CANCER THERAPIES:
REPURPOSED DRUGS & NATURAL SUBSTANCES
July 17, 2021 PART TWO

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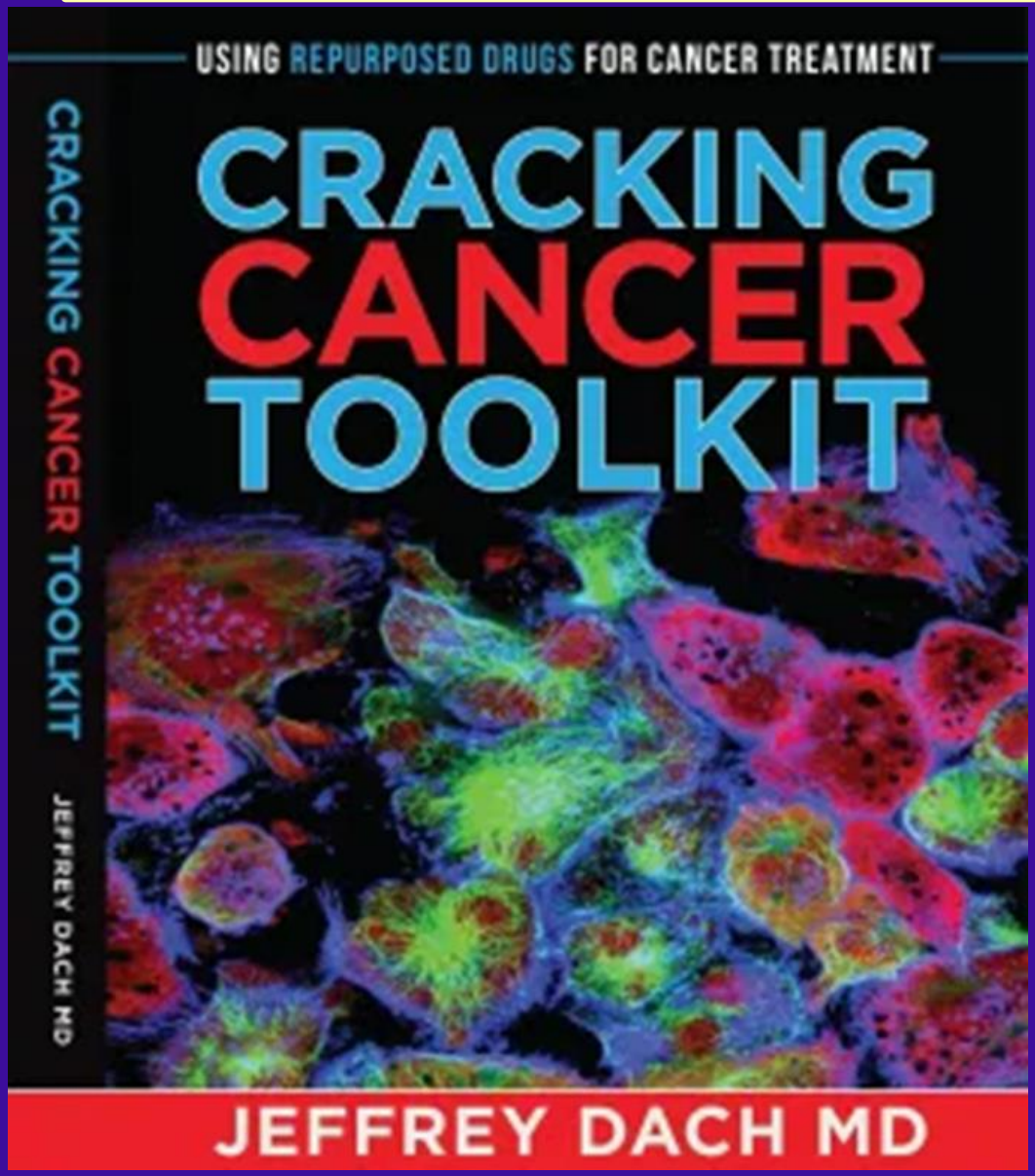
Cancer As a Parasitic Disease



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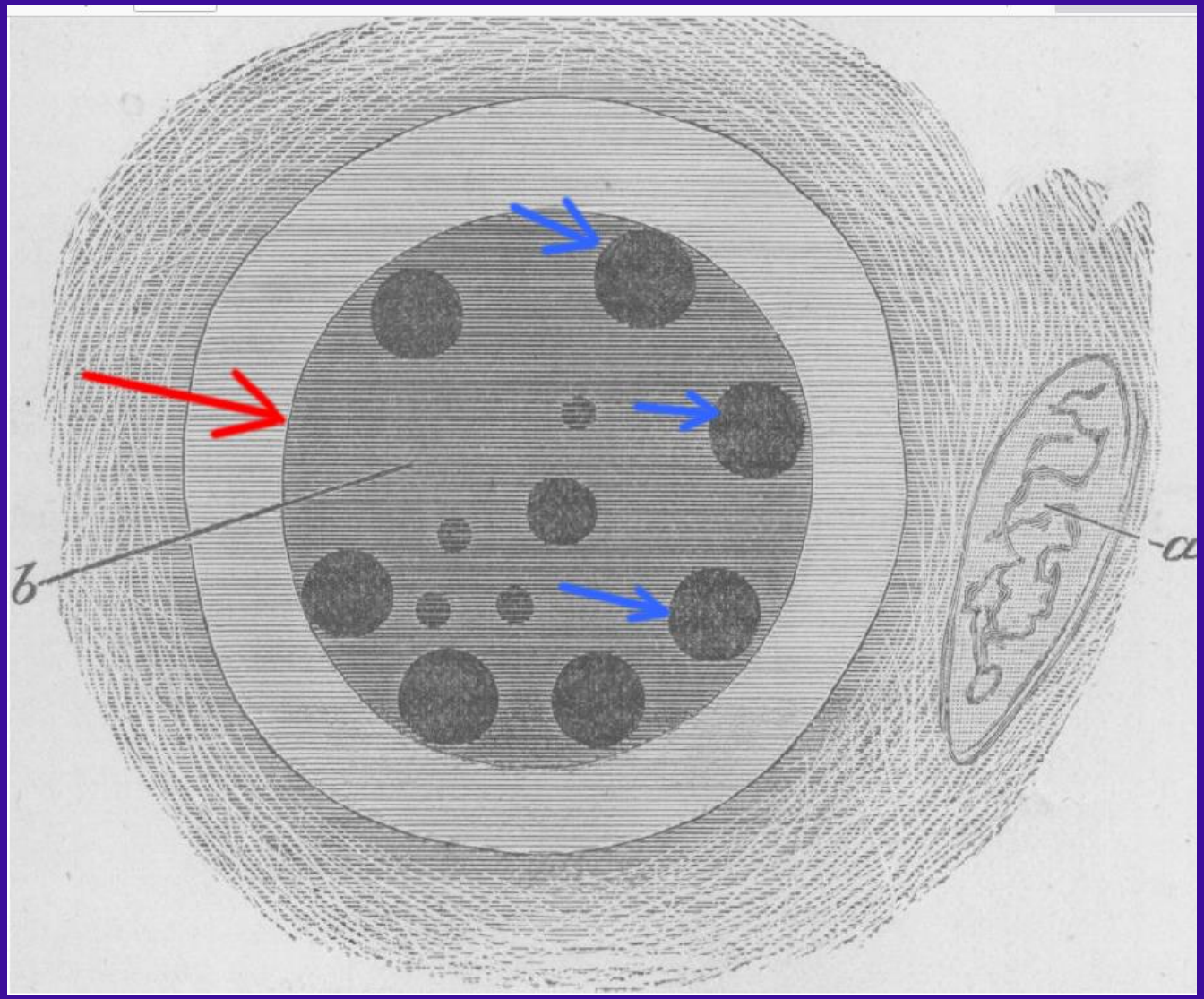
Early Pathologists Thought Cancer was a Parasitic Disease

- 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.

