinium

97) Hamilton, Gerhard, and Barbara Rath. "Repurposing of Anthelminthics as Anticancer Drugs."Mutat Res. 2014 Oct; 768:16-21.
98) Klinkert, M-Q., and V. Heussler. "The use of anticancer drugs in antiparasitic chemotherapy." Mini reviews in medicinal chemistry 6.2 (2006): 131-143.

Anti-Malarials – Artemisinin/Artesunate

- 2015 Dr Tu You You Receives Nobel Prize for Discovering Artemisinin,
- Artesunate First Line Treatment for Malaria
- 2015 Dr Sanjeev Krishna Randomized trial in 20 colon cancer pts waiting for “curative resection”. Half took artesunate.
- Five years later: One Recurrence in artesunate group (10%). SIX Recurrences in placebo group (60%) (Krishna, 2015)

1) Krishna, Sanjeev, et al. “A randomised, double blind, placebo-controlled pilot study of oral artesunate therapy for colorectal cancer.” EBioMedicine 2.1 (2015): 82-90.
2) 3) Das, A. K. “Anticancer effect of antimalarial artemisinin compounds.” Annals of medical and health sciences research 5.2 (2015): 93-102.

Anti-Malarials – Artemisinin/Artesunate

- 2015 Dr Das: Artesmisinin (derivatives) Effective Against 55 cancer cell lines
- Potentiates Effect of Doxorubicin Chemo in drug resistant leukemia Cell Model.
- Yang 2014: Endoperoxide Bridge Reacts with Iron, Fenton Reaction triggers ROS induced mitochondrial apoptosis.
- Selective to Cancer Cells which have increased iron content and iron transport.

Das, A. K. "Anticancer effect of antimalarial artemisinin compounds." Annals of medical and health sciences research 5.2 (2015): 93-102.

Yang, Nai-Di, et al. "Artesunate induces cell death in human cancer cells via enhancing lysosomal function and lysosomal degradation of ferritin." Journal of Biological Chemistry 289.48 (2014): 33425-33441.

Artesunate Restricted in US April 2019

- IV artesunate 60 mg vials are widely used as first-line malaria treatment in Third World areas.
- Inside the U.S. this drug, is neither FDA approved nor commercially available. The drug has been made available, however, through an investigational new drug application (IND).
- 2019 Drs. Phillip Rosenthal and Katherine Tan discuss the distress and confusion encountered by physicians in the U.S. when trying to treat a malaria patient (1700 cases per year) with IV artesunate in a timely fashion: Call cdc hotline for drug delivery
- Obviously, this "IND protocol" arrangement makes it virtually impossible to treat cancer patients in the U.S. with IV artesunate, a promising nontoxic drug that competes with chemotherapy.

Guidance for Using Intravenous Artesunate for Treating Severe Malaria in the United States. The Centers for Disease Control and Prevention. Content source: Center for Preparedness and Response (CPR) Page last reviewed: March 6, 2019

Rosenthal, Philip J., and Kathrine R. Tan. "Expanded Availability of Intravenous Artesunate for the Treatment of Severe Malaria in the United States." The American journal of tropical medicine and hygiene 100.6 (2019): 1295

Anti-Malarials – Mefloquine, Chloroquine, HydroxyChloroquine- Autophagy Inhibitors

- Mefloquine most potent, associated with Neuropsychiatric and retinal adverse side effects. Effective Cancer Stem Cell Agent.
- Mefloquine- Dosage for travelers 250 mg tab weekly for a few weeks before the trip.
- Drug is trapped and accumulates in Lysosomes, increases pH, Prevents fusion of lysosome to autophagosome,
- Expansion and disruption of Lysosomes
- interrupts micropinocytosis
- Dr Sukai 2013: Highly Active Against Leukemia which has enlarges lysosomes, upregulated larger lysosomes in leukemia

24) Sukhai, Mahadeo A., et al. “Lysosomal disruption preferentially targets acute myeloid leukemia cells and progenitors.” The Journal of clinical investigation 123.1 (2013): 315-328

Mefloquine Synergy w/ Tyrosine Kinase Inhibitors in Leukemia CML

- 2019, Dr. Hui Lam Yi: imatinib, dasatinib and ponatinib- B Cell receptor TKI's in CML cell lines, in vitro.
- This is true, in general, for TKI's combined with **ANY** Autophagy Inhibitor.
- Mefloquine preferentially targets CSC's

43) Yi, Hui Lam, et al. "Lysosome Inhibition by Mefloquine Preferentially Enhances the Cytotoxic Effects of Tyrosine Kinase Inhibitors in Blast Phase Chronic Myeloid Leukemia." Translational oncology 12.9 (2019): 1221-1228

Mefloquine in Colon Cancer in Vivo

- 2019, Dr. M Takeda: mouse xenografts
- Disruption of lysosomal activity (endosomal RAB5/7 proteins) with Mefloquine key to eliminating Cancer Stem Cells.
- Mefloquine more effective than HCQ and CQ
- Potent Inhibition Drug Efflux Pumps (Pgp-Drug -resistance)

Takeda, Mitsunobu, et al. “Disruption of endolysosomal rab5/7 efficiently eliminates colorectal cancer stem cells.” Cancer research 79.7 (2019): 1426-1437.
Mereddy, G. R., and C. T. Ronayne. “Repurposing Antimalarial Drug Mefloquine for Cancer Treatment.” Transl Med (Sunnyvale) 8.199 (2018): 2161-1025.

Mefloquine in Colon Cancer in Vivo 2

- Autolysosome-activated cells are tumor-initiating and long-term dye-retaining cells.
- Indicates cell dormancy and slow growth as unique characteristics of CSCs.
- Chemotherapy increased CSC fraction (84%). MQ decreased it (9.4%).
- The combination of mefloquine with chemotherapy dramatically decreased CSC population (0.1%).
- Combination “drastically reduces” tumor volume
- Safe with no adverse effects.

Takeda, Mitsunobu, et al. “Disruption of endolysosomal rab5/7 efficiently eliminates colorectal cancer stem cells.” Cancer research 79.7 (2019): 1426-1437.

Mefloquine in Colon Cancer in Vivo 3

- "We expect that mefloquine may induce depletion of CSCs and, due to a synergistic effect, demolish the cancer hierarchy, including cancer precursor cells, when given in combination with cytotoxic anti-cancer drugs … Accordingly, we suggest that mefloquine is a promising candidate for colon CSC-targeting therapy. " (45)

Takeda, Mitsunobu, et al. "Disruption of endolysosomal rab5/7 efficiently eliminates colorectal cancer stem cells." Cancer research 79.7 (2019): 1426-1437.

Mefloquin Effective for Various Cancer Cells Types 1

- Breast cancer (23)
- Prostate cancer (31–32)
- Cervical cancer (33)
- CLL chronic lymphocytic leukemia (34)
- Esophageal squamous cell cancer
- Neuroblastoma (36)

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Mefloquin Effective for Various Cancer Cells Types 2

- Colorectal cancer (37) (inhibits NF-kB)
- Liver cancer (38) (targets Wnt/β-Catenin)
- Acute myeloid leukemia (AML) (24)(39)
- Enhancement of chemotherapy in MDR drug resistance (40–41) (inhibits p-glycoprotein)
- Glioblastoma (42) (inhibits ATP synthase)
- Blast-phase chronic leukemia—synergy with tyrosine kinase inhibitors (43–44)

Takeda, Mitsunobu, et al. "Disruption of endolysosomal rab5/7 efficiently eliminates colorectal cancer stem cells." Cancer research 79.7 (2019): 1426-1437.

Mefloquin References 1

- 23) Sharma, Natasha, et al. “Inhibition of autophagy and induction of breast cancer cell death by mefloquine.” Cancer Let 326.2 (2012): 143
- 24) Sukhai, Mahadeo A., et al. “Lysosomal disruption preferentially targets acute myeloid leukemia cells and progenitors.” The Journal of clinical investigation 123.1 (2013): 315-328.
- 32) Yan, Kun-Huang, et al. “Mefloquine exerts anticancer activity in prostate cancer cells.” Oncology letters 5.5 (2013): 1541-1545.
- 33) Li, Hui, et al. “mefloquine against cervical cancer.” Canadian journal of physiology and pharmacology 95.1 (2017): 43-50.
- 34) Das, Subhadip, et al. “Antimalarial drugs trigger cell death in chronic lymphocytic leukemia (CLL)” Leuk research 70 (2018): 79-86.
- 35) Xie, Yifei. “Mefloquine Inhibited Esophageal Squamous Carcinoma by Induction of Mitochondrial Autophagy.” (2019).
- 36) Kumar, Abhishek, Debasish Kumar Ghosh, and Akash Ranjan. “Mefloquine binding to human acyl- CoA binding protein leads to redox stress mediated apoptotic death of human neuroblastoma cells.” NeuroToxicology (2020).

Mefloquin References 2

- 37) Xu, Xin, et al. “Antimalarial drug mefloquine inhibits NFkB signaling and induces apoptosis in colorectal cancer” Cancer Sci (2018): 1220
- 38) Li, Yu-Hui, et al. “Mefloquine targets β-catenin pathway in the treatment of liver cancer.” Microbial pathogenesis 118 (2018): 357
- 39) Phan, Jessica L., et al. “The Evaluation of Mefloquine Drug Repurposing on Acute Myeloid Leukemia.” 2018
- 40) Fujita, R “Enhancement of doxorubicin activity in multidrug-resistant cells by mefloquine.” Methods Find Exper Clin Pharm 2000
- 41) Kim, Ju-Hwa, et al. “Co-treatment with anti-malarial drugs mefloquine and primaquine highly sensitizes drug-resistant cancer cells by increasing P-gp inhibition.” Biochem and biophysical (2013)
- 42) Sharma, Natasha “Reduced glucose uptake and inhibition of ATP synthase by mefloquine results in death of Glioblastoma.” (2013)
- 43) Yi, Hui Lam, et al. “Lysosome Inhibition by Mefloquine Preferentially Enhances Cytotoxic Effects of Tyrosine Kinase Inhibitors in Blast Phase Chronic Myeloid Leukemia.” Translational oncology 12.9 (2019): 1221-1228.

Mefloquine Dosage

- Cytotoxic effects at 4-10 MicroM
- 3-4 micromolar with malaria prophylaxis for travelers (weekly 250 mg tablet)
- 2-23 microM with antimalaria therapy (1250 mg PO once)

Sukhai, Mahadeo A., et al. “Lysosomal disruption preferentially targets acute myeloid leukemia cells and progenitors.” The Journal of clinical investigation 123.1 (2013): 315-328.
Yan, Kun-Huang, et al. “Mefloquine exerts anticancer activity in prostate cancer cells via ROS-mediated modulation of Akt, ERK, JNK and AMPK signaling.” Onc letter (2013): 1541
Reuter, Stephanie E., et al. “pharmacokinetics of mefloquine in healthy volunteers and patients with uncomplicated Plasmodium malaria.” J of Antimicrob Chemo (2014): dku430

Mefloquine

- 2018, Drs. G. Mereddy
- "Although long-term usage of MQ has psychiatric and neurological side effects (and Retinal) in some patients, its utility may be justified in late-stage cancer patients with limited treatment options … MQ's ready and inexpensive availability and long-standing record of clinical use qualify this drug for repurposing for anti-cancer applications". (50)

Mereddy, G. R., and C. T. Ronayne. "Repurposing Antimalarial Drug Mefloquine for Cancer Treatment." Transl Med (Sunnyvale) 8.199 (2018): 2161-1025.

Niclosamide History / Dosage

- 1953 Drug Discovered.
- 1962 Treats Tapeworm
- 1982 FDA Approved for Tapeworm
- 2 grams PO QD X 7 Days

30) Li, Yonghe, et al. “Multi-targeted therapy of cancer by niclosamide: A new application for an old drug.” Cancer letters 349.1 (2014): 8-14.

Niclosamide Broader Applications

- Anti-Cancer
- Bacterial (C Diff Enterocolitis, H Pylori)
- Viral Infection (COVID)
- Type II AODM
- Fatty Liver Disease
- Endometriosis
- Neuropathic Pain
- Rheumatoid Arthritis
- Scleroderma Graft Vs Host Disease

1) Chen, Wei “Niclosamide: beyond an antihelminthic drug.” Cell Signal41 (2018): 89-96.

Niclosamide Anti Cancer Stem Cell Agent

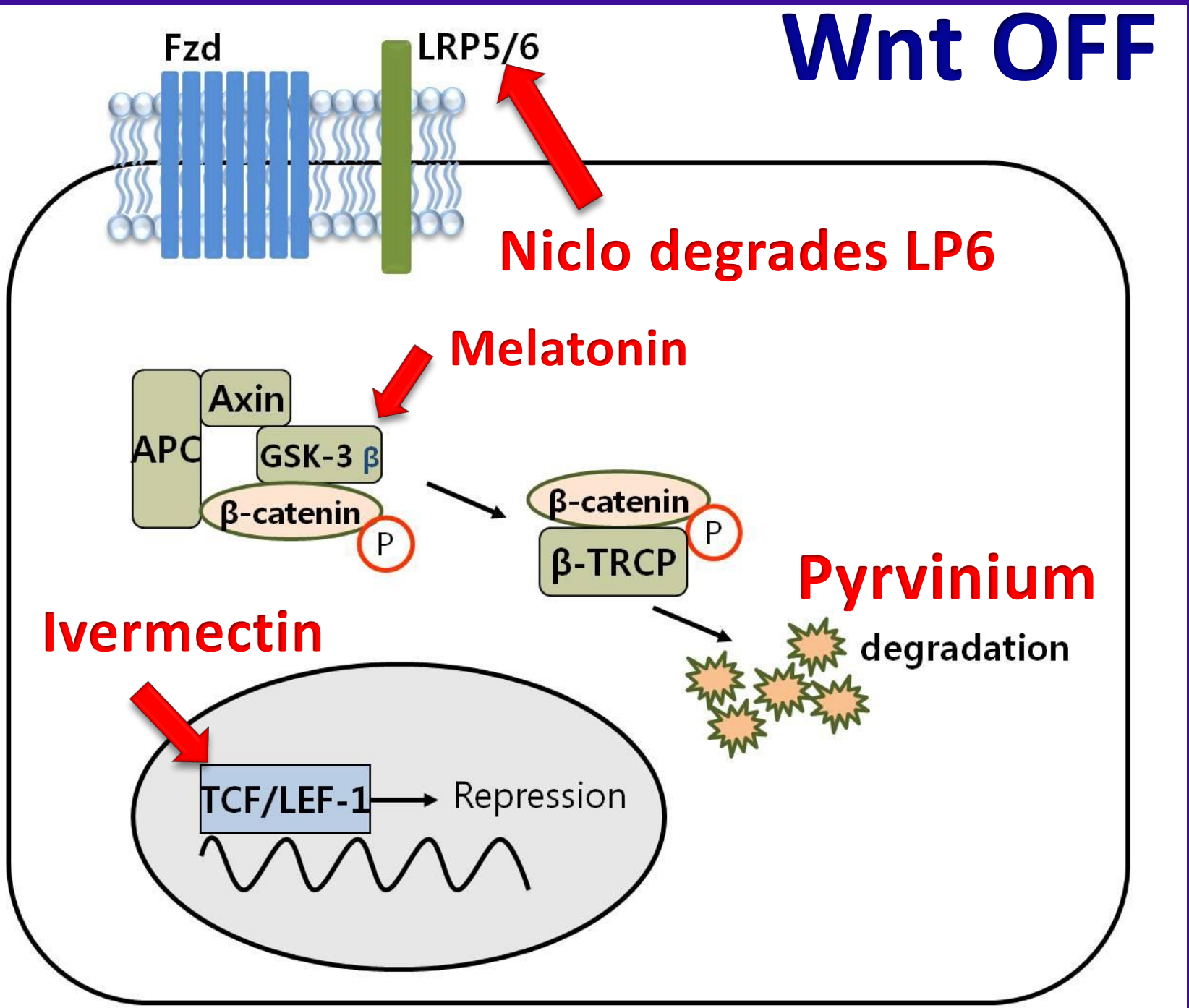
- High Thruput Screen: Niclosamide potent inhibitor of Wnt/Beta Catenin/ and NF-kB
- “Holds promise in eradicating cancer stem cells.” (3)

3) Pan, Jing-Xuan “Niclosamide, an old antihelminthic agent antitumor activity blocking multiple signaling pathways of cancer stem cells.” Chinese J Cancer 31.4 (2012): 178.

