Cracking Cancer Toolkit: Using Repurposed Drugs for Cancer Treatment

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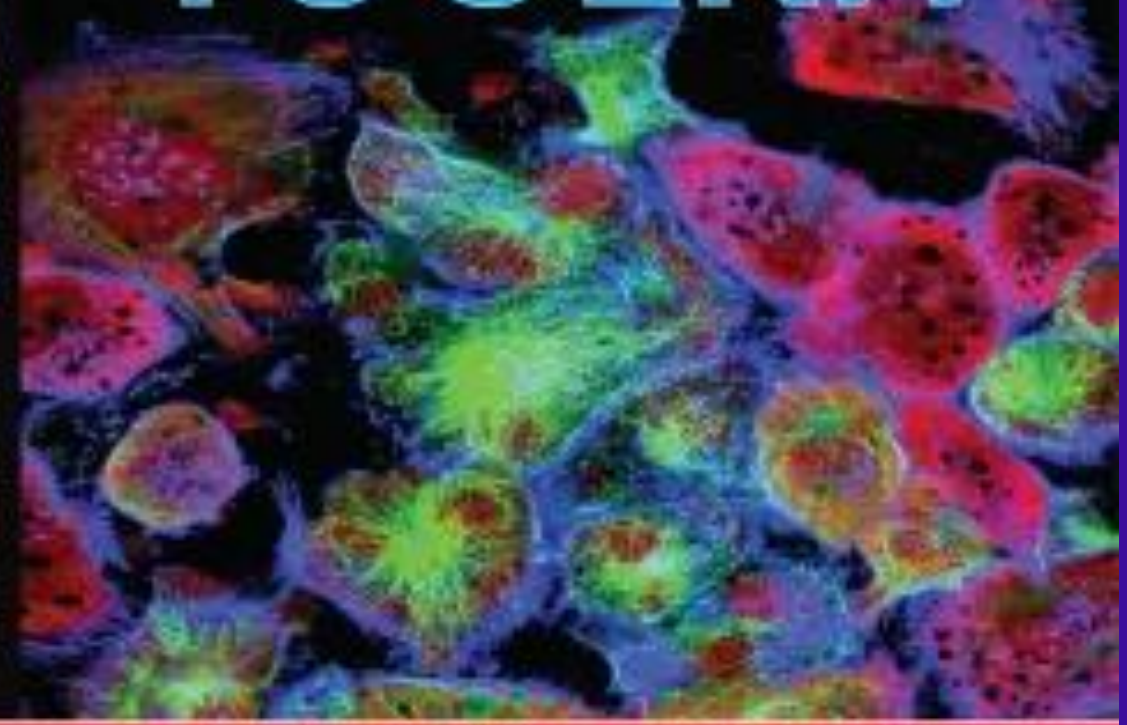
USING REPURPOSED DRUGS FOR CANCER TREATMENT

CRACKING CANCER TOOLKIT



JEFFREY DACH MD

CRACKING CANCER TOOLKIT JEFFREY DACH MD

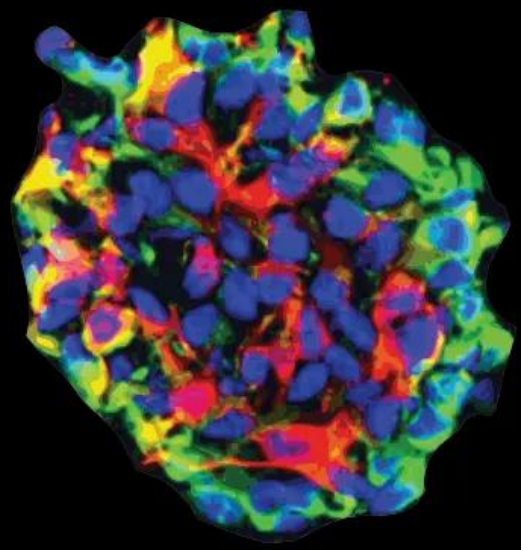
The Chemotherapy Paradigm

- Causes Massive Inflammation,
- Activation of NFkB, COX-2
- Worsens Immunosuppression
- Does Not Eradicate Cancer Stem Cells (Increased)
- Recognized Need for New Therapy to Eradicate Cancer Stem Cells.
- New Paradigm: “Cancer as a Metabolic Disease”