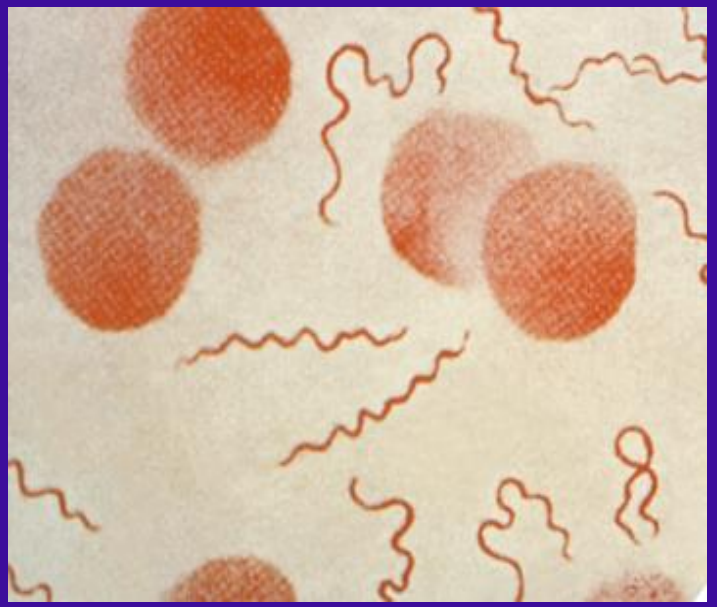
Drawings by William Russell 1890



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: intracellular parasite transmitted by ticks, resembles Borrelia Lyme parasite in humans.
- T. parva highly pathogenic for cattle, causes 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).

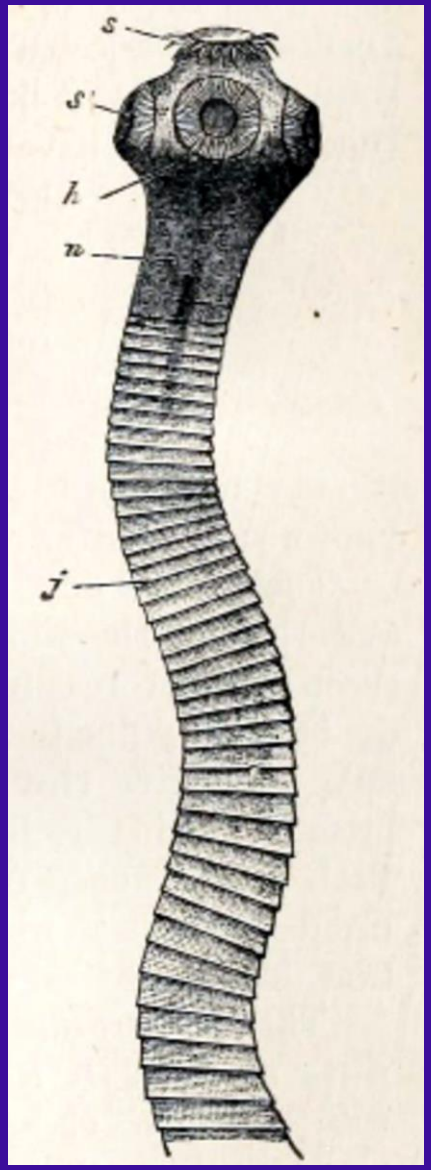
Cryptosporidium Mouse Model of Colon Cancer

- 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. Muehlenbachs Case Report:
- Immunosuppressed Pt w/ enlarged lymph nodes invaded by malignant 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
- Niclosamide
- Ivermectin
- Mebendazole (Vermox), Fenbendazole
- Nitazoxanide (Alinia)
- Pyrvinium

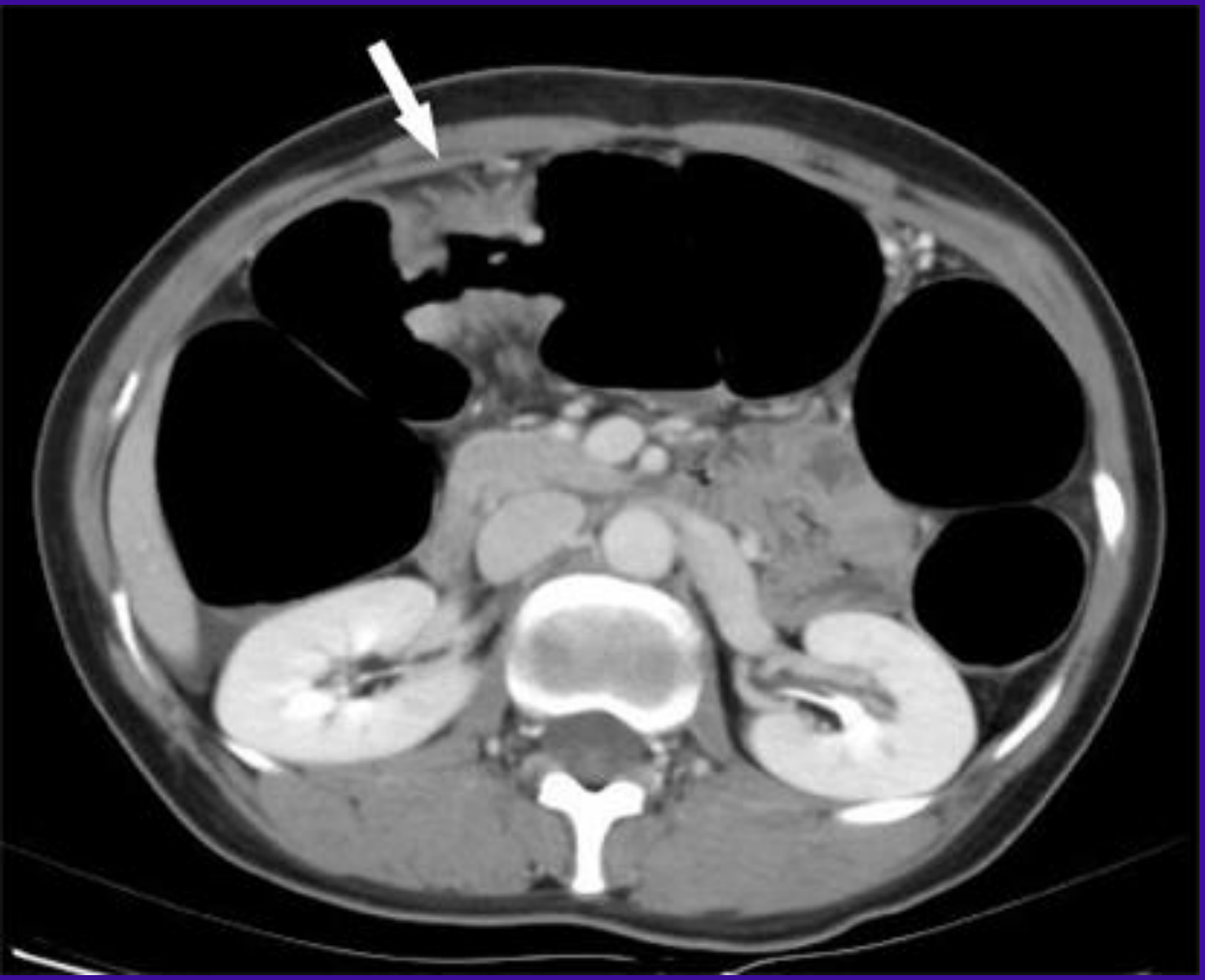
97) Hamilton, Gerhard, and Barbara Rath. "Repurposing of Anthelminthics as Anticancer Drugs."Mutat Res. 2014 Oct; 768:16-21.
98) Klinkert, M-Q., and V. Heussler. "The use of anticancer drugs in antiparasitic chemotherapy." Mini reviews in medicinal chemistry 6.2 (2006): 131-143.

Artemisinin/Artesunate

- 2015 Tu You You (Pharmaceutical Chemist) Receives Nobel Prize for Discovering Artemisinin,
- IV Artesunate First Line Treatment for Malaria inexpensive and widely available outside US 60 mg vials.
- Artesunate for Injection was not FDA approved until May 26, 2020 (for treatment of severe malaria). Previously, solely available from CDC as investigational new drug (IND).

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

Artesunate for Colon Cancer Pre-OP



- Kim, Joo Hee, et al. “Occlusive colorectal cancer: usefulness of CT colono-graphy according to tumor location." Yonsei medical journal 48.6 (2007): 934.

Anti-Malarials – Artemisinin/Artesunate

- 2015 Dr Sanjeev Krishna Randomized Trial on 23 colon cancer pts waiting for “curative resection”.
- Pt Randomized to Artesunate 200 mg tab or Placebo PO X 14 days Pre-OP.
- Five years later: One Recurrence in artesunate group (10%). SIX Recurrences in placebo group (60%) (Krishna, 2015)

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.
Das, A. K. “Anticancer effect of antimalarial artemisinin compounds.” Ann med and health sci research 5.2 (2015): 93-102.