Niclosamide Inhibits Wnt pathway

- Targets LRP6 Wnt Co-receptor on cell membrane
- Effective at Low Concentrations IC < 1 MicroM

Lu, Wenyan, et al. “Niclosamide suppresses cancer cell growth by inducing Wnt co-receptor LRP6 degradation and inhibiting the Wnt/β-catenin pathway.” PloS one 6.12 (2011) e29290


Wnt OFF
Fzd
LRP5/6
Niclo degrades LP6
Melatonin
APC
Axin
GSK-3 β
β-catenin
P
β-catenin
β-TRCP
P
Pyrvinium
degradation
Ivermectin
TCF/LEF-1
Repression

Niclosamide Targets Lysosomes Inhibits Antegrade Trafficking

- High Thruput Screen 2,210 drugs and supplements.
- Niclosamide Identified as Best Candidate.
- Decreases Lysosomal pH, Acid Released into cytosol inhibiting Glycolysis.
- Therefore Niclosamide is Autophagy Inhibitor.

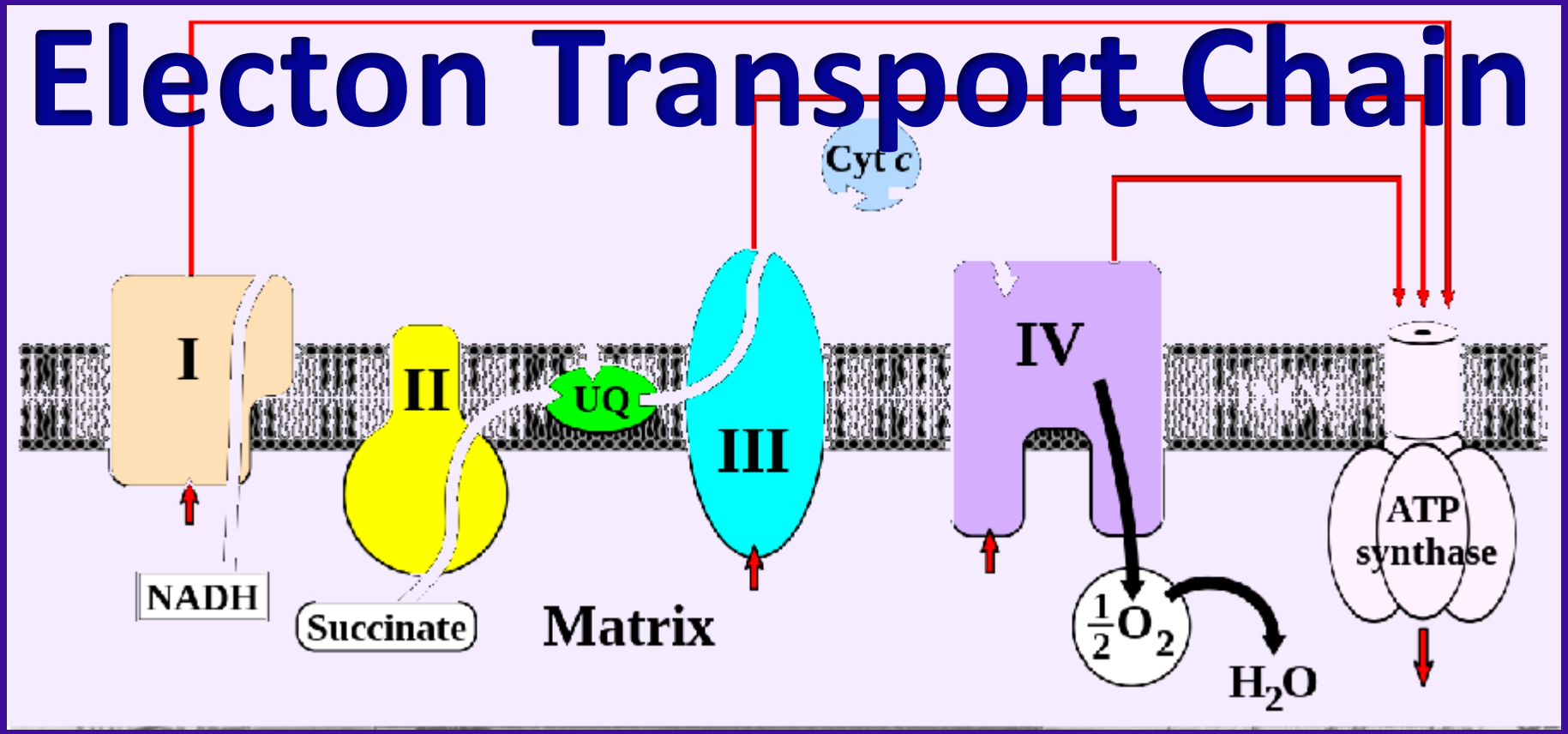
8) Circu, Magdalena L., et al. “A Novel High Content Imaging-Based Screen Identifies the Anti-Helminthic Niclosamide as an Inhibitor of Lysosome Anterograde Trafficking and Prostate Cancer Cell Invasion.” PLoS ONE 11.1 (2016).

Niclosamide Mitochondrial Uncoupling Agent – OXPHOS INHIBITOR

- Uncouples Mitochondrial OXPHOS.
- No ATP production even though electrons flow through ETC, resulting in AMPK activation, mTOR inhibition, induces “protective autophagy” and shift to GLYCOLYSIS, Synergy with GLYCOLYSIS Inhibitors (DCA)

10) Tran, Uyen Thi, and Toshimori Kitami. “Niclosamide activates the NLRP3 inflammasome by intracellular acidification and mitochondrial inhibition.” Communications biology 2.1 (2019): 1-14.

Niclosamide Mitochondrial Uncoupling Agent



10) Tran, Uyen Thi, and Toshimori Kitami. “Niclosamide activates the NLRP3 inflammasome by intracellular acidification and mitochondrial inhibition.” Communications biology 2.1 (2019): 1-14.

Niclosamide for Ovarian Cancer

- 14,000 deaths annually.
- Presents late with metastatic spread to peritoneal cavity with Malignant Ascites.
- Platinum Based Chemo Remission- 75% relapse within 5 years.

12) Yo, Yi-Te, et al. “Growth Inhibition of Ovarian Tumor–Initiating Cells by Niclosamide.” Molecular Cancer Therapeutics 11.8 (2012): 1703-1712.

Niclosamide for Ovarian Cancer

- 2012 Dr Yi Te Yo : High Thruput Screen 1,200 approved drugs against OV CA.
- Niclosamide most promising candidate.
- Effective as monotherapy, or combined with Conventional Chemotheraapy.

12) Yo, Yi-Te, et al. “Growth Inhibition of Ovarian Tumor–Initiating Cells by Niclosamide.” Molecular Cancer Therapeutics 11.8 (2012): 1703-1712.

Niclosamide for Ovarian Cancer 1

- 2014 Dr Rebecca Arend isolated Ov Ca Cells from 34 pts malignant ascites.
- Cells treated w/ Niclosamide combined with Carboplatin .
- Synergy 32/34 samples.
- Niclosamide potent Wnt/Beta Cat inhibitor.

13) Arend, R. C., et al. “Inhibition of Wnt/β-catenin pathway by niclosamide: a therapeutic target for ovarian cancer.” Gynecologic oncology 134.1 (2014): 112.

Niclosamide for Ovarian Cancer 2

- 2016 Dr Rebecca Arend: Ov CA Upregulated Cancer Pathways: Wnt,mTOR,STAT3.
- All Three are inhibited by Niclosamide.
- Niclosamide targets Chemo Resistant CD133+ OV CA stem cells.
- Induces Metabolic Shift to Glycolysis (OXPHOS INHIBITOR)
- Synergy with Glycolysis Inhibitor (DCA, Quercetin ?

14) Arend, Rebecca C., et al. “Niclosamide potent inhibitors of Wnt/β-catenin, mTOR and STAT3 signaling in ovarian cancer.” Oncotarget 7.52 (2016): 86803.
Sekulovski, Nikola, et al. "Niclosamide’s potential direct targets in ovarian cancer." Biology of Reproduction (2021).

Niclosamide for P53 Deficient OV CA Mitochoindrial Uncoupling

- 2018 Dr R Kumar studied p53 deficient Ovarian Cancer cells and d xenografts.
- Hi Thuput Screen 1,600 drugs PHARMAKON Library
- Niclosamide most potent for P53 def Ov Ca
- Effective at 2 Micro M
- Uncoupling of OXPHOS. (no ATP production even though electrons flow through ETC), AMPK activation, mTOR inhibition.
- Niclosamide Drug of Choice for Non Functioning P53

21) Kumar, R., et al. “Mitochondrial uncoupling reveals a novel therapeutic opportunity for p53-defective cancers.” Nature Communications 9 (2018).
22) Figarola, James L., et al. “ Mitochondria uncouplers SR4 and niclosamide prevents proliferation and growth of treatment-naïve and vemurafenib-resistant melanomas.” Oncotarget 9.97 (2018): 36945.

Niclosamide for Colonic Polyposis/ Colon CA

- Wnt Pathway Upregulated
- 2011 Dr Takayu Osada mice with implanted human colon Ca xenografts
- Niclosamide well tolerated, plasma and tumor levels associated with biologic activity, led to tumor control (26, 27)

26) Osada, Takuya, et al. “Antihelminth compound niclosamide downregulates Wnt signaling and elicits antitumor responses in tumors with activating APC mutations.” Cancer research 71.12 (2011): 4172-4182

27) Park, So-Yeon, et al. “Inhibition of LEF1-mediated DCLK1 by niclosamide attenuates colorectal cancer stemness.” Clinical Cancer Research 25.4 (2019): 1415-1429.

Niclosamide for Colonic Polyposis/ Colon CA

- 2016 Dr Susan Burock High thruput Screen of S100A4 expression. Niclosamide best candidate
- Human trials Niclosamide for Colon Cancer are Under Way.

28) Dahlmann, Mathias, et al. “S100A4 in cancer metastasis: Wnt signaling-driven interventions for metastasis restriction.” Cancers 8.6 (2016): 59.

29) Burock, Susen, et al. “Phase II trial to investigate the safety and efficacy of orally applied niclosamide in patients with metachronous or sychronous metastases of a colorectal cancer progressing after therapy: the NIKOLO trial.” BMC Cancer 18 (2018)..

Niclosamide for Lymphoma

- 2015 Dr Junaid Ansari Aggressive B Cell Lymphoma In Vitro.
- Niclosamide Effective Induces Apoptosis low concentration of 0.1 MicroM
- Normal Lymphocytes are spared.

31) Ansari, Junaid, et al. “Potent Inhibition of the Growth and Induction of Apoptosis in Lymphoma by the Anthelminthic Drug Niclosamide: In Vitro Data. Blood (2015) 126 (23): 5131-5131.

Niclosamide for Multiple Myeloma "Better Than Chemo"

- 2011 Dr FL Khanim Screened 100 drugs for anti-myeloma activity.
- Niclosamide better than anti-myeloma drugs.
- Rapid reduction in light chain production.(32)
- Standard Anti-helminthic Dosing in humans achieves effective serum concentration in the study (3.2 microM)

32) Khanim, F. L., et al. "Redeployment-based drug screening identifies the anti-helminthic niclosamide as anti-myeloma therapy that also reduces free light chain production." Blood cancer journal 1.10 (2011): e39.

Niclosamide for Breast Cancer Stem Cells

- 2013 Dr Yu Chi Wang screened LOPAC library 1258 compounds. Niclosamide was best inhibitor of BCSC.
- 2014 Dr Ye Br CA in vitro and in vivo Mouse model, decreased KI-67, VEGF pos cells, Microvessel density, increased apoptosis, reduced MDSC Myeloid derived suppressor cells, blocked pulmonary mets.
- Potent STAT3 inhibitor, Targets NFKB, Notch, Wnt, mTOR.

33) Wang, Yu-Chi, et al. “Drug screening identifies niclosamide as an inhibitor of breast cancer stem-like cells.” PloS one 8.9 (2013): e74538.
34) Ye, Tinghong, et al. “The anthelmintic niclosamide induces apoptosis, impairs metastasis and reduces immunosuppressive cells in breast cancer model.” PloS one (2014

TME Tumor Microenvironment

- Cells and tissues around the cancer mass playing a supportive role in feeding the cancer mass with nutrients and growth factors.
- Dr. Freja Venning (2015):
- “the tumor micro-environment includes: immune cells, fibroblasts, pericytes, endothelial cells, adipocytes, and mesenchymal stem cells, and also the interstitial fluids and the extracellular matrix [ECM].” (36)

36) Venning, Freja A., Lena Wullkopf, and Janine T. Erler. “Targeting ECM disrupts cancer progression.” Frontiers in oncology 5 (2015): 224.
37) Gyamfi, Jones, et al. “Niclosamide reverses adipocyte induced epithelial-mesenchymal transition in breast cancer cells via suppression of the interleukin- 6/STAT3 signalling axis.” Scientific reports 9.1 (2019): 1-14.

Niclosamide Prevents EMT Induced by Adipocytes in TME

- Adipocytes surrounding the cancer mass induce "epithelial mesenchymal transition (EMT) of breast.
- Cancer cells through paracrine IL-6/Stat3 signaling." (Gyamfi, 2019).
- Niclosamide inhibits IL-6/STAT3 which reverses adipocyte-induced EMT.

36) Venning, Freja A., Lena Wullkopf, and Janine T. Erler. "Targeting ECM disrupts cancer progression." Frontiers in oncology 5 (2015): 224.
37) Gyamfi, Jones, et al. "Niclosamide reverses adipocyte induced epithelial-mesenchymal transition in breast cancer cells via suppression of the interleukin- 6/STAT3 signalling axis." Scientific reports 9.1 (2019): 1-14.

Niclosamide Synergistic with Checkpoint Inhibitors

- 2019 Dr Fan Luo Niclosamide combined with Checkpoints Inhibitors blocks STAT3 binding to promoter of PDL1.
- Niclosamide "Enhanced cancer cell lysis mediated by T Cells in presence of PD-L1 blockade, (46)

46) Luo, Fan, et al. "Niclosamide, an antihelmintic drug, enhances efficacy of PD-1/PD-L1 immune checkpoint blockade in non-small cell lung cancer." Journal for immunotherapy of cancer 7.1 (2019): 1-13.

Other Agents Enhance Checkpoint Inhibitors

- Beta Glucans DeGraff, 2018
- Ivermectin Dragonov, 2021
- Probiotics Kroemer, 2018
- Metformin (Afzal, 2018)
- Wnt Pathway Inhibitors Feng, 2019

de Graaff, Priscilla, et al. “Consumption of β-glucans to spice up T cell treatment of tumors: A review.” Expert opinion on biological therapy 18.10 (2018):1023-1040.

Draganov, Dobrin, et al. "Ivermectin synergizes with immune checkpoint blockade for treatment of breast cancer." NPJ breast cancer 7.1 (2021): 1-11.

Kroemer, Guido “Cancer immunotherapy in 2017: The breakthrough of the microbiota.” Nature Reviews Immunology 18.2 (2018): 87.53)

Afzal, Muhammad Zubair, Rima R. Mercado, and Keisuke Shirai. “Efficacy of metformin in combination with immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) in metastatic malignant melanoma.” Journal for immunotherapy of cancer 6.1 (2018): 64.