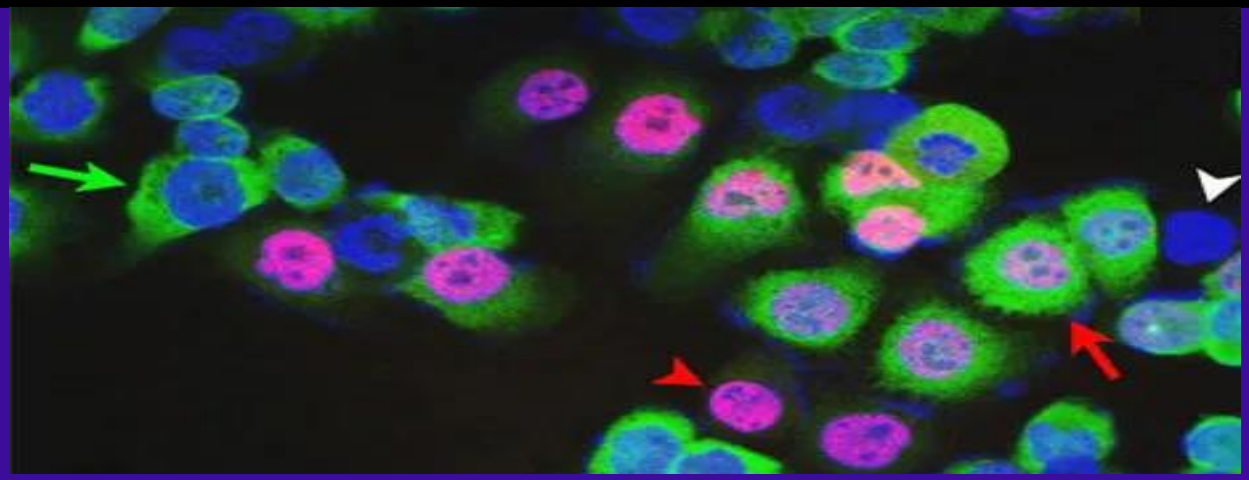
Pecqueur, Claire, et al. “Targeting metabolism to induce cell death in cancer cells and cancer stem cells.” International journal of cell biology 2013 (2013).

Cancer Stem Cells

Cancer Stem Cell Conference



September 20-23, 2016 | Hilton Cleveland Downtown



Cancer Stem Cells

- Attend National Meetings, Yet CSC are Ignored by Oncologists in Clinical Practice.
- CSC -The Cause for Cancer Relapse After Chemotherapy.
- Oncology Literature Recognizes Need to Address Cancer Stem Cells to Prevent Relapse

"The successful elimination of cancer

requires an anti-cancer therapy that will affect both differentiated cancer cells and CSCs…. At present, conventional therapy that includes radio-, chemo-, and immunotherapy kills rapidly proliferating and differentiated cells. These treatments may cause the tumor to shrink but will not prevent tumor recurrence. Thus, a combination of treatments targeting both rapidly proliferating cancer cells and quiescent or slow-proliferating CSCs would be ideal… A reversal of tumor metabolism to "normal" might impair tumor growth of cancer cells, causing tumor regression, and differentiation/sensitization to cell death of CSCs, impairing the recurrence of the tumor." (Pecquer, 2013)

Pecqueur, Claire, et al. "Targeting metabolism to induce cell death in cancer cells and cancer stem cells." International journal of cell biology 2013 (2013).

Can Chemotherapy Kill Cancer Stem Cells ?

- "Generally, conventional chemotherapy can only inhibit tumor growth and lead to drug resistance, but cannot kill Cancer Stem Cells". (Du, Fang-Yu, 2019)

Du, Fang-Yu, et al. "Targeting cancer stem cells in drug discovery: Current state and future perspectives." World journal of stem cells 11.7 (2019): 398.