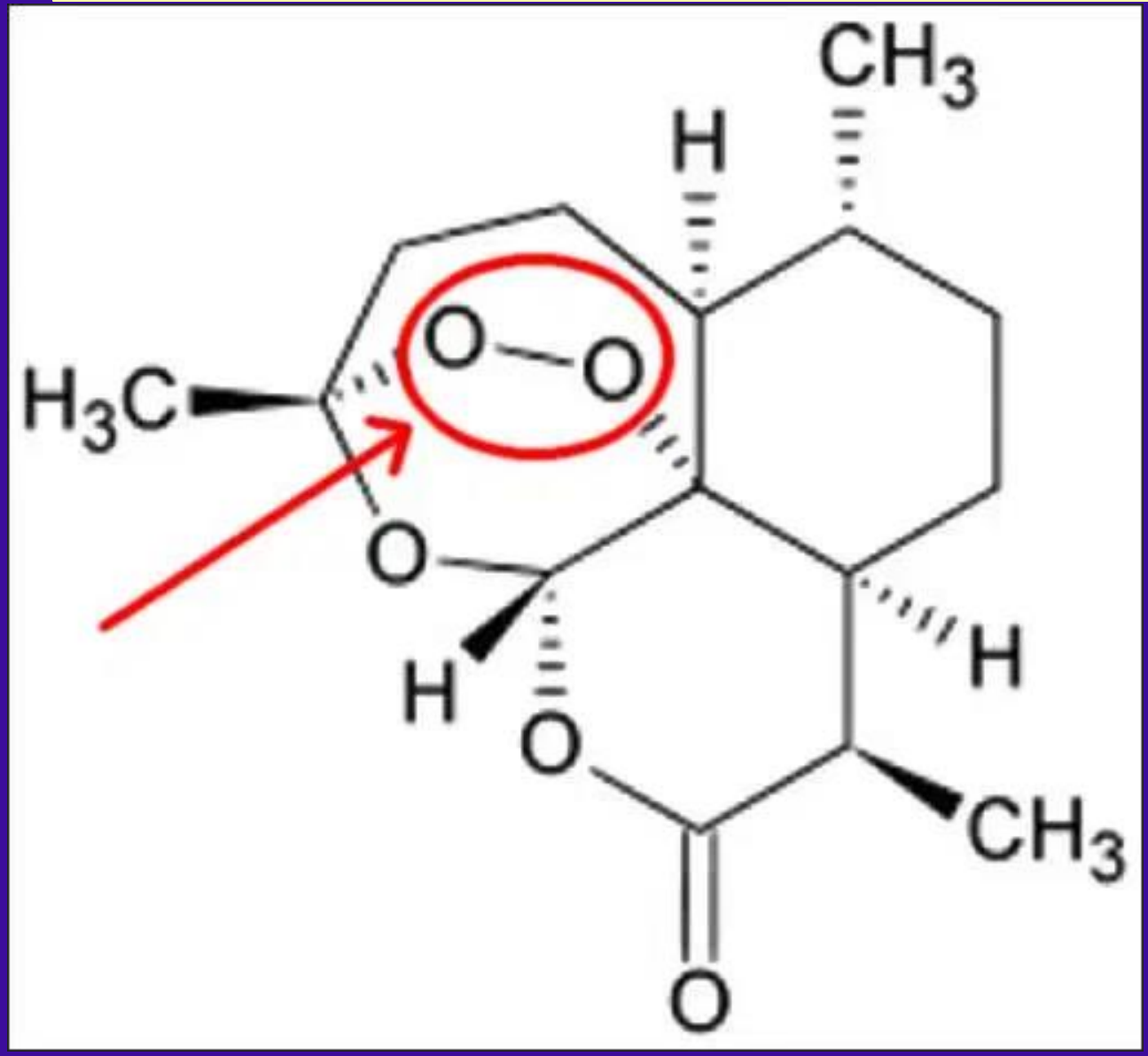
Artemisinin/Artesunate

- 2015 Dr Das: Artemisinin (derivatives) Effective Against 55 cancer cell lines.
- Potentiates Effect of Doxorubicin Chemo in Drug Resistant Leukemia Cell Model.
- MOA: 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.” J Biol Chem 289.48 (2014)

Artemisinin Structure



- Endo Peroxide Bridge (Red Arrow) Skeletal formula of artemisinin Courtesy of Wikimedia Commons

Artemisinin/Artesunate

- Clinical Trials Disappointing:
  "currently available phase I clinical trial results of ARTs for treating cancer are still largely limited and the number of participating patients is small." (Xu, 2020)
- DCA with Artesunate Fatal liver and bone marrow toxicity in Gliob pt. (Ohl, 2016)

Xu, Cangcang, et al. "Artemisinins as anticancer drugs: Novel therapeutic approaches, molecular mechanisms, and clinical trials." Frontiers in Pharmacology 11 (2020): 1608.
Ohl, Martin,Thomas Efferth."Fatal liver and bone marrow toxicity by combination treatment of dichloroacetate and artesunate in a glioblastoma multiforme patient: case report and review of the literature." Frontiers in oncology 6 (2016):

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

- MQ is trapped and accumulates in Lysosomes, increases pH, Prevents fusion of lysosome to autophagosome. Expands and disrupts Lysosomes.
- Dr Sukai 2013: Highly Active Against Leukemia which has upregulated larger lysosomes .
- Mefloquine most potent of three, effective Cancer Stem Cell Agent. Associated with Neuropsychiatric and retinal adverse side effects.
- Mefloquine- Dosage for travelers 250 mg tab weekly for a few weeks before the trip.

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)

- This is true for TKI's combined with **ANY** Autophagy Inhibitor.
- 2019, Dr. Hui Lam Yi: imatinib, dasatinib and ponatinib- B Cell receptor TKI's in CML cell lines, in vitro.
- 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 MQ in Colon Cancer in Vivo 2

- Chemotherapy Increased CSC fraction 84%.
- MQ alone decreased CSC to 9.4%.
- MQ + Chemo Dramatically Decreased CSC population to 0.1%.
- MQ + Chemo "**Drastically Reduces**" Tumor Volume.
- MQ is 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**." (Takeda 2019)

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
- Traveler Malaria Prophylaxis (weekly 250 mg tablet) 3-4 micromolar.
- Anti-Malaria Therapy (1250 mg PO once) 2-23 microM.

Reuter, Stephanie E., et al. “pharmacokinetics of mefloquine in healthy volunteers and patients with uncomplicated Plasmodium malaria.” J of Antimicrob Chemo (2014): dku430

Mefloquine Adverse Effects

- 2018, Drs. G. Mereddy :"Although long-term use 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".** (Mereddy 2018)

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

Other Safer Autophagy Inhibitors

- Chloroquine Antimalarial
- Clarithromycin (Azithro) Potently blocks late stage autophagy.
- Dipyridamole Anti-Platelet Agent
- Doxycycline Down-Regulates Autophagy Marker LC3B.
- Hydroxychloroquine Anti-Malarial
- Loratidine Claritin® CAD Antihistamine
- Mefloquine Anti-Malarial
- Niclosamide strongly blocks late stage autophagy by inducing lysosomal dysfunction.
- PPI's Proton Pump Inhibitors (Inhibit V-ATPase)
- Propranolol B-Blocker OXPHOS and Autophagy Inhibitor
- Pyrvinium Anti-parasitic, suppress transcription autophagy genes.
- Thymoquinone Black Seed, inhibition of autophagy at the gene transcriptional level, induces lysosomal dysfunction.