Feng, M.“Pharmacological inhibition of β-catenin/BCL9 interaction overcomes resistance to immune checkpoint blockades by modulating Treg cells.” Sci Adv 5.5 (2019): eaau5240.

Niclosamide Autophgay Inhibitor

- 2014 Dr Yng Dao studied effect of Niclosamide on Lysosomes.
- Inhibits mTOR which induces “protective autophagy”.
- Yet the Drug Blocks Late Stage Autophagy (accumulation of LCIII and P62).
- Increases pH of lysososmes.
- Releases of Cathepsins into Cytosol.

81) Gao, Ying, et al. “Niclosamide blocks autophagy via lysosomal dysfunction (663.18).” FASEB Journal (2014): 663-18

Niclosamide Dosing

- 2018 Dr Susen Burdock : Nicolo Trial Niclosamide for Colon Cancer Clinical Trial.
- 2 grams niclosamide orally per day until progression or toxicity.

29) Burock, Susen, et al. “Phase II trial to investigate the safety and efficacy of orally applied niclosamide in patients with metachronous or sychronous metastases of a colorectal cancer progressing after therapy: the NIKOLO trial.” BMC Cancer 18 (2018).

Other Anti-Parasitic Drugs
Ivermectin

- Ivermectin
- Artemisinin, Artesunate
- Mebendazole, Fenbendazole
- Pyrvinium
- Alinia

29) Burock,

Ivermectin Nobel Prize

- 1981 William C. Campbell and Satoshi Ōmura Discover Ivermectin.
- 1987 FDA Approved Antiparasitic.
- 2015 Nobel Prize in Medicine
- “Astonishingly safe… Wonder drug … one of the Greatest Medical Accomplishments of the 20th Century.”
- Eliminates River Blindness parasite, Lymphatic Filariasis (Elephantiasis)

Crump, Andy, and Satoshi Omura. “Ivermectin, Wonder Drug from Japan: the human use perspective.” Proceedings of the Japan Academy, Series B 87.2 (2011): 13-28.

Ivermectin Anti-Parasitic Drug

- Humans: strongyloidiasis, ascariasis, cutaneous larva migrans, gnathostomiasis and
- trichuriasis, pediculosis (lice) and scabies (mites) 200 million humans globally have taken the drug for parasitic diease
- Veterinary: Antiparasitic for Billions of pets, horses, farm animals
- Heartworm in dogs

3) Khan Sharun, T. S., et al. “Current therapeutic applications and pharmacokinetic modulations of ivermectin.” Veterinary World 12.8 (2019): 1204.

Ivermectin Anti-Cancer Drug Targeting

- Akt/mTOR pathway
- Wnt -TCF pathways
- Purinergic P2X receptors (ATP sensitive receptors)
- PAK-1 protein (P21-activated kinase)
- Chloride channel receptors
- Cancer stem cells
- Multidrug Resistance Protein (MDR)
- Cancer-related epigenetic deregulators such as SIN3A and SIN3B, RNA helicase(5)

5) Juarez, Mandy, Alejandro Schcolnik-Cabrera, and Alfonso Dueñas-Gonzalez. “The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug.” American journal of cancer research 8.2 (2018): 317.

Ivermectin Anti-Cancer Effect Achievable at Antiparasitic Dosage

- 2018 Dr. Mandy Juarez:
- “Importantly, the in vitro and in vivo anti-tumor activities of ivermectin are achieved at concentrations that can be clinically reachable based on the human pharmacokinetic studies done in healthy and parasite patients. Thus, existing information on ivermectin could allow its rapid move into clinical trials for cancer patients.”

5) Juarez, Mandy, Alejandro Schcolnik-Cabrera, and Alfonso Dueñas-Gonzalez. “The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug.” American journal of cancer research 8.2 (2018): 317.

Ivermectin Dosing

- Usual Adult Dose for Scabies 0.2 mg/kg orally once, and repeated in 2 weeks.
- For Covid-19:
  0.2 -0.3 mg/kg daily x 1-5 days.

5) Juarez,.

Ivermectin Hi Throughput Screen Leukemia

- 2010, Dr. Sharmeen Screened 100 drugs for anti-leukemic activity.
- Ivermectin most promising at low MicroM concentration.
- Synergy with Cytarabine and Daunorubicin
- Does Not Cross Blood Brain Barrier, no adverse neurologic effects, not suitable for brain tumors.

Sharmeen, Sumaiya, et al. “The antiparasitic agent ivermectin induces chloride-dependent membrane hyperpolarization and cell death in leukemia cells.” Blood 116.18 (2010): 3593-3603.

Ivermectin Cancer Stem Cell Agent

- (2014), Dr. Alice Melotti Screened 1,040 drugs as inhibitor of Wnt/TCF pathway.
- Only one agent Ivermectin perfectly tracked gene expression profile of Blocking TCF Gene and Inhibiting Wnt Pathway: Ivermectin.
- 2012 Dr Hallet: Ivermectin Eradicates Breast Cancer Stem Cells.

Melotti, Alice, et al. “The river blindness drug Ivermectin and related macrocyclic lactones inhibit WNT-TCF pathway responses in human cancer.” EMBO molecular medicine 6.10 (2014): 1263-1278.
Hallett, Robin M.“Small molecule antagonists of the Wnt/beta-catenin pathway target breast tumor-initiating cells in a Her2/Neu mouse model of breast cancer.” PloS one 7.3 (2012): e33976.

Ivermectin Breast Cancer TME

- 2015, Dr. Dobrin Dragonov Tumors have upregulated P2X7 receptors which regulate high ATP concentrations in the tumor micro-environment, promoting tumor progression.
- Ivermectin sensitizes CATION channels to ATP, opening them further, allowing influx of large CATIONS, causing cancer cell death.
- “Ivermectin kills mouse and human breast cancer [TNBC] cells through augmented P2X7-dependent purinergic signaling associated with caspase-1 and caspase-3 activation.”

Draganov, Dobrin, et al. “Modulation of P2X4/ P2X7/pannexin-1 sensitivity to extracellular ATP via ivermectin induces a non-apoptotic and inflammatory form of cancer cell death.” Scientific reports 5 (2015).

Ivermectin Breast Cancer

- TNBC Cells: Ivermectin effective at low concentrations: 2 MicroM w/24 hr exposure.
- IVER Induces Immunogenic Cell Death, robust anti-cancer immune response…may induce long term or permanent remission.

Draganov, Dobrin, et al. “Modulation of P2X4/P2X7/pannexin-1 sensitivity to extracellular ATP via ivermectin induces a non-apoptotic and inflammatory form of cancer cell death.” Scientific reports 5 (2015).

Ivermectin Anti-Viral Effects

- Activity against RNA viruses (adenovirus, coronavirus, yellow fever virus, dengue fever).
- Inhibition of nuclear transport performed by the Importin α/β1 Heterodimer.
- 2020, Dr. Leon Caly: Single treatment with ivermectin reduced viral RNA 5,000-fold after 48 hours in a cell culture infected with SARS-coV-2 virus in vitro.

Yang, Sundy NY, et al. "The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer." Antiviral research (2020): 104760.

Caly, Leon, et al. "The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro." Antiviral research (2020): 104787

Ivermectin Effective for All Phases of Disease

- **18 RCTs** of ivermectin in COVID-19: Large, Statistically Significant Reductions in Mortality, Time to clinical Recovery, and Time to Viral Clearance.
- Numerous Controlled Prophylaxis Trials: Significantly reduced risk of contracting COVID-19 with the regular use of ivermectin.
- Ivermectin distribution campaigns lead to rapid population-wide decreases in morbidity and mortality.

Kory, Pierre, et al. "Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19." American Journal of Therapeutics 28.3 (2021): e299.

Ivermectin for Rosacea

- Soolantra topical cream

Kory, Pierre,.

Other Anti-Parasitic Drugs
Pyrvinium (Vanquin)

- FDA Approved for Pinworm
- Available Scandaniavia, Germany, Not in US (replaced by Mebendazole)
- Potent Wnt Inhibitor Cancer Stem Cell Agent at 10 MicroM
- Activates CK1-Alpha degrades Beta Catenin, inhibiting Wnt Signalling
- Blast Cell Leukemia, Lymphoma, Breast

Pyrvinium (Vanquin) Inhibits Mitochondrial Respiration: NADH Fumarate Reductase

- NADH Fumarate reductase system functions in parasites under hypoxic conditions.
- Pyrvinium has anti-cancer effect within tumour-mimicking microenvironments, inhibited NADH Fumarate activities in both parasites and mammalian mitochondria. (44) (Tomitsiku)

Pyrvinium (Vanquin) References

- 37) Thorne, Curtis A et al. “Small-Molecule Inhibition of Wnt Signaling Activation of Casein Kinase 1α.” Nature chem biol 6.11 (2010):
- 38) Xu, Liang, et al. “WNT pathway inhibitor pyrvinium inhibits self-renewal and metastasis of breast cancer stem cells.” Int j oncology 48.3 (2016): 1175
- 39) Xiao, Meifang, et al. “Pyrvinium induces apoptosis of lymphoma cells through impairing mitochondrial functions and JAK2/STAT5.” Biochem and biophys res comm 469.3 (2016): 716
- 40) Xu, Wei, et al. “The antihelmintic drug pyrvinium pamoate targets aggressive breast cancer.” PloS one 8.8 (2013): e71508.
- 41) Ishii, Isao et al “Reprofiling pyrvinium as an anti-cancer drug targeting mitochondrial respiration.” Frontiers in Onc 2 (2012): 137.
- 42) Xiang, Wei, et al. “Pyrvinium selectively targets blast phase-chronic myeloid leukemia.” Oncotarget 6.32(2015)
- 44) Tomitsuka, Eriko et al. “pyrvinium pamoate inhibits the NADH–fumarate reductase system—a unique mitochondrial energy metabolism in tumour microenvironments.”J of biochem (2012):

Nitazoxanide (NTZ) Alinia c-Myc Inhibitor

- C-Myc OncoGene Considered "Undruggable" x 40 years
- 2013 Dr Fan Minogue Hi Thruput screen 5,000 compounds for c-Myc Inhibitor. NTZ was "most potent hit"

62) Fan-Minogue, Hua, et al. "A c-Myc activation sensor-based high throughput drug screening identifies an anti-neoplastic effect of Nitazoxanide." Molecular cancer therapeutics 12.9 (2013): 1896

Nitazoxanide (NTZ) Alinia c-Myc Inhibitor

- Wnt and IL6 Inhibitor
- Suppresses PDI- Protein Disulfide Isomerase (protein folding)
- OXPHOS inhibitor
- High Plasma Concentrations
- “highest drug positioning potential

62) Fan-Minogue, Hua, et al. “A c-Myc activation sensor-based high throughput drug screening identifies an anti-neoplastic effect of Nitazoxanide.” Molecular cancer therapeutics 12.9 (2013): 1896

Nitazoxanide (NTZ) References

- 63) Qu, Yi, et al. “nitazoxanide promotes [beta]-catenin citrullination and inhibits Wnt signaling in cancer.” Nature ChemBiology (2017).
- 64) Hong, Seong Keun, et al. “Nitazoxanide suppresses IL-6 production in LPS-stimulated mouse macrophages and TG-injected mice.” International immunopharmacology 13.1 (2012): 23-27.
- 65) Di Santo, Nicola, and Jessie Ehrisman. “Research perspective: potential role of nitazoxanide in ovarian cancer treatment. Old drug, new purpose?” Cancers 5.3 (2013): 1163-1176.
- 66) Lee, Eunyoug, and Do Hee Lee. “Emerging roles of protein disulfide isomerase in cancer.” BMB reports 50.8 (2017): 401
- 67) Xu, Shili, Saranya Sankar, and Nouri Neamati. “Protein disulfide isomerase: a promising target for cancer therapy.” Drug discovery today 19.3 (2014): 222-240.
- 68) Kuo, T. F., et al. “Protein disulfide isomerase a4 acts as a novel regulator of cancer growth through the procaspase pathway.” Oncogene (2017). Oncogene. 2017 Sep 28; 36(39):5484-5496.

Nitazoxanide (NTZ) References

- 69) Badolato, Mariateresa, et al. “Synthesis and Experimental Validation of New PDI Inhibitors with Antiproliferative Activity.” Journal of Chemistry 2017 (2017).
- 70) Di Santo, Nicola, and Jessie Ehrisman. “A functional perspective of nitazoxanide as a potential anticancer drug.” Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 768 (2014): 16-21.
- 72) Shakya, Anshul, Hans R. Bhat, and Surajit Kumar Ghosh. “Update on nitazoxanide: a multifunctional chemotherapeutic agent.” Current drug discovery technologies 15.3 (2018): 201-213.

Nitazoxanide (NTZ) References

- 69)

Mebendazole (Vermox)

- 1968 First synthesized by Janssen Pharm
- FDA-approved in 1972 (pinworm, roundworm)
- Dosage 100 mg PO BID (w/fatty meal)
- Good Toxicity Profile
- Pharmacokinetics: therapeutic concentrations at Disease Site,
- Ease of administration
- Low price.

87) Guerini, Andrea Emanuele, et al. “Mebendazole as a Candidate for Drug Repurposing in Oncology: An Extensive Review of Current Literature.” Cancers 11.9 (2019): 1284.

Mebendazole (Vermox)

- Microtubule Disruptor, Impairs Spindle Formation, Prevents Cell Division
- Downregulates BCL2 (anti-apoptosis protein) similar to Venetoclax
- Microtubule Chemotherapy: taxane, paclitaxel, docetaxel, vinblastine, vincristine, nocodazole,and colchicine, etc.

87) Guerini, Andrea Emanuele, et al. “Mebendazole as a Candidate for Drug Repurposing in Oncology: An Extensive Review of Current Literature.” Cancers 11.9 (2019): 1284.

Mebendazole (Vermox)

- 2008 Dr Doudican Hi Thruput Screen 2,000 common drugs against malignant melanoma.
- Mebendazole most promising agent.
- Downregulates BCL2 (anti-apoptosis protein)
- "the antineoplastic effects of mebendazole in human melanoma cells result from differential Bcl-2 – mediated cellular responses to mebendazole-induced tubulin disruption." (88)

88) Doudican, Nicole, et al. "Mebendazole induces apoptosis via Bcl-2 inactivation in chemoresistant melanoma cells." Molecular Cancer Research 6.8 (2008): 1308-1315..

Mebendazole (Vermox)

- 2017 Dr Zhang head and neck squamous cell CA
- Mebendazole more potent than Cisplatin.

91) Zhang, Fugui, et al. “Anthelmintic mebendazole enhances cisplatin’s effect on suppressing cell proliferation and promotes differentiation of head and neck squamous cell carcinoma (HNSCC).” Oncotarget 8.8 (2017): 12968.

Mebendazole (Vermox) Synergy with Autophagy Inhibitor

- 2019 Dr So Jung Sung Endothelial Cells
- Pronounced induction of “Protective Autiophagy”
- Synergy with Chloroquine

91) Zhang, Fugui, et al. “Anthelmintic mebendazole enhances cisplatin’s effect on suppressing cell proliferation and promotes differentiation of head and neck squamous cell carcinoma (HNSCC).” Oncotarget 8.8 (2017): 12968.

Mebendazole Case Report Metastatic Adrenocortical Cancer

- 2011 Dr Dobrosotskaya
- 48 Y/o metastatic adrenocortical CA.
- Conventional chemoradiation unsuccessful.
- 100 mg PO BID Mebendazole sole treatment
- Initial regression, then stable over 19 months.
- 24 months progressive disease
- Better result with addition of HCQ ?

9) Dobrosotskaya, I. Y., et al. “Mebendazole monotherapy and long-term disease control in metastatic adrenocortical carcinoma.” Endocrine practice: 17.3 (2011): e59.

Mebendazole Hi Thruput Screen

- 2018 Dr Licai
- High Thu Put Screen 1,000 drugs for AML
- Mebendazole best candidate

11) Nygren, Peter, and Rolf Larsson. “Drug repositioning from bench to bedside: Tumour remission by the antihelmintic drug mebendazole in refractory metastatic colon cancer.” Acta Oncologica 53.3 (2014): 427-428.