Technological Innovations Making Possible Targeting Cancer Stem Cells With Repurposed Drugs and Supplements

- PET Scan with 18 FDG
- Automated High Thru-Put Drug Screening
- Message Groups Sharing information

Haider,

Cancer as Metabolic Disease

- Warburg Effect (Aerobic Glycolysis/fermentation) High Lactate Generation, Low Glucose Oxidation.
- Hexokinase II Relocated to the VDAC on Outer Mitochondrial Membrane
  - Resulting in Immortalization of Cancer Cell-Preventing Apoptosis.
  - Resulting in Massive Glucose Uptake and Utilization
- Positive on PET Scans using 17-FDG
- Metabolic Plasticity

Three Pillars of Cancer Cell Metabolism

GLYCOLYSIS

OXPHOS

Autophagy

Metabolic Plasticity of the Cancer Cell

GLYCOLYSIS | OXPHOS | Autophagy

The metabolic plasticity of the cancer cell requires combination of two or more anti-cancer agents to block all three pathways, thereby achieving “Synthetic Lethality.”

Fourth Pillar

Restore Host Immune System

Fifth Pillar

Inflammation

Inhibit
NF-kB, IL-6
cytokines

The Cancer Stem Cell

Cause of Cancer Relapse

Negative on PET

Dormant State

Circulating Tumor Cells (CTC)