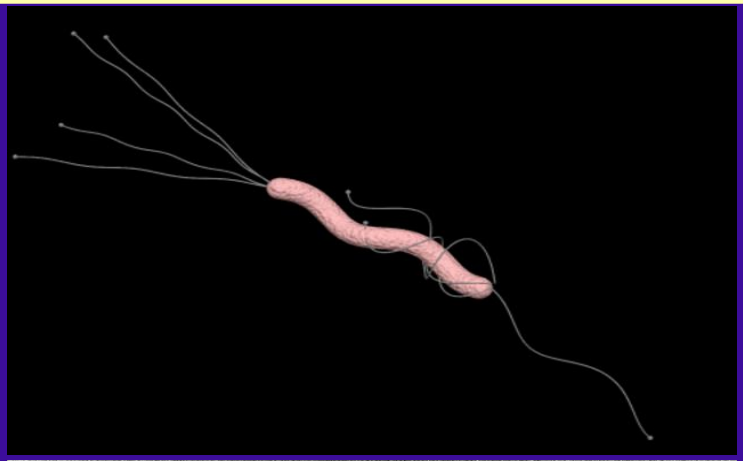
Niclosamide

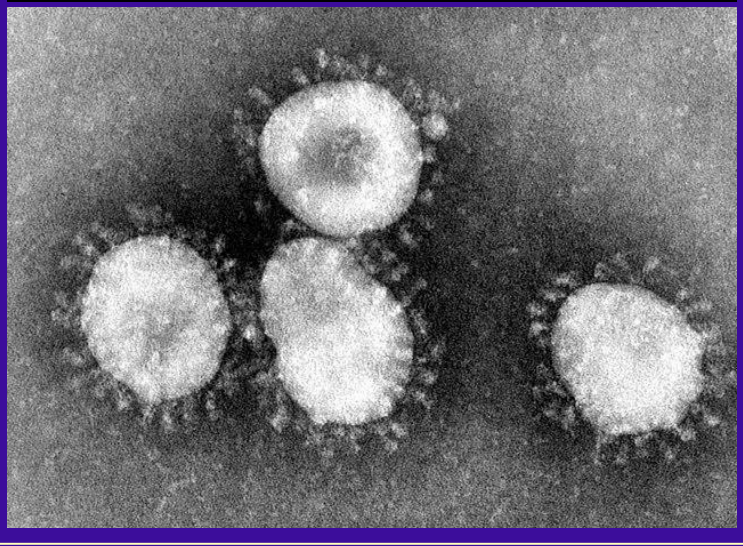
- 1953 Niclosamide Bayer Lab Kill Snails
- 1962 Yomesan for Tapeworm.
- 1982 FDA Approved for Tapeworm.
- 2 Grams PO QD X 7 Days,

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 Off-Label Use

- Anti-bacterial for: C.Difficile Enterocolitis, Helicobacter Pylori
- Anti-Viral nM to microMr potency, SARS-CoV, MERS-CoV, ZIKV, HCV, and human adenovirus.
- Endometriosis .
- Anti-Cancer.





Chen, Wei “Niclosamide: beyond an antihelminthic drug.” Cell Signal (2018): 89-96
Xu, Jimin, et al. "Broad spectrum antiviral agent niclosamide and its therapeutic potential." ACS infectious diseases 6.5 (2020): 909-915.

Niclosamide Anti Cancer Stem Cell Agent

- Dr Pan Review 2012: Niclosamide potent inhibitor of Wnt/Beta Catenin/ and NF-kB
- Targets LRP6 Wnt Co-receptor on cell membrane
- Effective at Low Concentrations IC < 1 MicroM
- Targets NF-kB, Wnt/β-catenin, and Notch paths.
- "Holds promise in eradicating cancer stem cells." (Pan, 2012)

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 Autophgay Inhibitor

- 2014 Dr Gao studied effect of Niclosamide on Lysosomes.
- Niclo Inhibits mTOR which induces “protective autophagy”.
- Yet Niclo Blocks Late Stage Autophagy (accumulation of LCIII and P62).
- Niclo Increases pH of lysososmes, causing release of Cathepsins into Cytosol.

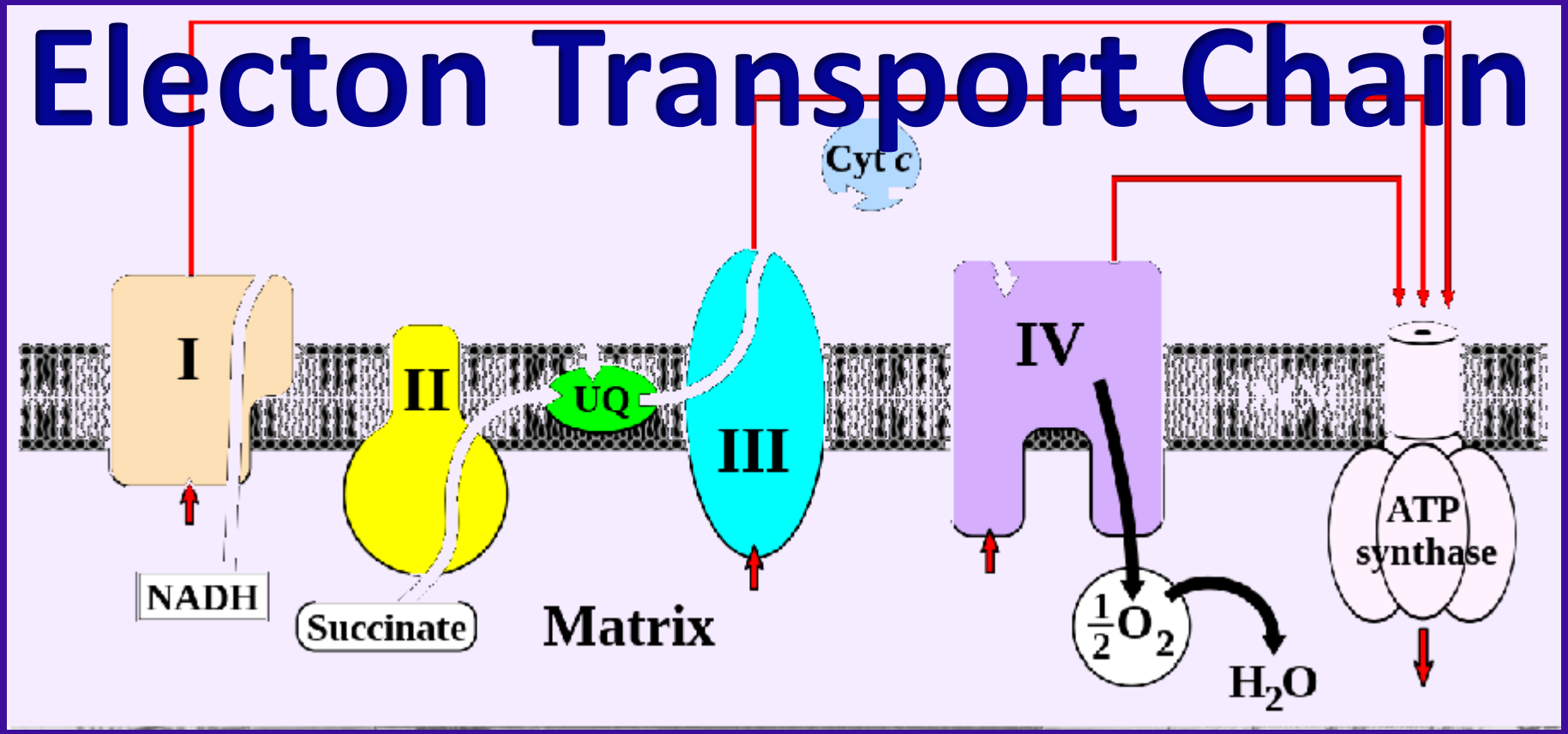
81) Gao, Ying, et al. “Niclosamide blocks autophagy via lysosomal dysfunction (663.18).” FASEB Journal (2014): 663-18

Niclosamide Targets Lysosomes Inhibits Antegrade Trafficking

- 2016 Dr Circu Prostate Cancer: High Thruput Screen 2,210 drugs and supplements.
- Niclosamide Identified as Best Candidate for inhibiting Antegrade Trafficking.
- 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



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 – OXPHOS INHIBITOR

- Uncouples Mitochondrial OXPHOS.
- Even though electrons flow through ETC, there is No ATP production !!
- This results in AMPK activation, and mTOR inhibition which induces “protective autophagy” and shift from OXPHOS to GLYCOLYSIS
- There is Synergy with GLYCOLYSIS Inhibitors (DCA)