Mebendazole Case Report Metastatic Colon Cancer

- 2014 Dr Peter Nygren
- 74 Y/O Metastatic Colon CA refractory to chemo.
- 100 mg PO BID Mebendazole sole treatment
- CAT Scans Show near complete remission of metastatic lung lesions, partial remission of liver lesions.
- Better result with addition of HCQ ?

11) Nygren, Peter, and Rolf Larsson. “Drug repositioning from bench to bedside: Tumour remission by the antihelmintic drug mebendazole in refractory metastatic colon cancer.” Acta Oncologica 53.3 (2014): 427-428.

Mebendazole - Immunotherapy

- 2017 Dr Blom MB upregulates anti-tumor immune function (13)
- 2018 Dr Rubin, MB enhances T cell activation and tumor killing. (14)

13) Blom, Kristin, et al. “The anticancer effect of mebendazole may be due to M1 monocyte/macrophage activation via ERK1/2 and TLR8-dependent inflammasome activation.” Immunopharmacology and immunotoxicology 39.4 (2017): 199-210.

14) Rubin, Jenny, et al. “Mebendazole stimulates CD14+ myeloid cells to enhance T-cell activation and tumour cell killing.” Oncotarget 9.56 (2018): 30805.

Mebendazole - Pathways

- Inactivates BCL-2 (the anti-apoptotic protein)(23)
- Hedgehog inhibitor (Cancer Stem Cell Pathway) (36–37)(43–47)
- Inactivates C-Myc (39)
- Downregulates MDM drug resistance (40)

13) 199-210.

Mebendazole – Drug Synergies

- Autophagy inhibitors: chloroquine/ hydroxychloroquine, clarithromycin, thymoquinone, etc.
- Metformin
- Metronomic chemotherapy
- Taxanes of vinca alkaloids microtubule agents
- Albendazole
- Itraconazole
- Cimetidine
- Diclofenac (NSAID)

13) 199-210.

Fenbendazole – Joe Tippens

- Autophagy inhibitors: chloroquine/

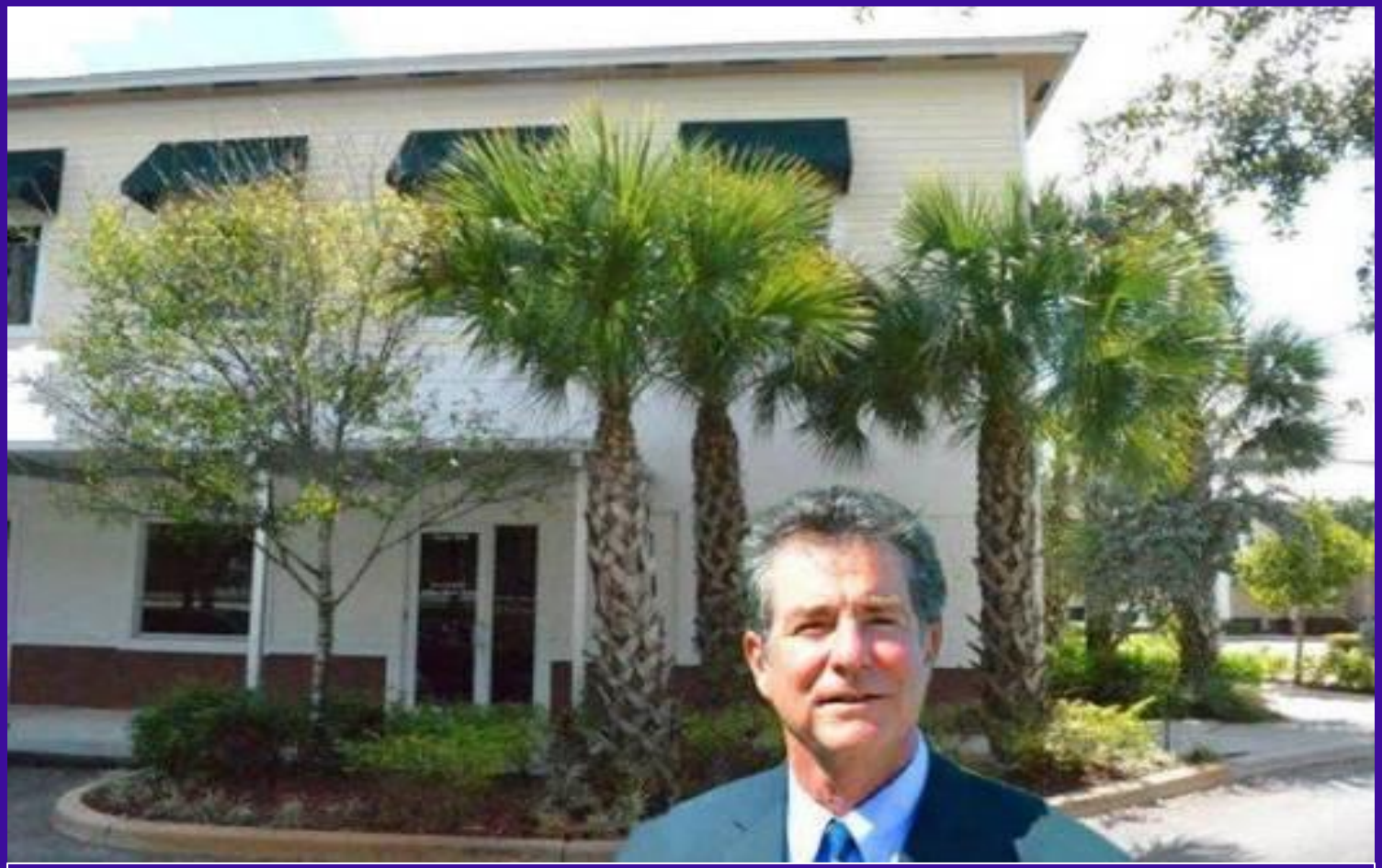
13) 199-210.

Artemisinin/Artesunate Gift from China

- Nobel Prize 2015 Dr Too You

13) 199-210.

Thank You – Any Questions?



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Extra Slides After This Point

Synergy with Chemo Radiation

- DCA Alone (Lu, Xiao, et al, 2018)Note: DCA alone induces protective autophagy, however, when used with chemotherapy, DCA inhibits protective autophagy induced by chemo, and is therefore synergistic.
- DCA + Propranolol (Lucido, 2018)
- Sulforaphane.(Milczarek 2017) (Lee2018)
- Chloroquine-doubled the median survival time in glioblastoma (Pascolo, Steve.2016) Pascolo, Steve. “Time to use a dose of chloroquine as an adjuvant to anti-cancer chemotherapies.” European journal of pharmacology 771 (2016): 139-144.
- Ivermectin (Liu, Jian, 2020)

Autophagy Inhibitors -Synergy with Drugs, Chemo Radiation

- Both CQ and HCQ can effectively increase the efficacy of various anti-cancer drugs….in combination with CQ or HCQ include[ing] chemotherapeutic drugs, tyrosine kinase inhibitors, various monoclonal antibodies, hormone therapies and radiotherapy.

Verbaanderd, Ciska, et al. “Repurposing Drugs in Oncology (ReDO)—chloroquine and hydroxychloroquine as anti-cancer agents.” ecancermedicalscience 11 (2017).

Pagotto, Anna, et al. “Autophagy inhibition reduces chemoresistance and tumorigenic potential of human ovarian cancer stem cells.” Cell death & disease 8.7 (2017): e2943-e2943

Zhang, Le, et al. “Mebendazole Potentiates Radiation Therapy in Triple-Negative Breast Cancer.” International Journal of Radiation Oncology, Biology, Physics. 103.1 (2019): 195-207.

Mefloquine Synergy with Chemo

- Mefloquine Enhances chemotherapy in MDR drug resistance (inhibits p-glycoprotein)

40) Fujita, R., et al. “Enhancement of doxorubicin activity in multidrug-resistant cells by mefloquine.” Methods and findings in experimental and clinical pharmacology 22.5 (2000): 281-284.
41) Kim, Ju-Hwa, et al. “Co-treatment with the anti-malarial drugs mefloquine and primaquine highly sensitizes drug-resistant cancer cells by increasing P-gp inhibition.” Biochemical and biophysical research communications 441.3 (2013): 655-660.

Mefloquine Synergy w/ Tyrosine Kinase Inhibitors = imatinib or ponatinib

- Blast-phase chronic myeloid leukemia

43) Yi, Hui Lam, et al. “Lysosome Inhibition by Mefloquine Preferentially Enhances the Cytotoxic Effects of Tyrosine Kinase Inhibitors in Blast Phase Chronic Myeloid Leukemia.” Translational oncology 12.9 (2019): 1221-1228.

44) Xiang, Wei, et al. “Mefloquine enhances the cytotoxic effects of tyrosine kinase inhibitors in blast phase chronic myeloid leukaemia by lysosome membrane disruption.” (2017): 1050-1050.

Autophagy Inhibitor plus TKI Eliminates Cancer Stem Cells

- “CML stem cells are completely eliminated by combination treatment with tyrosine kinase inhibitors (TKIs), such as IM, nilotinib, or dasatinib, and autophagy inhibitor . Autophagy inhibitors promote the therapeutic effect of TKIs in CML treatment.” Yun, 2021

Bellodi, C.; et al. Targeting autophagy potentiates tyrosine kinase inhibitor–induced cell death in Philadelphia chromosome–positive cells, including primary CML stem cells. J. Clin. Investig. 2009, 119, 1109–1123.
Yun, Chul Won, et al. "The Dual Role of Autophagy in Cancer Development and a Therapeutic Strategy for Cancer by Targeting Autophagy." International Journal of Molecular Sciences 22.1 (2021): 179.

Autophagy Inhibitor /Statin and 2DG

- Lovastatin and 2-DG synergistically reduced cell viability, arrested cells in the G2/M phase, and induced apoptosis.
- Energy depletion activated AMPK, inhibited mTOR and RAS, **inducing autophagy**,
- Inhibition of autophagy by chloroquine enhanced the cytotoxic effect of lovastatin and 2-DG
- Concurrently targeting Glycolysis, OXPHOS, and Autophagy may be promising for RAS-driven colorectal cancers." (Huang, 2021)

Huang, Xiao-ming, et al. "Autophagy inhibitors increase the susceptibility of KRAS-mutant human colorectal cancer cells to a combined treatment of 2-deoxy-D-glucose and lovastatin." Acta Pharmacologica Sinica (2021): 1-13.

Autophagy Inhibitor /Statin and 2DG

- Lovastatin –OXPHOS Inhibitor
- 2-DG – Glycolysis Inhibitor (such as DCA)
- Induces Protective Autophagy
- Adding Autophagy Inhibitor (Chloroquine)
- Lethal Synergy

Huang, Xiao-ming, et al. "Autophagy inhibitors increase the susceptibility of KRAS-mutant human colorectal cancer cells to a combined treatment of 2-deoxy-D-glucose and lovastatin." Acta Pharmacologica Sinica (2021): 1-13.

Mefloquine Synergy w/ Chemotherapy in Colon Cancer Xenograft Model

- Mefloquine/chemo 5-FU, Oxaliplatin dramatically decreased CSC pop.(0.1%).
- Mouse xenografts, MQ/chemo "drastically reduced" tumor volume compared to single-agent use.
- Safe with no adverse side effects

45) Takeda, Mitsunobu, et al. "Disruption of endolysosomal rab5/7 efficiently eliminates colorectal cancer stem cells." Cancer research 79.7 (2019): 1426-1437.

AntiMalarials Synergy w/ Chemotherapy Breast Cancer

- “The combination of chloroquine, artesunate and mefloquine with DOX and PTX was synergic (CI < 1). The combination of DOX and mefloquine after 48 h incubation demonstrated the highest cytotoxicity against MCF-7 cells, and the combination of DOX and artesunate was the most synergic. These results suggest antimalarials could act synergistically with DOX/PTX for breast cancer therapy.” (Duarte 2020)

Duarte, Diana, and Nuno Vale. "New Trends for Antimalarial Drugs: Synergism between Antineoplastics and Antimalarials on Breast Cancer Cells." Biomolecules 10.12 (2020): 1623.

Synergy with Chemo Radiation

- Ivermectin/Cisplatin....Zhang, Xiaohong, et al. “Ivermectin Augments the In Vitro and In Vivo Efficacy of Cisplatin in Epithelial Ovarian Cancer by Suppressing Akt/mTOR Signaling.” The American Journal of the Medical Sciences 359.2 (2020): 123-129.
- COX-2 inhibitors downregulate the MDR gene reducing expression of P-glycoprotein (P-gp) thus downregulating the efflux pump and increasing chemotherapy drug concentration in the cancer cells.

Synergy with Chemo Radiation

- Celecoxib, a selective inhibitor of COX-2, at 25 microM concentration increased the accumulation of doxorubicin in HepG2 cells and enhanced the sensitivity of the cells to doxorubicin **by tenfold**. (75)
- in 2018, Dr. Torres-Collado suggested using celecoxib in combination with CD-19 CAR T therapy in NHL to overcome apoptosis resistance.

75) Roy, Karnati R., et al. "Celecoxib inhibits MDR1 expression through COX-2-dependent mechanism in human hepatocellular carcinoma (HepG2) cell line." Cancer chemotherapy and pharmacology 65.5 (2010): 903-911

Synergy , Sensitizing to Chemo therapy

- Doxycycline Synergy with DOXOrubicin chemo in Prostate CA

70) Zhu, Chao, et al. “Doxycycline synergizes with doxorubicin to inhibit the proliferation of castration-resistant prostate cancer cells.” Acta biochimica et biophysica Sinica 49.11 (2017): 999-1007.

Sulforaphane Synergy with Chemo therapy

- 2017 and 2018, studies by Drs. Milczarek and Lee showed sulforaphane synergizes with chemotherapy agents,
- 5-FU in triple-negative breast cancer and
- Cisplatin in mesothelioma.
- (92–93)

92) Milczarek, Małgorzata, et al. “Autophagic cell death and premature senescence: New mechanism of 5-FU and sulforaphane synergistic anticancer effect in MDA-MB-231 triple negative breast cancer cell line.” Food and Chemical Toxicology 111 (2018): 1-8.
93) Lee, Yoon-Jin, and Sang-Han Lee. “Pro-oxidant activity of sulforaphane and cisplatin potentiates apoptosis and simultaneously promotes autophagy in malignant mesothelioma cells.” Molecular Medicine Reports 16.2 (2017): 2133-2141

Metformin Synergy with Chemo therapy Prevents Relapse after Chemo

- 2013, Dr. Heather Hirsch
- Metformin plus Doxorubicin prevented relapse in
- Mouse xenograft model of prostate cancer,
- Also in a lung cancer model. (9)

9) Hirsch, Heather A., Dimitrios Iliopoulos, and Kevin Struhl. “Metformin inhibits the inflammatory response associated with cellular transformation and cancer stem cell growth.” Proceedings of the National Academy of Sciences 110.3 (2013): 972-977.

Mebendazole Synergy w Chemo/Rad Tx

- Sorafenib for Hepatocellular Carcinoma(15)
- Docetaxel for prostate cancer (16)
- Navitoclax in Non-Small-Cell Lung Cancer (17)
- Radiation Therapy for Breast Cancer (18–19)

15) Younis, Nancy S., Amal MH Ghanim, and Sameh Saber. “Mebendazole augments sensitivity to sorafenib by targeting MAPK and BCL-2 signalling in n-nitrosodiethylamine- induced murine hepatocellular carcinoma.” Scientific Reports 9.1 (2019): 1-16.
16) Rushworth, Linda K., et al. “Repurposing screen identifies mebendazole as a clinical candidate to synergise with docetaxel for prostate cancer treatment.” British Journal of Cancer (2019): 1-11.
17) Lam, Lloyd T., et al. “Antihelminthic benzimidazoles potentiate navitoclax (ABT-263) activity by inducing Noxa-dependent apoptosis in non-small cell lung cancer (NSCLC) cell lines.” Cancer cell international 15.1 (2015): 5.
18) Zhang, Le, et al. “Mebendazole Potentiates Radiation Therapy in Triple-Negative Breast Cancer.” International Journal of Radiation Oncology* Biology* Physics 103.1 (2019): 195-207.
19) Skibinski, Christine G., Tara Williamson, and Gregory J. Riggins. “Mebendazole and radiation in combination increase survival through anticancer mechanisms in an intracranial rodent model of malignant meningioma.” Journal of neuro-oncology 140.3 (2018): 529-538.