Cancer Stem Cell Pathways

- Wnt/Beta Catenin
- Hedgehog
- Notch

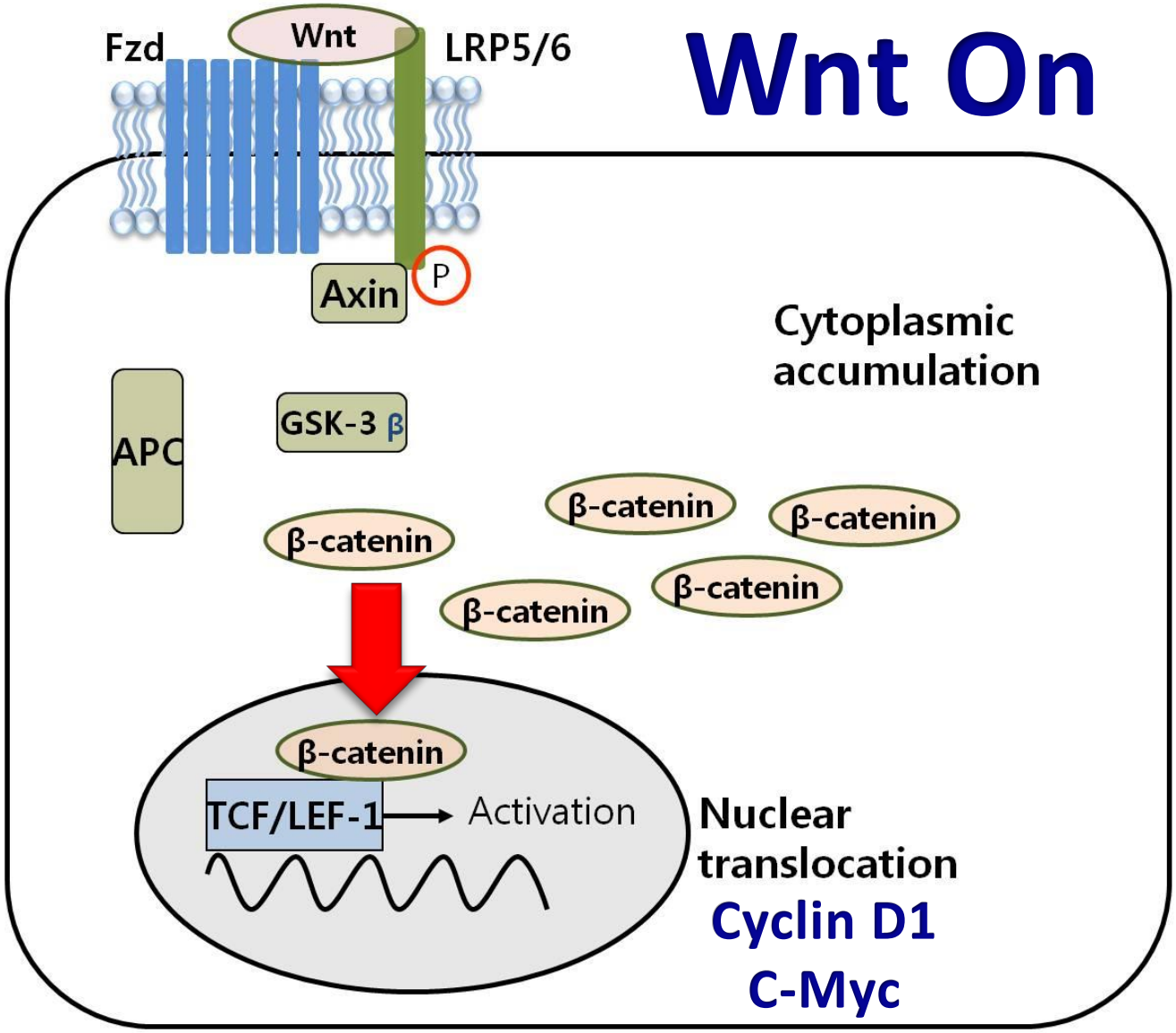
d,

Targeting Cancer Stem Cells by Inhibiting Wnt Signaling

- "Our results suggest that the inability of conventional chemotherapy to kill MCL-ICS (Lymphoma Cancer Stem Cells) can be overcome by adding inhibitors of Wnt signaling" (Mathur, Rohit, et al,2015)

Mathur, Rohit, et al. "Targeting Wnt pathway in mantle cell lymphoma-initiating cells." Journal of hematology & oncology 8.1 (2015): 63

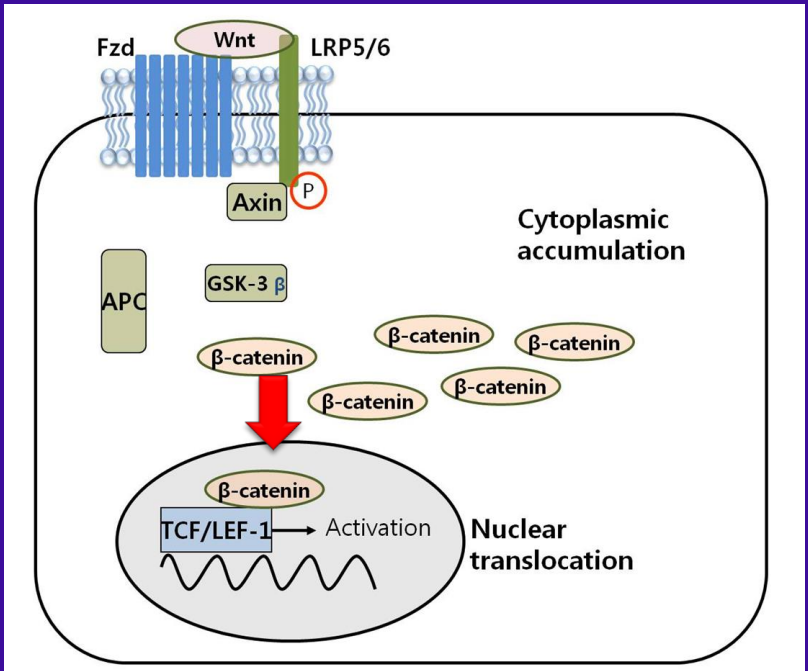
Wnt Cancer Stem Cell Pathway



Han, Jae-Ik, and Ki-Jeong Na. "Wnt/β-Catenin signaling pathway in canine skin melanoma and a possibility as a cancer model for human skin melanoma." Melanoma in the Clinic-Diagnosis, Management and Complications of Malignancy. IntechOpen, 2011.