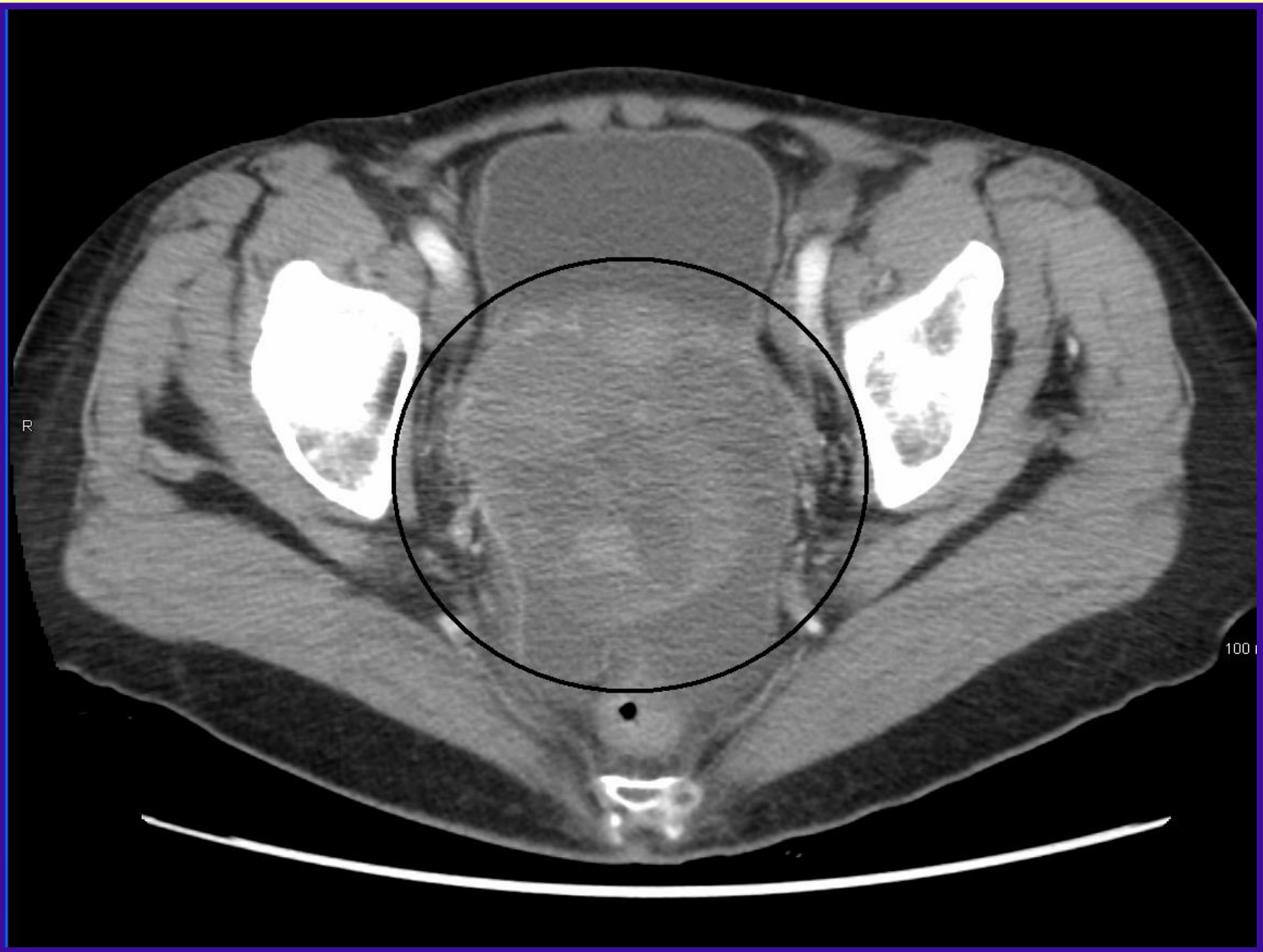
Tran, Uyen Thi, and Toshimori Kitami. “Niclosamide activates the NLRP3 inflammasome by intracellular acidification and mitochondrial inhibition.” Communications biology 2.1 (2019): 1-14.

Niclosamide for Ovarian Cancer

- 14,000 deaths annually.
- Presents late with metastatic spread to peritoneal cavity with Malignant Ascites.
- Platinum Based Chemo Remission- However, 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



Niclosamide for Ovarian Cancer 1

- 2012 Dr Yi Te Yo : High Thruput Screen 1,200 approved drugs against OV CA.
- Niclosamide most promising candidate.
- Effective Against CSCs, Alone or Combined with Conventional Platinum based Chemo.

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 2

- 2014 Dr Rebecca Arend isolated Ov Ca Cells from 34 pts malignant ascites.
- OV CA cells treated w/ Niclo+Carboplatin.
- Synergy found in 32/34 samples.
- Niclosamide potent Wnt/BetaCatenin 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 3

- 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 ?)

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

- 2018 Dr R Kumar studied p53 deficient Ovarian Cancer cells and Xenografts. Hi Thruput Screen 1,600 drugs PHARMAKON Library.
- Niclosamide most potent for P53 def Ov Ca at 2 Micro M.
- Uncouples OXPHOS. (no ATP production even though electrons flow through ETC), AMPK activation, mTOR inhibition.

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, achieved 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 (Wnt). Niclosamide best candidate.
- Human trials Niclosamide for Colon Cancer are Under Way. Susen Burock Berlin Germany

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 safety and efficacy of oral niclosamide in patients with metastases of Colorectal Cancer progressing after therapy: NIKOLO trial.” BMC Cancer 18 (2018).

Niclosamide Dosing

- 2018 Dr Susen Burock: Nicolo Trial Niclosamide for Colon CA 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).

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 used in their 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 Wang screened LOPAC library 1258 compounds. Niclosamide was best inhibitor of BCSC.
- 2014 Dr Ye Br CA in vitro and in vivo Mouse model, increased apoptosis, decreased KI-67, VEGF pos cells, Microvessel density, reduced MDSC Myeloid derived suppressor cells, blocked pulmonary mets.
- Potent STAT3 inhibitor, Targets NF-kB, 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 Reversal of Adipocyte Induced EMT

- Adipocytes surrounding the cancer mass induce EMT Epithelial to Mesenchymal Transition of Breast Cancer cells through paracrine IL-6/Stat3 signaling (Inflammatory Cytokines). (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
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.

Other Anti-Inflammatory Drugs and Natural Substances Reversing EMT

- Celecoxib, ASA and Dipyridamole (Harb, 2019) Lichtenberger 2019):
- Melatonin (Goncalves, 2016),
- Doxycycline (Zhang 2017) (Zhong, 2017)
- Phytochemicals: Allicin/Garlic, Pterostilbene (methylated version of resveratrol), Quercetin, Sulforaphane (found in broccoli) Resveratrol (from grape skins), Curcumin (from turmeric) Genistein (phyto-estrogen from soy), Epigallocatechin-3-gallate (EGCG) (from green tea) Parthenolide(Feverfew) (Liscova, 2019)
- PPIs (Feng,2016)
- Thymoquinone Black Seed Oil (Zhang, 2018)
- Tocotrienol Vit E
- Solomons Seal (Inhibits EGFR)

References Other Reversing EMT

- Harb, Jerry, Pen-Jen Lin, and Jijun Hao. “Recent development of Wnt signaling pathway inhibitors for cancer therapeutics.” Cur onc reports 21.2 (2019): 12.
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- Zhong, Weilong,“Doxycycline inhibits breast cancer EMT and metastasis through PAR-1/NF-κB/ miR-17/E-cadherin pathway.” Oncotarget 8.62 (2017):
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- Zhang, Yujiao, et al. “Thymoquinone inhibits the metastasis of renal cell cancer cells by inducing autophagy via AMPK/mTOR signaling pathway.” Oncology letters 15.1 (2018): 1012-1019.

References Other Reversing EMT

- Feng, Li-Min, Xue-Feng Wang, and Qing-Xian Huang. “Thymoquinone induces cytotoxicity and reprogramming of EMT in gastric cancer cells by targeting PI3K/Akt/mTOR pathway.” Journal of biosciences 42.4 (2017): 547-554.
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- Shah, Parag P. “Common cytotoxic chemotherapeutics induce epithelial-mesenchymal transition (EMT) downstream of ER stress.” Oncotarget (2017)
- Guo, Yi, et al. “Platelets promote invasion and induce epithelial to mesenchymal transition in ovarian cancer cells by TGF-β signaling pathway.” Gynecologic oncology 153.3 (2019): 639-650.
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- Xu, Qilin, et al. “EGF induces epithelial-mesenchymal transition and cancer stem-like cell properties in human oral cancer cells via promoting Warburg effect.” Oncotarget 8.6 (2017): 9557.
- Thurnher, Martin, and Georg Gruenbacher. “Mevalonate Metabolism Promotes Cancer Stemness and Immunity via EMT-like Reverse Differentiation.” Frontiers in Oncology 8 (2018): 394.