Mebendazole Synergy w Chemotherapy

- Cisplatin Head/Neck Squamous cell
- Cyclophosphamide Burkit Lymphoma
- Gemcitabine Breast Cancer.

Cisplatin : Zhang, Fugui, et al. "Anthelmintic mebendazole enhances cisplatin's effect on suppressing cell proliferation and promotes differentiation of head and neck squamous cell carcinoma (HNSCC)." Oncotarget 8.8 (2017): 12968.

Cyclophaphamide: Béogo, Rasmané, et al. "Endemic Burkitt lymphoma of maxillofacial region: Results of induction treatment with cyclophosphamide plus methotrexate in West Africa." Pediatric blood & cancer 56.7 (2011): 1068-1070.

Gemcitabine : Coyne, C. P., Toni Jones, and Ryan Bear. "Gemcitabine-(C4-amide)-[anti-HER2/neu] anti-neoplastic cytotoxicity in dual combination with mebendazole against chemotherapeutic-resistant mammary adenocarcinoma." Journal of clinical & experimental oncology 2.2 (2013).

Mebendazole Synergy with Docetaxel in Prostate Cancer

16) Rushworth, Linda K., et al. “Repurposing screen identifies mebendazole as a clinical candidate to synergise with docetaxel for prostate cancer treatment.” British Journal of Cancer (2019): 1-11.

Thymoquinone Synergy with Docetaxel in Prostate Cancer

70) Singh, Santosh Kumar, et al. “Docetaxel Combined with Thymoquinone Induces Apoptosis in Prostate Cancer Cells via Inhibition of the PI3K/AKT Signaling Pathway.” Cancers 11.9 (2019): 1390.

Thymoquinone Synergy w Chemo for Glioblastoma

- In 2016, Dr. Monao Pazhouhi et al. showed that TQ synergistically potentiates the cytotoxicity of chemo drug temozolomide in a glioblastoma cell line through inhibition of autophagy. (13–14)
- Most chemotherapy drugs induce protective autophagy, conferring drug resistance and cell survival. Addition of an autophagy inhibitor will overcome the drug resistance and make the chemotherapy more effective.

13) Pazhouhi, Mona, et al. “Thymoquinone synergistically potentiates temozolomide cytotoxicity through the inhibition of autophagy in U87MG cell line.” Iranian journal of basic medical sciences 19.8 (2016): 890.

Tocotrienol Vit E Synergy with Docetaxel in Prostate Cancer

Asay, Spencer, et al. “γ-Tocotrienol and α-Tocopheryloxyacetic Acid Increase the Effectiveness of Docetaxel Treatment of PC-3 Prostate Cancer Cells and Docetaxel-resistant PC-3 Cells.” The FASEB Journal 33.S1 (2019): 647-2.

PPI Pantoprazole Synergy with Docetaxel in Breast Cancer, prostate, and epidermoid skin cancer

- Like other chemo drugs, Docetaxol induces "Protective Autophagy"
- Adding Autophagy Inhibitor such as PPI drug Provides Synergy

30) Tan, Q., et al. "Effect of pantoprazole to enhance activity of docetaxel against human tumour xenografts by inhibiting autophagy." British journal of cancer 112.5 (2015): 832-840.

CAD Antihistamines Synergy w/Chemo

- Clinically relevant concentrations of cationic amphiphilic antihistamines sensitize cancer cells to chemotherapy and revert multidrug resistance. (56).
- Loratadine (Claritin) w/ cisplatin

56) Ellegaard, Anne-Marie, et al. “Repurposing cationic amphiphilic antihistamines for cancer treatment.” EBioMedicine 9 (2016): 130-139

68) Adly, Nouran. “Evaluation of cytotoxic potential of loratadine and the combination of loratadine and cisplatin on hepatocellular carcinoma cell lines.” (2017).

A More Robust Prostate Cancer Protocol

- DCA (plus poly-MVA) or diclofenac- glycolysis inhibitor.
- Autophagy Inhibitor PPI drug such as pantoprazole, loratadine 10 mg/day
- Fenofibrate OXPHOS inhibitor, 400 mg per day with evening meal.
- Propranolol OXPHOS and autophagy inhibitor (80 mg per day) or
- niclosamide (dual OXPHOS/autophagy inhibitor)
- Sulforaphane (broccoli extract) depletes glutathione and is synergistic
- with autophagy inhibitors, eradicates CSCs.
- melatonin, thymoquinone, curcumin, boswellia, pterostilbene, iodine, poly-MVA (alpha lipoic and thiamine) etc.
- Dipyridamole

Itraconazole Synergy with Paclitaxel , Doxorubicin, 5FU

- Separates HII from VDAC
- Inhibits P-GlycoProt MDM

Ghadi, Mahdi, et al. "Itraconazole synergistically increases therapeutic effect of paclitaxel and 99mTc-MIBI accumulation, as a probe of P-gp activity, in HT-29 tumor-bearing nude mice." European Journal of Pharmacology 895 (2021): 173892.

3) Gu, Juan J., et al. “Itraconazole, an Oral Antifungal Drug, Is Active in Chemotherapy Resistant B-Cell Non- Hodgkin Lymphoma and Enhances the Anti-Tumor Activity of Chemotherapy Agents.” Blood. (2016): 5138-5138. doxorubicin (1μM),

35) Hu, Qiang, et al. “Itraconazole induces apoptosis and cell cycle arrest via inhibiting Hedgehog signaling in gastric cancer cells.” Journal of Experimental & Clinical Cancer Research 36.1 (2017): 50. 5FU

Vit D3 Synergy w Chemotherapy

- Gemcitabine in Pancreatic Cancer

19) Yu, Wei-Dong, et al. “Calcitriol enhances gemcitabine antitumor activity in vitro and in vivo by promoting apoptosis in a human pancreatic carcinoma model system.” Cell cycle 9.15 (2010): 3094-3101.

Dipyridamole Synergy w Chemotherapy

- Dipyridamole (DP) synergy combined with imatinib (Gleevac®), bortezomib, and chemotherapy drugs, vincristine, etoposide, and 5FU has been demonstrated. (52–57), prevents platelet activation, autophagy inhibitor

52) Hirose, M., et al. "Synergistic inhibitory effects of dipyridamole and vincristine on the growth of human leukaemia and lymphoma cell lines." British journal of cancer 56.4 (1987): 413-417.

53) Howell, Stephen B., et al. "Dipyridamole enhancement of etoposide sensitivity." Cancer research 49.15 (1989): 4147-4153.

54) Grem, Jean L., and P. H. Fischer. "Enhancement of 5-fluorouracil's anticancer activity by dipyridamole." Pharmacology & therapeutics 40.3 (1989): 349-371.

55) Grem, Jean L., and Paul H. Fischer. "Augmentation of 5-fluorouracil cytotoxicity in human colon cancer cells by dipyridamole." Cancer research 45.7 (1985): 2967-2972.

56) Goda, Ahmed E., et al. "Preclinical evaluation of bortezomib/dipyridamole novel combination as a potential therapeutic modality for hematologic malignancies." Molecular oncology 9.1 (2015): 309-322.

57) El-Sisi, Alaa E., et al. "Enhanced anticancer activity of combined treatment of imatinib and dipyridamole in solid Ehrlich carcinoma-bearing mice." Naunyn-Schmiedeberg's Archives of Pharmacology (2020): 1-17.

Ibrutiniub Synergy w Autophagy Inhibitors

- Antihistamine- H1 Loratidine Autophagy Inhibitor in malignant B cell lines and primary chronic lymphocytic leukemia cells." (Chanas 2019).
- Macrolide Antibiotics (Azithromycin, Clarithromycin)

Chanas-LaRue, Aaron. "Antihistamines induce synergistic cell death when combined with ibrutinib in malignant B cell lines and primary chronic lymphocytic leukemia cells." (2019).

Fenofibrate- FASN Inhibitors

- Fenofibrate
- Quercetin
- Orlistat (Xenical) Obesity Drug

34) Heuer, Timothy S., et al. “FASN inhibition and taxane treatment combine to enhance anti-tumor efficacy in diverse xenograft tumor models through disruption of tubulin palmitoylation and microtubule organization EBioMedicine 16 (2017): 51-62.

FASN Inhibitor w Taxane Chemo

- Combination of FASN inhibition and a taxane drug: near complete tumor regression in a variety of diverse tumor cell-line-and patient-derived tumor models that include lung, ovarian, pancreatic, and prostate tumor models …
- Results provide **compelling mechanism- and efficacy-based evidence** for combined FASN and taxane therapy as a cancer therapy. (34)
- Fenofibrate + Mebendazole/fenbendazole ?

34) Heuer, Timothy S., et al. "FASN inhibition and taxane treatment combine to enhance anti-tumor efficacy in diverse xenograft tumor models through disruption of tubulin palmitoylation and microtubule organization EBioMedicine 16 (2017): 51-62.

Mebendazole Synergy With:

- Sorafenib for hepatocellular carcinoma (15)
- Docetaxel for prostate cancer (16)
- Navitoclax in Non-Small-Cell Lung Cancer (17)
- Radiation Therapy for Breast Cancer (18–19)

15) Younis, Nancy S., Amal MH Ghanim, and Sameh Saber. "Mebendazole augments sensitivity to sorafenib by targeting MAPK and BCL-2 signalling in n-nitrosodiethylamine- induced murine hepatocellular carcinoma." Scientific Reports 9.1 (2019): 1-16.

16) Rushworth, Linda K., et al. "Repurposing screen identifies mebendazole as a clinical candidate to synergise with docetaxel for prostate cancer treatment." British Journal of Cancer (2019): 1-11..

17) Lam, Lloyd T., et al. "Antihelminthic benzimidazoles potentiate navitoclax (ABT-263) activity by inducing Noxa-dependent apoptosis in non-small cell lung cancer (NSCLC) cell lines." Cancer cell international 15.1 (2015): 5.

18) Zhang, Le, et al. "Mebendazole Potentiates Radiation Therapy in Triple-Negative Breast Cancer." International Journal of Radiation Oncology* Biology* Physics 103.1 (2019): 195-207.

Autophagy Inhibitors

- Propranolol- inhibitor of the PAP [phosphatidate phosphatase] activity of lipins, inhibits autophagy flux. (Brohée, Laura, 2018),
- Propranolol may be a Chloroquine CQ-like autophagy inhibitor. (Li, Yuan,2016)
- Doxycycline may inhibit autophagy in Breast cancer. (Zhang, Le,2017)
- Mefloquine, CQ, HCQ (anti-malarial)
- N

Autophagy Inhibitors 2

- mefloquine,
- chloroquine,
- hydroxychloroquine,
- pyrvinium,
- niclosamide-(stimulates protective autophagy, blocks late-stage autophagy),
- clarithromycin,
- thymoquinone,
- PPI drugs , omeprazole (Prilosec®).
- loratadine (Claritin®)

Autophagy Inhibitors 3 Synergies

- Chloroquine and Mebendazole, Fenbendazole
- 93) Sung, So Jung, et al. "Autophagy Is a Potential Target for Enhancing the Anti-Angiogenic Effect of Mebendazole in Endothelial Cells." Biomolecules & therapeutics 27.1 (2019): 117.
  94) Dogra, Nilambra, Ashok Kumar, and Tapas Mukhopadhyay. "Fenbendazole acts as a moderate microtubule destabilizing agent and causes cancer cell death by modulating multiple cellular pathways." Scientific reports 8.1 (2018): 11926.
- Chloroquine and Artemisinin..
  Ganguli, Arnab, et al. "Inhibition of autophagy by chloroquine potentiates synergistically anti-cancer property of artemisinin by promoting ROS dependent apoptosis." Biochimie 107 (2014): 338-349
- Chloroquine / Ivermectin Liu, Jingjing, et al. "Ivermectin induces autophagy-mediated cell death through the AKT/mTOR signaling pathway in glioma cells." Bioscience reports 39.12 (2019).

Autophagy Inhibitors 4 Synergies

- Chloroquine and Niclosamide Xiang, Di, et al. "Niclosamide, an anti-helminthic molecule, downregulates the retroviral oncoprotein Tax and pro-survival Bcl-2 proteins in HTLV-1-transformed T lymphocytes." Biochemical and biophysical research communications 464.1 (2015): 221-228.
- Mifepristone/autophagy inhibitor…. Ritch, Sabrina J., et al. "Advanced assessment of migration and invasion of cancer cells in response to mifepristone therapy using double fluorescence cytochemical labeling." BMC Cancer 19 (2019).
  Zhang, Lei, et al. "Mifepristone increases mRNA translation rate, triggers the unfolded protein response, increases autophagic flux, and kills ovarian cancer cells in combination with proteasome or lysosome inhibitors." Molecular oncology 10.7 (2016): 1099-1117.

Autophagy Inhibitors 5 Synergies

- Dr. Kinsey et al. then added the autophagy inhibitor hydroxychloroquine (HCQ) to the MEK inhibitor drug in the mouse xenograft model, finding the combination was now dramatically effective..

Kinsey, Conan G., et al. “Protective autophagy elicited by RAF→ MEK→ ERK inhibition suggests a treatment strategy for RAS-driven cancers.” Nature medicine 25.4 (2019): 620-627.

Clinical Trial- Chloroquine Glioblastoma

- Chloroquine doubled the median survival time in glioblastoma patients.
- 2006 clinical trial Dr. Julio Sotelo 30 post-op glioblastoma pts treated with chloroquine 150 mg per day for 12 months. Median survival after surgery was 24 months for chloroquine- treated patients and 11 months for controls. (53)

53) Sotelo, Julio, Eduardo Briceno, and Miguel Angel López-González. “Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial.” Annals of internal medicine 144.5 (2006): 337-343.

Case Report Pancreatic Cancer HCQ with Trametinib

- 81-year-old refractory pancreatic cancer patient in the clinic with the combination of hydroxychloroquine (600 mg twice daily) along with the MEK inhibitor (2mg of trametinib), finding a remarkable 50% regression of tumor size, resolution of debilitating pain, and dramatic reduction in the CA19–9 tumor marker, with no toxicity.

Kinsey, Conan G., et al. “Protective autophagy elicited by RAF→ MEK→ ERK inhibition suggests a treatment strategy for RAS-driven cancers.” Nature medicine 25.4 (2019): 620-627.

Case Report Pancreatic Cancer Bigelsen, Stephen

- Combination Therapy for Stage 4 Pancreatic Cancer: Hydroxychloroquine, Vitamin D3, and Chemotherapy

Bigelsen, Stephen. “AB091. P063. Case report: stage 4 pancreatic cancer to remission using paricalcitol and hydroxychloroquine in addition to traditional chemotherapy.” Annals of Pancreatic Cancer (2018).

Bigelsen, Stephen. “Evidence-based complementary treatment of pancreatic cancer: a review of adjunct therapies including paricalcitol, hydroxychloroquine, intravenous vitamin C, statins, metformin, curcumin, and aspirin.” Cancer Management and Research 10 (2018): 2003.