Niclosamide Synergistic with Checkpoint Inhibitors

- 2019 Dr Luo using lung cancer cells, 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" (Luo, 2019)

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 Enhancing Checkpoint Inhibitors

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

References Enhancing Checkpoint Inhibitors

de Graaff, Priscilla, et al. “Consumption of β-glucans to spice up T cell treatment of tumors” Expert Op biol ther 18.10 (2018):1023-1040.
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).
Draganov, Dobrin"Ivermectin synergizes with immune checkpoint blockade for treatment of breast cancer." NPJ breast CA 7.1 (2021)
Kroemer, Guido “Cancer immunotherapy in 2017: The breakthrough of the microbiota.” Nature Reviews Immunology 18.2 (2018): 87.53)
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):
Afzal, Muhammad et al “Metformin combination with immune checkpoint inhibitors in metastatic melanoma.” J Immun CA (2018):
Feng, M.“Inhibition of β-catenin/BCL9 interaction overcomes resistance to immune checkpoint blockades by modulating Treg cells.” Sci Adv 2019

Ivermectin Antiparasitic - 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 Onchocerciasis River Blindness, 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.

Volunteers Distribute Ivermectin

September 15 to 20, 2016. Community volunteers distribute Ivermectin to villagers in the District of Aboisso, southeast Cote d'Ivoire, as part of a nationwide mass campaign aimed at eliminating neglected tropical diseases . Courtesy of USAID in Africa.

Ivermectin Antiparasitic Drug

- Treats Human Parasites: Strongyloidiasis, Ascariasis, Cutaneous larva migrans, Gnathostomiasis and Trichuriasis, Pediculosis (lice) and Scabies (mites).
- 200 million humans globally have taken the drug for parasitic disease.
- Extensive Veterinary Use: Billions of pets, horses, farm animals, Heartworm in dogs

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

Ivermectin Cancer Pathway Targets

- PI3K/AKT/mTOR pathway (Cancer Pathway)
- Wnt -TCF pathways (Cancer Stem Cells)
- Purinergic P2X receptors (ATP sensitive receptors) Tumor Micro Environment.
- Degrades PAK-1 protein (P21-Activated Kinase involved in oncogenic signalling)
- Multidrug Resistance Protein (MDR)

Juarez, Mandy “The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug.” Amer J Cancer Res 8.2 (2018)

Anti-Cancer Effects 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 Hi Thruput 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.
- 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 Reverses Chemo Resistance

- 2019: Jiang using in vitro and in vivo xenografts with colorectal, breast and leukemia cells treated w/ Vincristine and Adriamycin (Doxorubicin) .
- Ivermectin Reverses Chemo Resistance at low concentrations.
- Decreases P-glycoprotein drug efflux pump by binding to EGFR at cell surface. This inhibited its downstream signaling cascade ERK/Akt/NF-κB.
- NF-kB inhibition leads to reduced P-gp Transcription.

Jiang, Lu, et al. "Ivermectin reverses the drug resistance in cancer cells through EGFR/ERK/Akt/NF-κB pathway." Journal of Experimental & Clinical Cancer Research 38.1 (2019): 1-18.

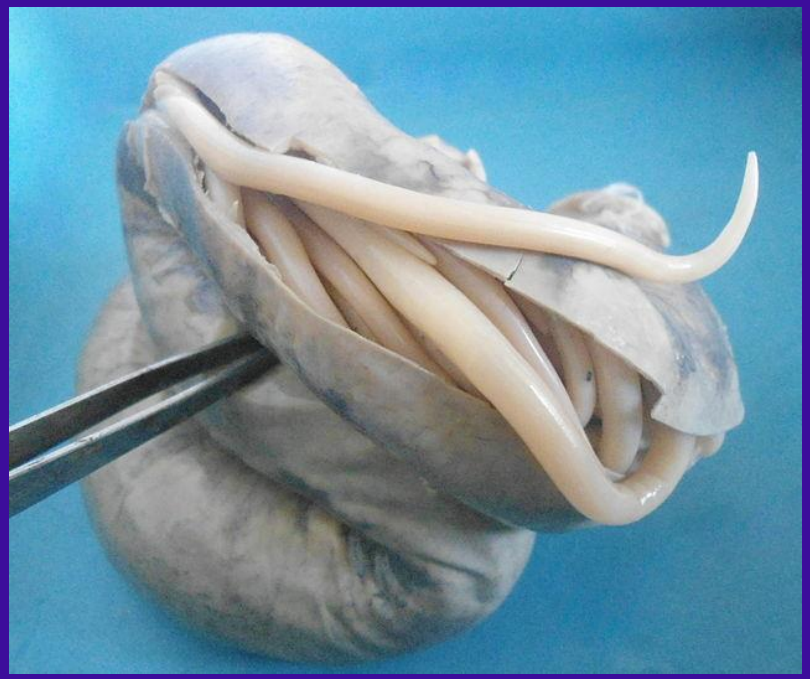
Ivermectin Dosing

- Usual Adult Dose for Scabies 0.2 mg/kg orally once, and repeated in 2 weeks. (12 mg for 60 kg)
- For Covid-19:
  0.2 -0.3 mg/kg daily x 1-5 days.
- 3 mg tabs 20 tabs for $30.

Fawcett, Robert S. "Ivermectin use in scabies." American Family Physician 68.6 (2003): 1089-1092.

Mebendazole (Vermox)

- 1968 First synthesized by Janssen Pharm.
- FDA-approved in 1972 (Pinworm, Ascaris Roundworm)
- Dosage 100 mg PO BID (w/fatty meal)
- Therapeutic Conc. at Disease Site.
- Good Toxicity Profile
- PO tablet, Low price.



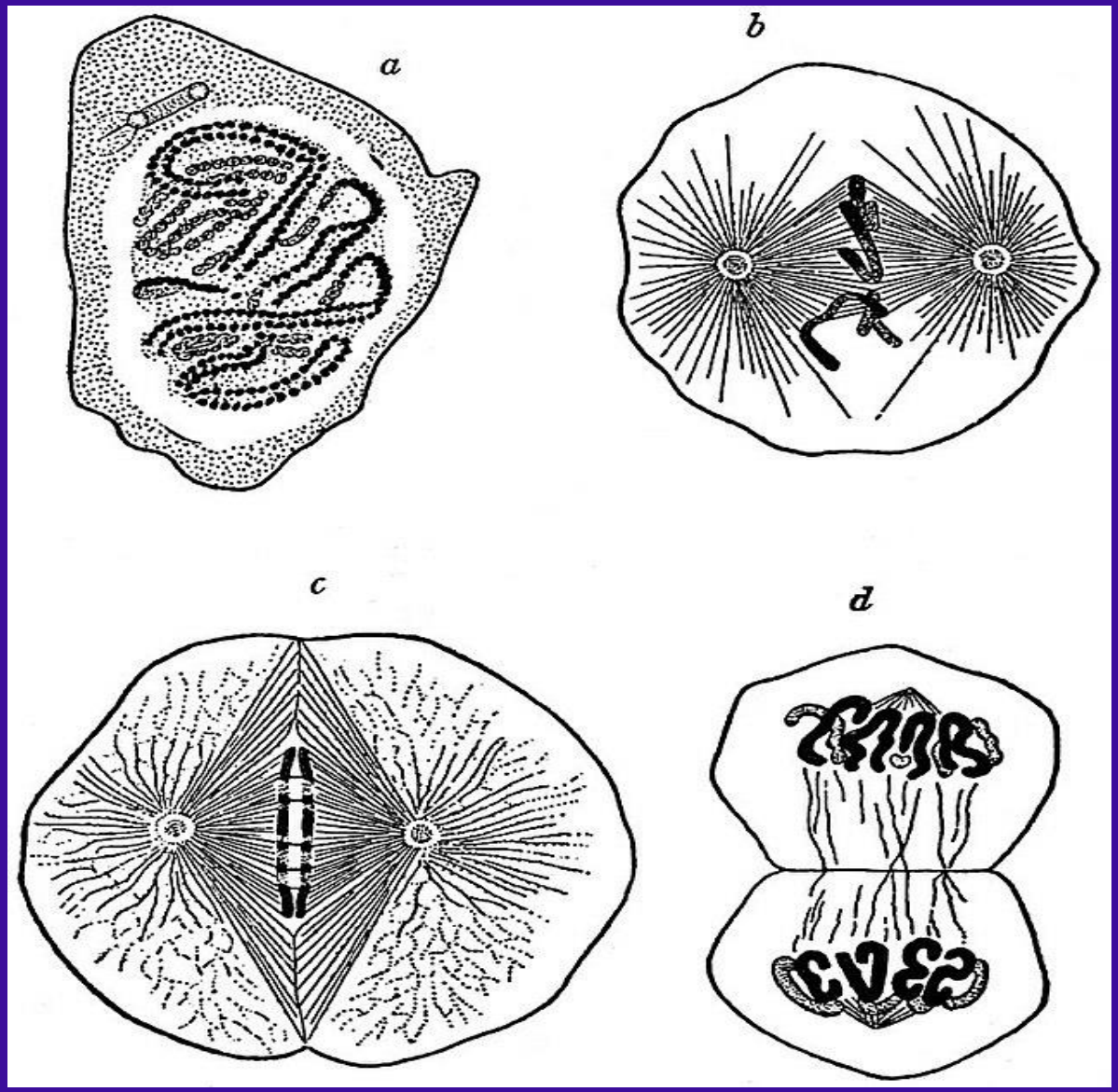
87) Guerini, Andrea Emanuele, et al. “Mebendazole as a Candidate for Drug Repurposing in Oncology: An Extensive Review of Current Literature.” Cancers 11.9 (2019): 1284.

Mebendazole Microtubule Disruptor

- Microtubule Disruptor, Impairs Spindle Formation (next slide), resulting in mitotic arrest.
- Downregulates BCL2 (anti-apoptosis protein) similar to Venetoclax. (ABT-199)
- Similar to Other Microtubule Inhibitors: taxanes, paclitaxel, docetaxel, vinblastine, vincristine, nocodazole,and colchicine, etc.
- MBZ Proposed to replace Vincristine in brain tumor Rx.

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.

Spindle Formation / Cell Division



- a, spireme stage; b, spindle formed; c, spindle complete; equatorial plate formed; d, Division completed.

Mebendazole Hi Thruput Screen AML

- 2018 Dr Licai He did High Thu Put Screen 1,000 drugs for AML.
- Mebendazole best candidate – “potent antileukemic activity”

He, Licai, et al. “Mebendazole exhibits potent anti-leukemia activity on acute myeloid leukemia.” Experimental cell research 369.1 (2018): 61-68

Mebendazole for Melanoma

- 2008 Dr Doudican Hi Thruput Screen 2,000 drugs at 1 MicroM 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 "Mebendazole induces apoptosis via Bcl-2 inactivation in chemoresistant melanoma cells." Mol Can Res (2008)
:Whitaker, Robert H., and William J. Placzek. "Regulating the BCL2 family to improve sensitivity to microtubule targeting agents." Cells 8.4 (2019): 346.

Mebendazole Tubulin Disruption

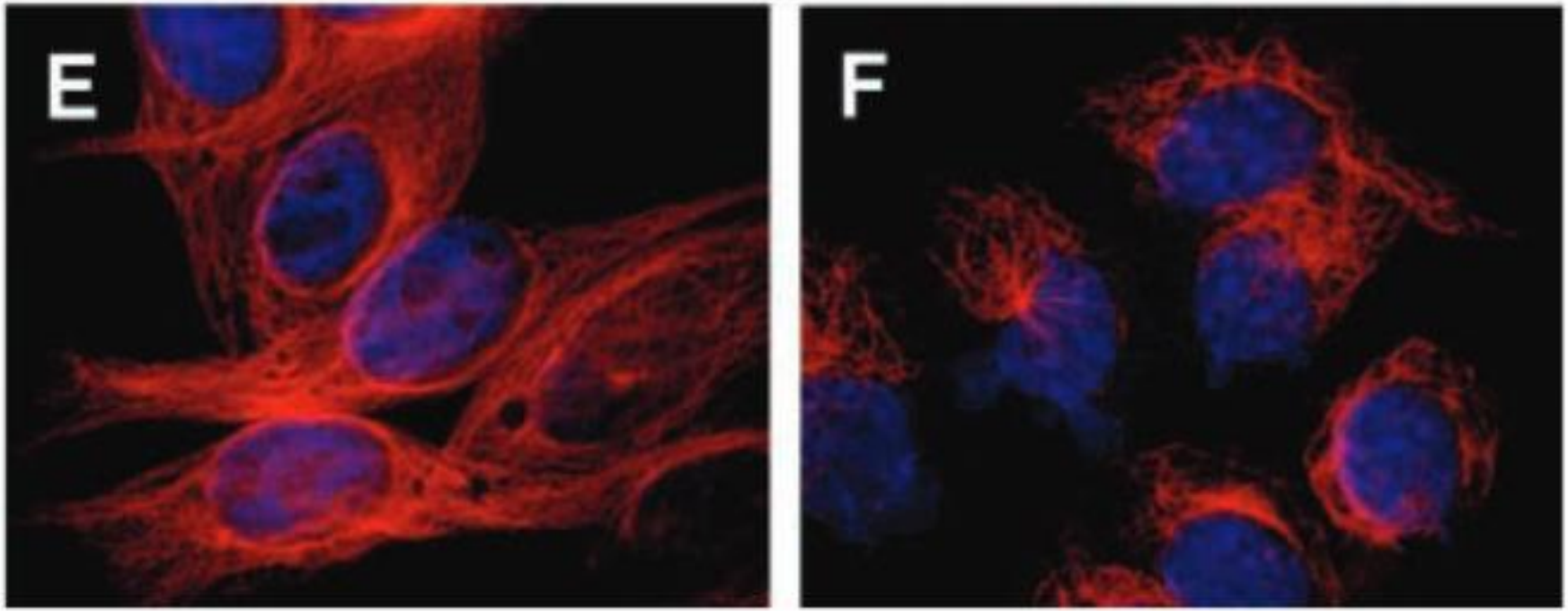


FIGURE 3.Mebendazole-induced microtubule disruption in melanoma cells Left vehicle, Right Mebenz. Cells stained with anti-a-tubulin antibody (Red) DAPI DNA stain (Blue). Doudican, N Mebendazole induces apoptosis via Bcl-2 inactivation in chemoresistant melanoma Mol Can Res 2008

Mebendazole HNSC

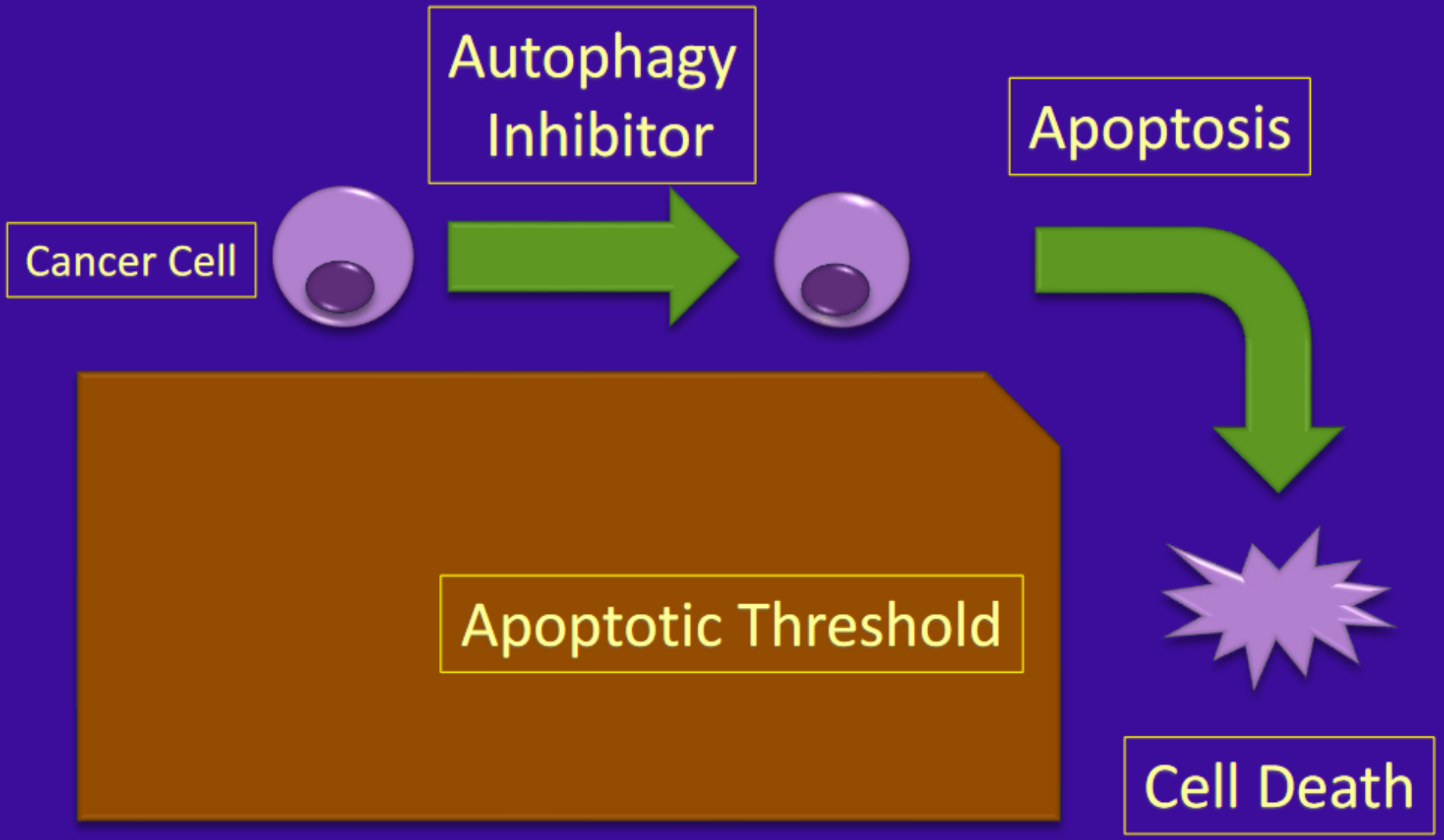
- 2017 Dr Zhang head and neck squamous cell CA .
- Mebendazole more potent than Cisplatin.