TME Tumor MicroEnvironment 1
Beta Blockers

- Beta-adrenergic signaling plays a role in the TME, inducing immunosuppression, and enhancing tumor immune evasion by impairing host anti-tumor immunity.(16–18) (Eng, Jason 2014)
- Cancer stem cells (CSCs) generate neurons (sympathetic and parasympathetic) in the micro-environment maintaining the cancer mass.(11–14) (Magnon, Claire, 2013) (Beta-Blocker)
- Propranolol/Metformin (forces Glycolysis) leads to glucose deprivation in TME (Rico, María, 2017)

TME Tumor MicroEnvironment 1 Solomon's Seal Inhibits CAFs

- Solomon's seal (Polygonatum odoratum and
- Polygonatum cyrtonema) inhibits Prostate cancer (CAFs = Cancer Associated Fibroblasts) (16)
- 16) Han, Shu-Yu, et al. "Polysaccharide from Polygonatum Inhibits the Proliferation of Prostate Cancer-Associated Fibroblasts Cells." Asian Pacific Journal of Cancer Prevention 17.8 (2016): 3829-3833)

TME Tumor Micro-Environment 2
Celecoxib for CAFS

- In 2019, Dr. Nassar Hashemi Goradel et al. reviewed the role of COX-2 in cancer with attention on cancer-associated fibroblasts (CAFs) in the tumor micro-environment (TME), which express COX-2 protein that then “feeds back” to the cancer-inducing CSC activity.

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TME Tumor Micro-Environment 3 Anti-Platelet Drugs- Restore Anti Tumor Immunity

- THE ROLE OF PLATELETs……..
- Platelet-Derived TGF-Beta Is an Immune Modulator In 2018,
- Dr. Min Soon Cho et al. studied a murine model of ovarian cancer, finding that platelet inhibition restores anti-tumor immune
- response and could be used as adjunct to checkpoint inhibitors and other immunotherapies. (36)S…

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TME Tumor Micro-Environment 3 Anti-Platelet Drugs - Dipyridamole

- ASA
- Dipyridamole Prevents Platelet Activation Upon platelet activation, granules containing growth factors such as VEGF, PDRF and TGF (transforming growth factor beta 1) are released into the tumor micro-environment, feeding and stimulating cancer cells.
- Dipyridamole blocks platelet activation by increasing cAMP (cyclic AMP) inside platelets, thus blocking release of growth factors. (2)(34)
- In 2017, Dr. Omar Elaskalani et al. write: Platelets are the major storage site for TGFβ1 [transforming growth factor beta 1] within the blood circulation, which is released from α-granules [platelet-derived granules] upon activation…. platelet-derived TGFβ1 … induce(s) a phenotypic conversion in cancer cells, from epithelial to mesenchymal-like cells [EMT], capable of invading extracellular matrices, migrating and surviving in the blood circulation … 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)

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TME Tumor Micro-Environment 3 Anti-Platelet Drugs - Aspirin

- Aspirin (ASA) In 2018, Dr. Chia-Chien Hsieh studied the effect of aspirin on the tumor micro-environmentin a triple-negative breast cancer (4T1) cell model in vitro, using a culture mediumsimulating the macrophage infiltration of the tumor micro-environment. Dr. Hsieh foundthat aspirin treatment decreased inflammatory cytokines in the tumor microenvironment,writing:[the aspirin] interfered with crosstalk between cancer cells and macrophages…and decreased angiogenic and inflammation-associated cytokine VEGF, PAI-1,MCP-1, IL-6, IL-10, and TGF-β production…suggesting that aspirin is a promising agentto prevent tumor progression. (44)

44) Hsieh, Chia-Chien, and Chih-Hsuan Wang. “Aspirin disrupts the crosstalk of angiogenic and inflammatory cytokines between 4T1 breast cancer cells and macrophages.” Mediators of Inflammation 2018 (2018).

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TME Tumor Micro-Environment 4 Anti-Platelet Drugs

- Platelets Inhibit Anti-Cancer Immunity
- In 2017, Dr. Saleh Rachidi et al. showed that platelets are the main culprits for impairing anti-cancer T cell immunity and that platelet inhibition is beneficial in restoring T cell function and anti-cancer immunity and synergizing with immunotherapies.
- Transforming growth factor β [TGFβ] and lactate [are] the major platelet-derived soluble factors to obliterate CD4+ and CD8+ T cell functions [anti-cancer immunity] …platelets are the dominant source of functional TGFβ systemically as well as in the tumor micro-environment through constitutive expression of TGFβ-docking receptor Glycoprotein A Repetitions Predominant (GARP) … T cell therapy of cancer can be substantially improved by concurrent treatment with … antiplatelet agents. We conclude that platelets constrain T cell immunity though a GARP-TGFβ axis and suggest a combination of immunotherapy and platelet inhibitors as a therapeutic strategy against cancer. (64–66)

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TME Tumor Micro-Environment 4 Anti-Platelet Drugs

- References for previous slide
- 64) Rachidi, Saleh, et al. “Platelets subvert T cell immunity against cancer via GARP-TGFβ axis.” Science immunology 2.11 (2017).
- 65) Xu, Xiaohong Ruby, George M. Yousef, and Heyu Ni. “Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents.” Blood 131.16 (2018): 1777-1789.
66) Contursi, Annalisa, et al. “Platelets as crucial partners for tumor metastasis: from mechanistic aspects to pharmacological targeting.” Cellular and Molecular Life Sciences 74.19 (2017): 3491-3507.

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Celecoxib COX-2 Inhibitor Curative Efficacy

- COX-2 Inhibition Improves Chemo/Radiotherapy attenuates glutathione levels in human malignant B cells when coimbined with chemo,
- Celecoxib reduces cancer stem cell markers
- Inhibition of COX-2 prevents chemotherapy induced cancer stem cell survival and repopulation, potentially leading to "**curative efficacy".**

16A) Hashemi Goradel, Nasser, et al."Cyclooxygenase-2 in cancer: A review." Journal of cellular physiology 234.5 (2019): 5683-5699.

55A) Pang, Lisa Y., Emma A. Hurst, and David J. Argyle. "Cyclooxygenase-2: a role in cancer stem cell survival and repopulation of cancer cells during therapy." Stem cells international 2016 (2016).

Celecoxib COX-2 Inhibitor

- Combination of celecoxib and conventional chemotherapy dramatically increased the chemo-sensitivity of breast cancer cells …(56)
- Restores GSK3Beta, downregulates Beta-Catenin, Wnt pathway inhibitor, CSC pathway.
- COX-2 inhibition downregulates IDO gene expression and restores immune function,
- In a 2015, Dr. Hongzhong Li studied breast cancer cells and the TME,finding tumor associated macrophages (TAMS) express COX-2 protein.

56) Harb, Jerry, Pen-Jen Lin, and Jijun Hao. “Recent development of Wnt signaling pathway inhibitors for cancer therapeutics.” Current oncology reports 21.2 (2019): 12.

Celecoxib COX-2 Inhibitor

- COX-2 inhibitors enhance efficacy and restore sensitivity to chemotherapy agents. (71–73)

56) Harb, Jerry

Celecoxib COX-2 Inhibitor Synergy with Chemo

- Celecoxib combined with chemotherapy has "curative efficacy" in human clinical trials of advanced-stage metastatic cancer.

90) Ralph, Stephen John, et al. "NSAID celecoxib: potent mitochondrial pro-oxidant cytotoxic agent sensitizing metastatic cancers and cancer stem cells to chemotherapy." J Cancer Metastasis Treat 4.49 (2018): 1-26.

71) Hohenforst-Schmidt, Wolfgang, et al. "COX-2 Inhibitors, a Potential Synergistic Effect with Antineoplastic Drugs in Lung Cancer." Oncomedicine 2017; 2:28-36

Celecoxib COX-2 Inhibitor Synergy with Radiation Therapy

Celecoxib/ Radiotherapy Synergy

86) Davis, Thomas W., et al. “Synergy between celecoxib and radiotherapy results from inhibition of cyclooxygenase-2-derived prostaglandin E2, a survival factor for tumor and associated vasculature.” Cancer research 64.1 (2004): 279-285.

87) Kishi, Kazushi, et al. “Preferential enhancement of tumor radioresponse by a cyclooxygenase-2 inhibitor.” Cancer research 60.5 (2000): 1326-1331.

88) Petersen, Cordula, et al. “Enhancement of intrinsic tumor cell radiosensitivity induced by a selective cyclooxygenase-2 inhibitor.” Clinical Cancer Research 6.6 (2000): 2513-2520.

89) Sminia, P., et al. “COX-2 inhibitors act as radiosensitizer in tumor treatment.” Biomedicine & pharmacotherapy 59 (2005): S272-S275.

Enhancing Checkpoint Inhibitors

- Propranolol (Beta Blockers)
- Patel, Vaibhav G., et al. "Effect of concurrent beta-blocker (BB) use in patients receiving immune checkpoint inhibitors for metastatic urothelial (mUC) and renal cell carcinomas (mRCC)." (2019): 467-467.

Enhancing Checkpoint Inhibitors Celecoxib

- 2019, Dr. Yamaguchi:
- Celecoxib augments the effect of PD-1 blockade (checkpoint blockade) in a malignant glioma model. (100)

100) Yamaguchi, Izumi, et al. “Downregulation of PD-L1 via FKBP5 by celecoxib augments antitumor effects of PD-1 blockade in a malignant glioma model.” Neuro-Oncology Advances (2019).

Enhancing Checkpoint Inhibitors Ivermectin

- Combination of ivermectin and anti-PD1 antibody merits clinical testing in breast cancer patients. ivermectin induces immunogenic cancer cell death (ICD) and robust T cell infiltration into breast tumors., ivermectin also selectively targets immunosuppressive populations including myeloid cells and Tregs, resulting in enhanced Teff/Tregs ratio. combination therapy with ivermectin and checkpoint inhibitor anti-PD1 antibody achieved synergy in limiting tumor growth ($p = 0.03$) and promoted complete responses ($p < 0.01$), also leading to immunity against contralateral re-challenge with demonstrated anti-tumor immune responses.

Draganov, Dobrin, et al. "Ivermectin converts cold tumors hot and synergizes with immune checkpoint blockade for treatment of breast cancer." NPJ breast cancer 7.1 (2021): 1-11.

Enhancing Checkpoint Inhibitors Diclofenac

- Reducing Lactate in the TME with Diclofenac or any Glycolysis Inhibitor (DCA) restores anti-tumor immunity and has synergy with Checkpoint inhibitors
- Diclofenac Synergy with Checkpoint Inhibitors
- in 2019 Dr. Kathrin Renner, combined Diclofenac with checkpoint inhibitor therapy (anti-PD-1) in a melanoma cell model, finding augmented effects via inhibition of lactate transporters MCT1 and MCT4 in a COX-independent manner. (11)

11) Renner, Kathrin, et al. “Restricting glycolysis preserves T Cell effector functions and augments checkpoint therapy.” Cell Reports 29.1 (2019): 135-150.

Combinations to Avoid

- Rituximab IV for lymphoma, statins will interferewith efficacy of the drug. Concomitant use of statins with rituximab is not recommended.
- Itraconazole, should not be used with rituximab, as recruitment of the CD20 marker is inhibited. (142–143)

142) Winiarska, Magdalena, et al. “Statins impair antitumor effects of rituximab by inducing conformational changes of CD20.” PLoS medicine 5.3 (2008): e64.
143) Ringshausen, Ingo, et al. “Antifungal therapy with itraconazole impairs the anti-lymphoma effects of rituximab by inhibiting recruitment of CD20 to cell surface lipid rafts.” Cancer research 70.11 (2010): 4292-4296.

Combinations to Avoid

- Propranolol (Beta Blockers) with Statin Drug- both mitochondrial Toxins
- mitochondrial toxins such as most OXPHOS inhibitors, statins, beta blockers, doxycycline, clarithromycin, niclosamide, pyrvinium, etc.
- DCA with artesunate case report…102) Uhl, Martin, Stefan Schwab, and Thomas Efferth.“Fatal liver and bone marrow toxicity by combinationtreatment of dichloroacetate and artesunate in a glioblastoma multiforme patient: case report and review of the literature.” Frontiers in oncology 6 (2016): 204

Combinations to Avoid OXPHOS INHIBITORS

- mitochondrial toxins such as most OXPHOS inhibitors, statins, beta blockers, doxycycline, clarithromycin, niclosamide, pyrvinium, etc.
- Fenofibrate combined with statin drugs, flouro-quinolone antibiotics (ciprofloxin) or other OXPHOS inhibitors.

Combinations to Avoid OXPHOS INHIBITORS

- Ketoconazole plus statin drug Causes Rhabdomyolysis

Stein, C. A., Sanjay Goel, and Reza Ghavamian. “Hepatitis and rhabdomyolysis in a patient with hormone refractory prostate cancer on ketoconazole and concurrent lovastatin therapy.” Investigational new drugs 25.3 (2007): 277-278.

145) Watkins, Jack L., Bradley J. Atkinson, and Lance C. Pagliaro. “Rhabdomyolysis in a prostate cancer patient taking ketoconazole and simvastatin: case report and review of the literature.” Ann Pharmacother 45.2 (2011): e9.

Combinations to Avoid Vitamin E w/ Autophagy Inhibitors

- Dr. Cornet-Masana et al. found that vitamin E (alpha-tocopherol) protects lysosomal embranes and strongly prevented cytotoxicity induced by loratadine. For this reason, avoiding concurrent vitamin E use with lysosomal/ autophagy inhibitors is advised.

59) Cornet-Masana, Josep M., et al. “Dual lysosomal- mitochondrial targeting by antihistamines to eradicate leukaemic cells.” EBioMedicine 47 (2019): 221-234.

Retinal Adverse Effects w/ Autophagy Inhibitors

- In 2017, Dr. Ciska Verbaanderd et al. reviewed chloroquine (CQ) and HCQ as anti-cancer agents, writing: The usual dose for long-term use [rheumatoid
- arthritis and lupus] is 250 mg of CQ-phosphate per day. For HCQ, doses for
- long-term use range between 200 and 400 mg per day. It is advised that patients receiving chronic CQ or HCQ therapy be monitored through regular ophthalmic examinations [3–6 month intervals], full blood counts and blood glucose level checks. (Verbaanerd 2017)

63) Verbaanderd, Ciska, et al. “Repurposing Drugs in Oncology (ReDO)—chloroquine and hydroxychloroquine as anti-cancer agents.” ecancermedicalscience 11 (2017).

Drugs that Mimic Caloric Restriction
caloric-restriction mimetic

- ASA
- Metformin
- Fenofibrate

Tyrosine Kinase Inhibitors (TKI) Synergy w Autophagy Inhibitors

- Ivermectin synergizes with standard CML tyrosine kinase inhibitors. Wang, Jiaqiao 2018
- All Autophagy Inhibitors (Mefloquine, CQ, HCQ, Azith, CAM, Propranolol, Loratidine, etc)
- Dr. Carella: seven patients responding poorly to tyrosine kinase inhibitor (dasatinib). However, a dramatic change occurred when these same patients were treated with clarithromycin, inducing complete remission.

10) Carella, A. M., et al. “Inhibition of autophagy with clarithromycin: a new strategy to enhance sensitivity of CML stem cells to tyrosine kinase inhibitors.” Leukemia supplements 1.S2 (2012): S49.

Synergy AZM with Tyrosine Kinase Inhibitors

- The multi-kinase inhibitors appear to have a higher propensity for autophagy induction.
- Once autophagy was induced, blocking TKI-induced autophagy with AZM resulted in enhanced cytotoxicity via non-apoptotic cell death. These data suggested a clinical benefit in cancer therapy for the combination therapy of TKI and AZM. (38–39)

38) Tanaka, Hideki, et al. “Comparison of autophagy inducibility in various tyrosine kinase inhibitors and their enhanced cytotoxicity via inhibition of autophagy in combined treatment with azithromycin.” Biochem and Biophysics Reports 22 (2020): 100750.
39) Altman, Jessica K., and Leonidas C. Platanias. “A new purpose for an old drug: inhibiting autophagy with clarithromycin.” Leukemia & lymphoma 53.7 (2012): 1255.

Reversing Drug Resistance
Inhibitors of P-Glycoprotein

- Ivermectin…Jiang, Lu, et al. “Ivermectin reverses the drug resistance in cancer cells through EGFR/ERK/Akt/NF-KB pathway.” Journal of Experimental & Clinical Cancer Research 38.1 (2019): 265
- Mefloquine…Enhancement of chemotherapy in MDR drug resistance (40–41) (inhibits p-glycoprotein
- Celecoxib

Tumor Micro Environment

- Inflammatory cytokines generated by the tumour micro-environment [such as IL-6 and IL-8] with activation of NF-κB induce glycolysis with activation of PI3K and AKT and stimulate CSC [Cancer Stem Cell] self-renewal, which then may promote tumour growth and metastasis. (5)
- Drugs targeting IL-6 and IL-8 are being investigated as a therapeutic strategy specifically for CSCs

5) Peiris-Pagès, Maria, et al. “Cancer stem cell metabolism.” Breast Cancer Research 18.1 (2016): 55.

Drugs for Tumor Micro Environment

- Aspirin
- Celecoxib (TAMS) express COX-2 protein.

5)

TME/Tumor Micro Environment Immune Evasion/Autophagy Exosomes

- Dr. Dutta linked immune evasion of cancer stem cells to the lysosmal/ autophagy pathway. bCSC [breast cancer stem cell]-shed Exosomal FOXP3 [protein] helps create T-reg cells within the TME thus leading to tumor-induced immune suppression.

Dutta, A., et al. "338P A new insight into tumour immune-evasion: Crosstalk between cancer stem cells and T regulatory cells." Annals of Oncology 30.Supplement_9 (2019): mdz438-020.

Wee, Ian, et al. "Role of tumor-derived exosomes in cancer metastasis." Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1871.1 (2019): 12-19.

Wen, Zhi-Fa, et al. "Tumor cell-released autophagosomes (TRAPs) promote immunosuppression through induction of M2-like macrophages with increased expression of PD-L1." Journal for immunotherapy of cancer 6.1 (2018): 1-16.

Chen, Yong-Qiang, et al. "Tumor-released autophagosomes induces CD4+ T cell-mediated immunosuppression via a TLR2–IL-6 cascade." Journal for immunotherapy of cancer 7.1 (2019): 178.

DRUG Dosages Mefloquine

- In 2013, Dr. Kun-Huang Yan et al. mefloquine (MQ) in a prostate cancer cells
- Prostate cancer cells were sensitive to the cytotoxic effects of MQ at 10 micromolar,
- other normal cells such as fibroblasts were unaffected.
- mefloquine blood levels in the 2.1–23 micromolar range are typically found with antimalaria therapy, while blood levels in the 3–4 micromolar range are found with malaria prophylaxis for travelers.
- This can be compared to the 4–10 micromolar range found effective for cancer treatment in Dr. Sukhai's in vitro leukemia cell study. (24) (32)

32) Yan, Kun-Huang, et al. "Mefloquine exerts anticancer activity in prostate cancer cells via ROS-mediated modulation of Akt, ERK, JNK and AMPK signaling." Oncology letters 5.5 (2013): 1541-1545.

24) Sukhai, Mahadeo A., et al. "Lysosomal disruption preferentially targets acute myeloid leukemia cells and progenitors." The Journal of clinical investigation 123.1 (2013): 315-328.

DRUG Dosages Fenofibrate

- Dr. Zak's group states that effective serum levels of fenofibrate can be achieved at clinically relevant doses up to 400 mg per day, taken with the evening meal, which is well tolerated without significant adverse effects.

37) Zak, Z., P. Gelebart, and R. Lai. "Fenofibrate induces effective apoptosis in mantle cell lymphoma by inhibiting the TNFα/NF-κB signaling axis." Leukemia 24.8 (2010): 1476.

Fenofibrate Synergies

- The combination of OXPHOS inhibitor fenofibrate with a GLYCOLYSIS inhibitor (such as DCA, diclofenac or quercetin), an autophagy inhibitor (such as hydroxychloroquine, loratidine, thymoquinone,etc.) and a microtubule inhibitor (such as mebendazole) might prove synergistic.

Fenofibrate for HepatoCellular Adenoma

- In 2016, Dr. Poupon et al. reported a 52-year-old female who had been on oral contraceptives
- (OC) and presented with multiple inflammatory hepatocellular adenomas (IHCA) that regressed dramatically on treatment with fenofibrate 400 mg per day. After 6 months of fenofibrate, there was 50% regression of the lesions with no side effects. (69)

69) Poupon, Raoul, Dominique Cazals-Hatem, and Lionel Arrivé. “Fenofibrate-induced massive regression of multiple inflammatory hepatocellular adenoma.” Clinics and research in hepatology and gastroenterology 40.1 (2016): e1-e3.

START HERE

Restoring Immune Surveillance

- "The idea that the immune system, which so effectively protects the host from microbial pathogens, might also recognize and destroy tumor cells was first discussed over a century ago … **tumor immune surveillance**, whereby the immune system identifies cancerous and/or precancerous cells and eliminates them before they can cause harm. " (Swann, 2007)

Swann, Jeremy B., and Mark J. Smyth. "Immune surveillance of tumors." The Journal of Clinical Investigation 117.5 (2007): 1137-1146.

Restoring Immune Surveillance

- Equal in Importance to ALL Three Pillars
- Trophoblastic Theory (maternal-fetal tolerance) and PIBF-evasion of the immune system, blocked by Mifepristone (Alternate is Mebendazole).
- The SR/CR Mouse (Spontaneous Regression/Complete Resistance to cancer.)
- Checkpoint Inhibitors, CAR-T Therapy
- Coleys's Toxins
- Cimetidine
- AHCC- Beta Glucans
- Propranolol, Metformin, etc.

Restoring Anti-Tumor Immunity - ATRA

- ATRA Markedly Augments Anti-Tumor Immunity
- In 2019, Dr. Lu Huang et al. studied ATRA in lung cancer and colon cancer mouse xenografts, finding ATRA markedly upregulated anti-tumor immunity. Dr. Huang's group write:
- ATRA-treatment decreased the CD8+ T to T-reg cellular ratios while increasing the ratios of CD8+ T to T-reg cells… Taken together, this study uncovered a previously unrecognized role for ATRA in augmenting immunotherapy. These preclinical immunotherapy findings can be translated into the cancer clinic. 104) Huang, Lu, et al. "All-trans-retinoic acid (ATRA) markedly augments anti-tumor immunity." (2019): 3279-3279.

TME: Glycolysis Inhibitors, Lactate and Anti-Tumor Immunity

- Glycolysis Inhibitors, Diclofenac, DCA Reduce Lactate Excretion into TME , this Restores Anti-Tumor Immunity, Enhances checkpoint inhibitors.

11) Renner, Kathrin, et al. “Restricting glycolysis preserves T Cell effector functions and augments checkpoint therapy.” Cell Reports 29.1 (2019): 135-150.

Cancer as a Trophoblastic Disease

- “The

Swann, Jeremy.

PIBF Progesterone Induced Blocking Factor

- Both Placenta and Cancer to Escape Immune Surveillance.
- Pregnancy Lymphocytes secrete PIBF, allows pregnancy to proceed withour rejection.
- Cancer Cells Secrete PIBF, allows them to evade immune system.
- PIBF also stimulates Growth, Proliferation, Aggressive Behavior.
- Progesterone turns on PIBF production.
- RU-486 (mifepristone) turns off PIBF production, restoring immune competency.

PIBF Progesterone Induced Blocking Factor

- PIBF associated with the Centrosome (spindle)
- Mifepristone disrupts cytoskeleton, attenuates the migration, movement, and invasion of cancer cells, preventing metastatic disease.
- Mifepristone synergy with chloroquine, autophagy inhibitors.
- Mifepristone restricted abortion drug
- Mebendazole - Microtubule-disrupting drug disturbs production of PIBF.
- Use Mebendazole instead of Mifepristone?

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.

Cimetidine - Tagamet

- Tagamet FDA-Approved 1979
- OTC Antacid- H2 Histamine Receptor Blocker
- Enhances Cell-Mediated Immunity.
- Reverses Histamine-Mediated Immunosuppression
- Induces IL-18 in monocytes- (immunostimulatory cytokine with anti-tumor activity), promotes expansion of NK Cells.
- Useful for: Cancer, Viral Warts, Recalcitrant Urticaria, Interstitial Cytitis.

Pantziarka, Pan, et al. "Repurposing drugs in oncology (ReDO)—cimetidine as an anti-cancer agent." Ecancermedicalscience 8 (2014).

AHCC - Beta Glucans

- Plant polysaccharides (sugars) found in edible mushrooms, baker's yeast, and cereals.
- (PAMPS) pathogen associated molecular patterns.
- Replacement for Coley's Toxins ?
- Enhances Tumor Immune Surveillance.
- Eradicates HPV, has antiviral effects.

Gao, Yunfei, et al. "Active hexose correlated compound enhances tumor surveillance through regulating both innate and adaptive immune responses." Cancer Immunology, Immunotherapy 55.10 (2006): 1258-1266.

Corradetti, Bruna, et al. "Bioactive immunomodulatory compounds: a novel combinatorial strategy for integrated medicine in oncology? BAIC exposure in cancer cells." Integrative cancer therapies 18 (2019):

Other Immune Modulators

- **Iodine** for Breast Cancer Prevention and Treatment, activation of the anti-tumoral immune response, possible adjuvant in breast cancer therapy. directly induces apoptosis in cancer cells
- **Vitamin D,** steroid hormone immune modulator
- **Probiotics**, enhance checkpoint inhibitors, prevent C Diff, reduces mortality in Allo Transplant.

Probiotics - 2017
Year of the Breakthrough

- "In 2017, epidemiological studies in humans and experiments in mouse models showed that the intestinal microbiota determines the effectiveness of anti-cancer immunotherapies." (Kroemer ,2018)

Kroemer, Guido, and Laurence Zitvogel. "Cancer immunotherapy in 2017: The breakthrough of the microbiota." Nature Reviews Immunology 18.2 (2018): 87.

Mebendazole

- Old Antiparasitic Drug.
- Microtubule inhibitor, prevents spindle formation needed for cell replication.
- Immunomodulatory Effects – upregulates anti-cancer host immune function.
- Link to PIBF ? Replacement for Mifepristone ?
- Induces Apoptosis by inactivating BCL-2
- Induces “Protective Autophagy”, Synergy with Autophagy Inhibitors.
- Inhibits Hedgehog CSC pathway

Pantziarka, Pan, et al. "Repurposing Drugs in Oncology (ReDO)—mebendazole as an anti-cancer agent." ecancermedicalscience 8 (2014).

Immune Evasion/Autophagy Exosomes

- Dr. Dutta and colleagues linked together immune evasion of cancer stem cells to the lysosmal/ autophagy pathway.
- bCSC [breast cancer stem cell]-shed exosomal FOXP3 [protein] plays an important role in procreation of T-reg cells within the tumor micro-environment thus leading to tumor-induced immune suppression.

Dutta, A., et al. "338P A new insight into tumour immune-evasion: Crosstalk between cancer stem cells and T regulatory cells." Annals of Oncology 30.Supplement_9 (2019): mdz438-020.

Wee, Ian, et al. "Role of tumor-derived exosomes in cancer metastasis." Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1871.1 (2019): 12-19.

Wen, Zhi-Fa, et al. "Tumor cell-released autophagosomes (TRAPs) promote immunosuppression through induction of M2-like macrophages with increased expression of PD-L1." Journal for immunotherapy of cancer 6.1 (2018): 1-16.

Chen, Yong-Qiang, et al. "Tumor-released autophagosomes induces CD4+ T cell-mediated immunosuppression via a TLR2–IL-6 cascade." Journal for immunotherapy of cancer 7.1 (2019): 178.

Immune Evasion/Autophagy TME

- HCQ autophagy inhibition restores anti-tumor immunity in the micro-environment TME
- restrains T-reg functions," which then may enhance checkpoint inhibitor immunotherapy

Jacquin, Elise, and Lionel Apetoh. "Cell-intrinsic roles for autophagy in modulating CD4 T cell functions." Frontiers in immunology 9 (2018): 1023.
Schabowsky, Rich-Henry, et al. "Targeting CD4+ CD25+ FoxP3+ regulatory T-cells for the augmentation of cancer immunotherapy." Current opinion in investigational drugs (London, England: 2000) 8.12 (2007): 1002-1008.

Fifth Pillar - Inflammation

Hallmark of Cancer
NF-kB,
IL-6 - cytokines

Inflammation/ TME and Cancer Stem Cells

- Aspirin
- Celecoxib (COX2 inhibitor)
- Curcumin, affects the TME micro-environment around the cancer stem cells by suppressing release of pro-inflammatory cytokines IL-6 and IL-8. (Sordillo, 2015)
- All suppress release of IL6/IL8 from TME which inhibit Cancer Stem Cells

23) Sordillo, Peter P., and Lawrence Helson. “Curcumin and cancer stem cells: curcumin has asymmetrical effects on cancer and normal stem cells.” Anticancer Research 35.2 (2015): 599-614.

NF-kB Inflammatory Pathway Inhibitors

- Artemisinin
- Aspirin
- Azithromycin
- Berberine,
- Boswellia,
- Clarithromycin,
- Curcumin,
- Doxycycline,
- Fenofibrate
- Ivermectin
- Niclosamide
- Parthenolide,
- Pterostilbene,
- Sulforaphane,
- Sulfasalazine
- Statin drugs
- Thymoquinone

Stacpo

COX-2 Inhibitors - Celecoxib

Stacpoole,

CBD Cannabidiol

- Detaches HKII from VDAC.
- “Using microscale thermophoresis, we showed a direct interaction between purified fluorescently labeled VDAC1 and CBD.” (Rimmerman, 2013)
- Potent Anti-inflammatory Effect
- Immune Modulator

Rimmerman, N., et al. “Direct modulation of the outer mitochondrial membrane channel, voltage-dependent anion channel 1 (VDAC1) by cannabidiol: a novel mechanism for cannabinoid-induced cell death.” Cell death & disease 4.12 (2013): e949-e949.

Olivas-Aguirre, Miguel, et al. “Cannabidiol directly targets mitochondria and disturbs calcium homeostasis in acute lymphoblastic leukemia.” Cell death & disease 10.10 (2019): 1-19.

CBD targets VDAC Ca2+ Overload

- CBD directly interacts with and switches VDAC to a closed conformational substate . A similar mechanism was also reported for **curcumin** and **aspirin** and is considered to be the cause of the tumor cell death
- closed conformational is impermeable for large metabolites like adenine nucleotides, but highly permeable to Ca2+ [15]. The combination of these two factors can eventually lead to **mitochondrial Ca2+ overload**.(olivas,2021)

Olivas-Aguirre, Miguel, et al. "Phenolic Compounds Cannabidiol, Curcumin and Quercetin Cause Mitochondrial Dysfunction and Suppress Acute Lymphoblastic Leukemia Cells." International Journal of Molecular Sciences 22.1 (2021): 204.

Down Regulate Anti-Oxidant System

- Solomons's Seal
- Auranofin (inhibits thioredoxin reductase system),
- Celecoxib Cox-2 inhibitor
- Parthenolide (feverfew)
- PQQ (pyrroloquinoline-quinine)
- Sulfasalazine (Blocks Xct system cysteine uptake)
- Sulforaphane (downreglulates intracellular glutathione).

Stacpoole,

Dipyridamole Anti-Platelet Agents

- Sol

Stacpoole,

Sulforaphane OXPHOS Inhibitor

- 2017, Dr. DaCosta: sulforaphane MOA
- Acute pro-oxidant effect, Depletion of intracellular glutathione due to the formation and export of SFN glutathione complexes.
- SFN can also increase mitochondrial ROS generation by inhibiting complex III of the ETC.
- Accumulation of Ubisemiquinone, from which molecular oxygen receives electrons, resulting in the formation of superoxide and hydrogen peroxide.

Dacosta, Christopher, and Yongping Bao. “The role of MicroRNAs in the chemopreventive activity of sulforaphane from cruciferous vegetables.” Nutrients 9.8 (2017): 902.