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 Synergy w/Autophagy Inhibitor

- 2019 Dr So Jung Sung HUVECs Endothelial Cells
- MBZ: Inhibits Tumor Angiogenesis.
- MBZ: dose-dependently inhibits EC proliferation.
- Pronounced Induction of “Protective Autophagy”
- MBZ Synergy with Chloroquine, Autophagy Inhibitors.

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.
Tompkins, Kenneth D., and Andrew Thorburn. "Focus: Death: Regulation of apoptosis by autophagy to enhance cancer therapy." The Yale journal of biology and medicine 92.4 (2019): 707.



Tompkins, Kenneth D., and Andrew Thorburn. "Focus: Death: Regulation of apoptosis by autophagy to enhance cancer therapy." The Yale journal of biology and medicine 92.4 (2019): 707.

Mebendazole – Drug Synergies

- Autophagy inhibitors: chloroquine/ hydroxychloroquine, clarithromycin, thymoquinone, loratadine, PPI's etc.
- Metformin
- Metronomic chemotherapy (Low dose, chronic)
- Taxanes of vinca alkaloids microtubule agents
- Itraconazole (Sporonox, Anti-fungal, HKII/VDAC)
- Cimetidine (H2 blocker antiAcid/Immune stimulator
- Diclofenac (NSAID Anti-Inflammatory)

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
- No adverse effects, improved quality of life.
- 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 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.
- No Adverse effects, transient elevation LFT's.
- Better result with addition of HCQ ?

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

Mebendazole - Immunotherapy

- 2017 Dr Blom: MBZ upregulates anti-tumor immune function (13)
- MGZ Upregulates Genes related to monocyte macrophage M1 (Th-1) phenotype activation. (Not Th-2)
- 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 - Targeted Pathways

- Inactivates BCL-2 (the anti-apoptotic protein)(Doudican, 2008)
- Hedgehog inhibitor (Cancer Stem Cell Pathway) (Larsen 2015)
- Inactivates C-Myc (Pinto, 2019)
- Downregulates MDM drug resistance (Mrkvová, 2019)
- Immunotherapy- Restores Anti-Tumor Immune Function (Guerini, 2019)
- 6 Ongoing Human Clinical Trials

Mebendazole - Targeted Pathways References

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

Larsen, Andrew R., et al. “Repurposing the antihelmintic mebendazole as a hedgehog inhibitor.” Molecular cancer therapeutics 14.1 (2015): 3-13.

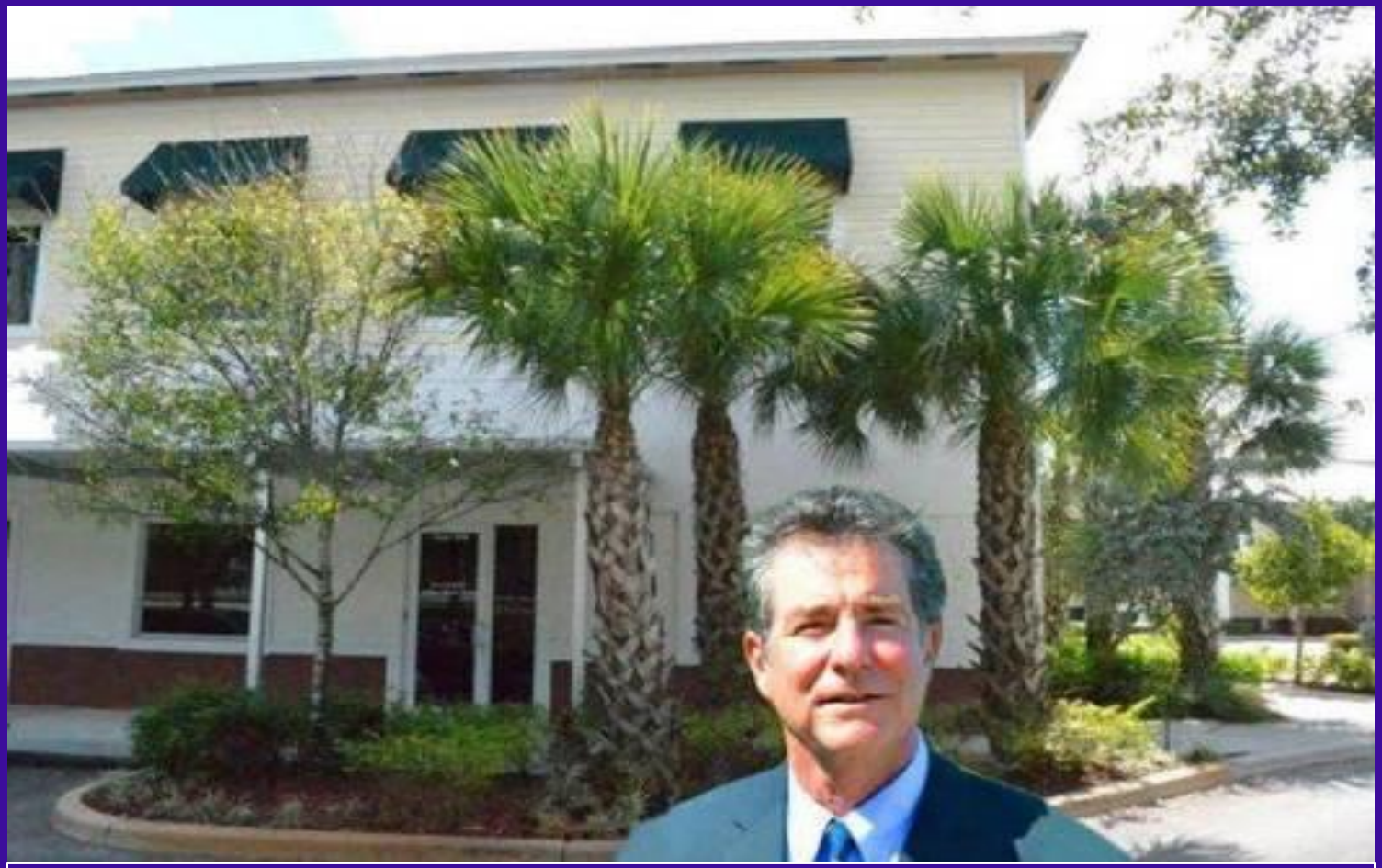
Pinto, Laine Celestino, et al. “Mebendazole induces apoptosis via C-MYC inactivation in malignant ascites cell line (AGP01).” Toxicology in Vitro (2019).

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

Summary Slide
Cancer As Parasitic Disease

- 1) The Study of Parasitic Disease Provides a Model for Understanding Cancer Biology.
- 2) Many AntiParasitic Drugs Can be Repurposed as Anti Cancer Drugs.
- 3) Artesunate (Antimalarial) from China.
- 4) Niclosamide
  Dual OXPHOS and Autophagy Inhibitor
- 5) Ivermectin Safe, Miracle Drug
- 6) Mebendazole Microtubule Inhibitor

Thank You – Any Questions?



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