Prostate Cancer – Sulforaphane Glutathione Levels Decrease by 90%

- 2005 Dr Singh: GSH levels in PC-3 [Prostate Cancer] cells treated for 3 and 6 h with 40 µm SFN were reduced by about 90 and 94%, respectively, compared with controls. (79)

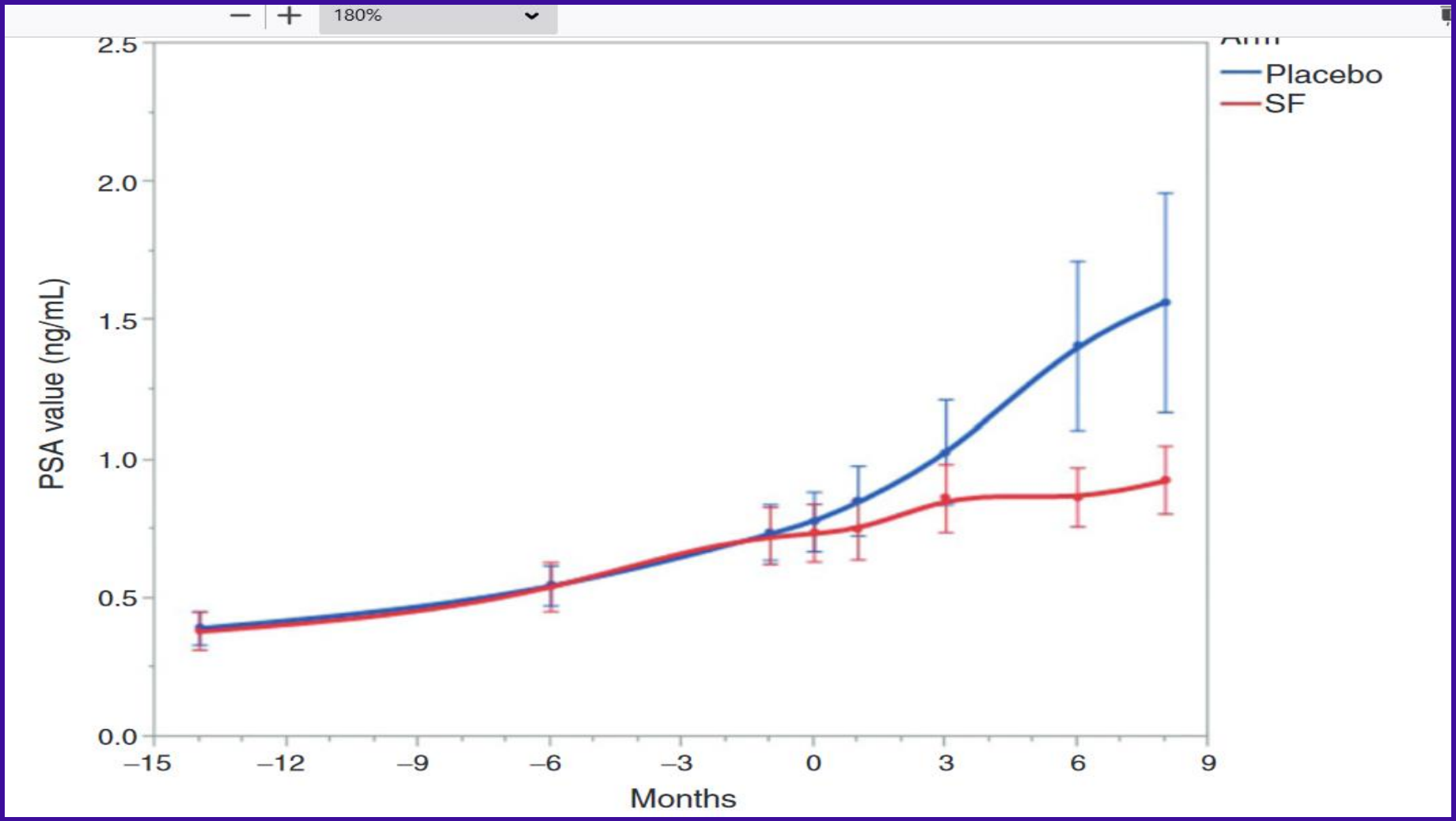
Singh, Shivendra V., et al. "Sulforaphane-induced cell death in human prostate cancer cells is initiated by reactive oxygen species." Journal of Biological Chemistry 280.20 (2005): 19911-19924.

Prostate Cancer - Sulforaphane

- Dr. Cipolla 2015: double-blinded randomized, placebo-controlled trial of sulforaphane
- 78 males with rising PSA levels after radical prostatectomy for prostate cancer.
- Treatment: 60 mg of sulforaphane for 6 months
- Sulforaphane group had a mean increase in PSA of 0.01 ng/ml compared to a 0.62 ng/ml increase for placebo. PSA doubling time in the sulforaphane group was 28.9 months compared to 15.5 months for the placebo group. (80)

Cipolla, Bernard G., et al. "Effect of sulforaphane in men with biochemical recurrence after radical prostatectomy." Cancer prevention research 8.8 (2015): 712-719.

Prostate Cancer - Sulforaphane



Cipolla, Bernard G., et al. "Effect of sulforaphane in men with biochemical recurrence after radical prostatectomy." Cancer prevention research 8.8 (2015): 712-719.

Sulforaphane CSC Agent, Synergy with:

- sulforaphane acts synergistically w TKI's sorafenib and imatinib
- quercetin, green tea catechins,
- Chemo Cisplatin, Gemcitabine, Doxorubicin 5-FU
- to eliminate CSC's
- pancreatic, prostate and leukemia CSCs
- and to inhibit initiation and growth of human pancreatic cancer in xenograft mice.

Naujokat, Cord, and Dwight L. McKee. "The "Big Five" phytochemicals targeting cancer stem cells: curcumin, EGCG, sulforaphane, resveratrol, and genistein." Current medicinal chemistry (2021).

Prostate Cancer PREVENTION - Aspirin

- 2016, Dr. F. Lapi:
- 5 year retrospective study of
- 13,453 males with ischemic CV disease.
- Low-dose aspirin use of less than 100 mg per day for five years
- Reduced prostate cancer risk by
- **57 per cent**. (8)

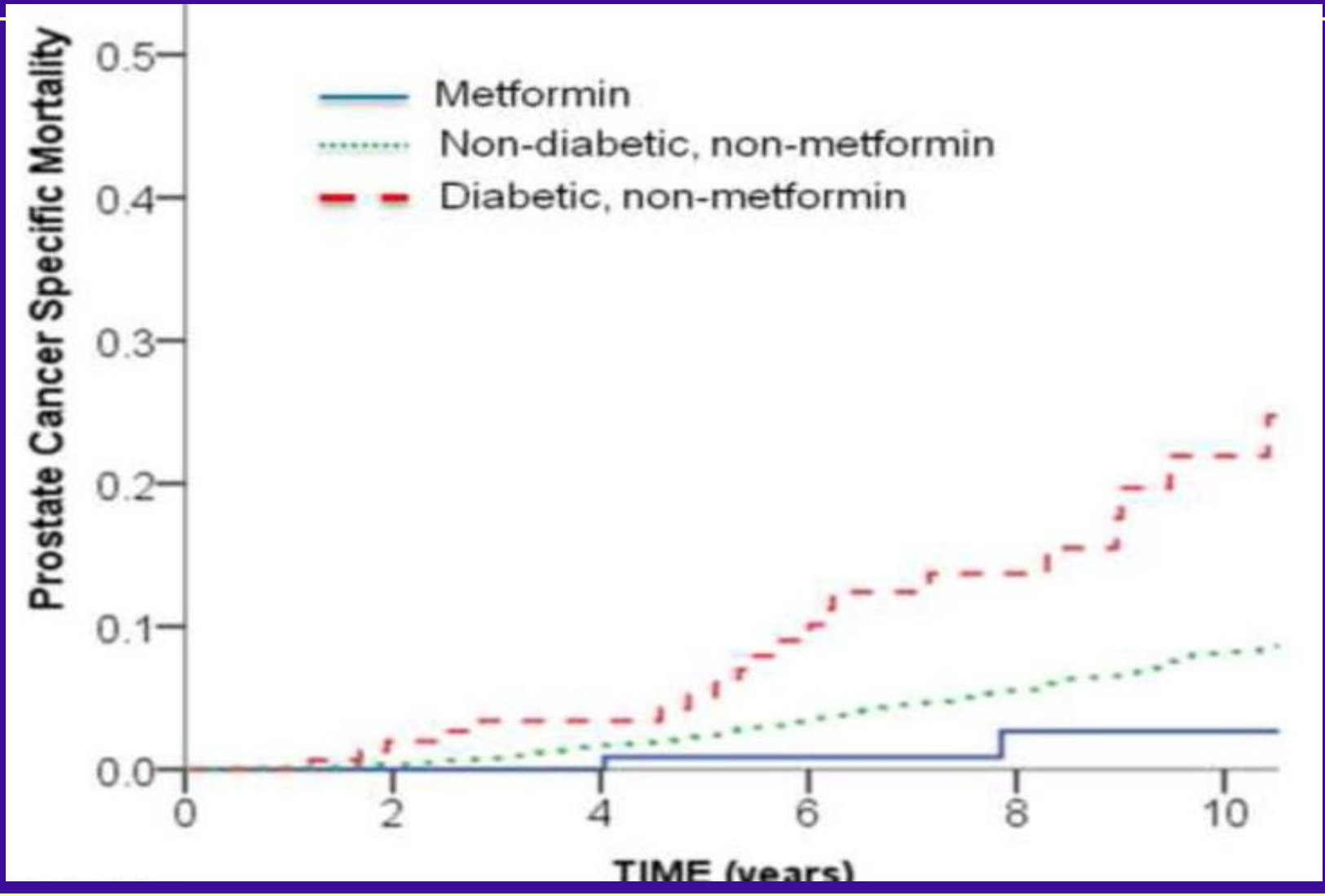
8) Lapi, F., et al. “Risk of prostate cancer in low dose aspirin users: A retrospective cohort study.” International journal of cancer 139.1 (2016): 205-211.

Metformin - Prostate Cancer after Radiation Therapy

- In 2013, Dr. Daniel Spratt 9 yr. retrospective study
- 2,901 men after Rad TX for Prostate CA
- After 9 years of follow-up, mortality from prostate cancer was :
- 2.7% for metformin users
- 22% mortality for diabetics NON-USER
- 8.2% mortality (non-diabetics) NON-USER
- Quote “Metformin decreased the risk of PSA recurrence, distant metastasis, and PCSM [prostate cancer specific mortality] compared with diabetic non-metformin patients. To our knowledge, this is the first clinical evidence that metformin may improve cancer- specific survival outcomes in prostate cancer. Furthermore, metformin strongly decreased the clinically defined transformation from androgen-sensitive prostate cancer to CRPC [castrate-resistant prostate cancer]. Dr Spratt

Spratt, Daniel E., et al. “Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality.” Eur Urol 63.4 (2013): 709-716

Metformin – Prostate Cancer



Spratt, Daniel E., et al. "Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality." Eur Urol 63.4 (2013): 709-716

Blocking Growth Factors

- Solomon's Seal: Competitive inhibitor of EGF receptor
- inactivation of EGF blocks activation of the PI3K/Akt downstream pathway, which inhibits glucose consumption, lactate production, and HK2 expression, thus inhibiting the Warburg effect.

5) 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): 1765-1771.

Financial Dislosure

None to Disclose

Cancer Prevention

- Selenium
- Iodine
- Vitamin D3
- Di-Indole Methane (DIM)

Haider,

LDN Low Dose Naltrexone

- Opiate Receptor Blocker
- Inhibits Tumor Growth

Stacpoole

Case Report Targeting Cancer Stem Cells Aggressivbe Squamous Cell CA 90 year old.

- Fenofibrate
- Itraconazole
- Mebendazole
- Exemestane
- Doxycycline

Mefloquine= Takeda, Mitsunobu, et al. "Disruption of endolysosomal RAB5/7 efficiently eliminates colorectal cancer stem cells." Cancer research 79.7 (2019): 1426-1437.

Alpha Lipoic Acid

- Cofactor which Increases PDC Activity.
- Shunts From Glycolysis to OXPHOS.
- Restores Apoptosis.
- Co-Factors are Thiamine, and Carnitine.
- Synergy with Melatonin (Glycolysis Inhibitor- Reverses Warburg Effect)

Bingham, Paul M. "Lipoic acid and lipoic acid analogs in cancer metabolism and chemotherapy." Expert review of clin pharmacology 7.6 (2014): 837-846.
Berkson, Burton M. "Revisiting the ALA/N (α-Lipoic Acid/Low-Dose Naltrexone) protocol for people with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases." Integrative cancer ther 8.4 (2009): 416-422.

Melatonin - Glycolysis Inhibitor

- Sleep Hormone from Pineal Gland.
- Reverses Warburg Effect via PDK inhibition.
- Bacteria and Mitochondria Make Melatonin Acetyl-CoA.
- Enters Cells via Glucose Transporters.
- Accumulates in Cancer Cells.
- Cancer Cell Mitochondria Lose ability to make Melatonin
- Melatonin has a Decoupling Effect on OXPHOS.
- Increases Electron Flow through ETC with Decoupling Effect Causes Excess Damaging ROS… apoptosis in cancer cells.

Pacini, Nicola, and Fabio Borziani. "Oncostatic-Cytoprotective Effect of Melatonin and Other Bioactive Molecules: A Common Target in Mitochondrial Respiration." International journal of molecular sciences 17.3 (2016): 341.

Melatonin and Cancer Stem Cells

- "Thus, the treatment with melatonin and the stimulation of mitochondrial metabolism [i.e., with DCA] constitute promising strategies against resistant CSCs." (Loureiro, Rute 2019)

Loureiro, Rute, et al. "Melatonin antiproliferative effects require active mitochondrial function in embryonal carcinoma cells." Oncotarget 6.19 (2015): 17081.

Melatonin and Cancer Stem Cells

- "Overall, the anti-cancer activity of melatonin, combined with its actions via multiple signaling pathways, is considered hugely exciting to use this drug as a **possible treatment strategy to cure cancer**." (Iravani, Shahrokh, 2019)

Iravani, Shahrokh, et al. "The Role of Melatonin in Colorectal Cancer." Journal of Gastrointestinal Cancer (2019): 1-6.

Melatonin Synergy with DCA Against Cancer Stem Cells

- Degrades Beta-Catenin via activation of GSK3-Beta
- Prevents Transcription of Wnt Target Genes
- Synergy with DCA against P19 Embryonal CSC (only effective treatment)
- DCA converts highly Glycolytic P19 cells to OXPHOS
- (OXPHOS) P19 cells are now sensitive to Melatonin

Loureiro, Rute, et al. “Melatonin antiproliferative effects require active mitochondrial function in embryonal carcinoma cells.” Oncotarget 6.19 (2015): 17081.

COC Protocol 4 Drugs- What is Missing ?

- COC Clinical Trial METRICS,
- Care Oncology Clinic, London (Health Clinics Limited), will use the combination of four metabolic inhibitors in 207 cancer patients compared to historic controls. (48)
- Metformin (OXPHOS inhibitor)
- Doxycycline (OXPHOS and Autophagy Inhibitor)
- Mebendazole (microtubule Inhibitor)
- Atorvastatin (HMG-Co reductase/mevalonate inhibitor)
- Missing: Glycolysis inhibitor (DCA, Quercetin, Diclofenac)

48) Study of the Safety, Tolerability and Efficacy of Metabolic Combination Treatments on Cancer (METRICS). Care Oncology Clinic, London (Health Clinics Limited) NCT02201381

Breast Cancer - Eliminating Cancer Stem Cells Start Here

- Degrades

Loureiro, Rute, et al. “.

Breast Cancer - Sulforaphane

- Degrades

Loureiro, Rute, et al. “.