Wnt Cancer Stem Cell Pathway

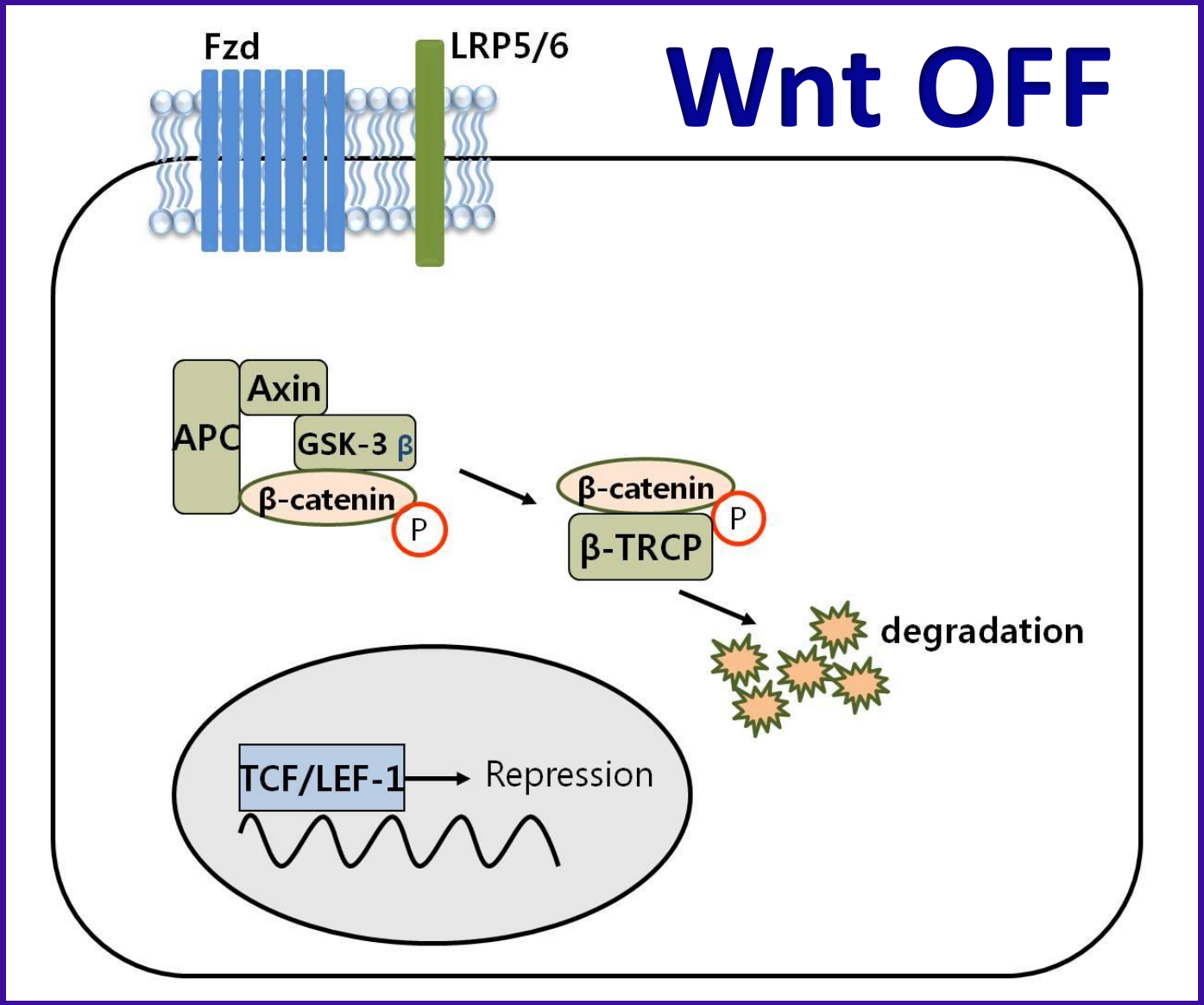
Wnt On



Wnt ON: βeta-catenin is NOT degraded, and instead the accumulated β-catenin enters the nucleus and activates the target gene TCF/LEF, and c-Myc and Cyclin D1.

Han, Jae-Ik, and Ki-Jeong Na. "Wnt/β-Catenin signaling pathway in melanoma." Melanoma in the Clinic-Diagnosis, Management of Malignancy. IntechOpen, 2011.

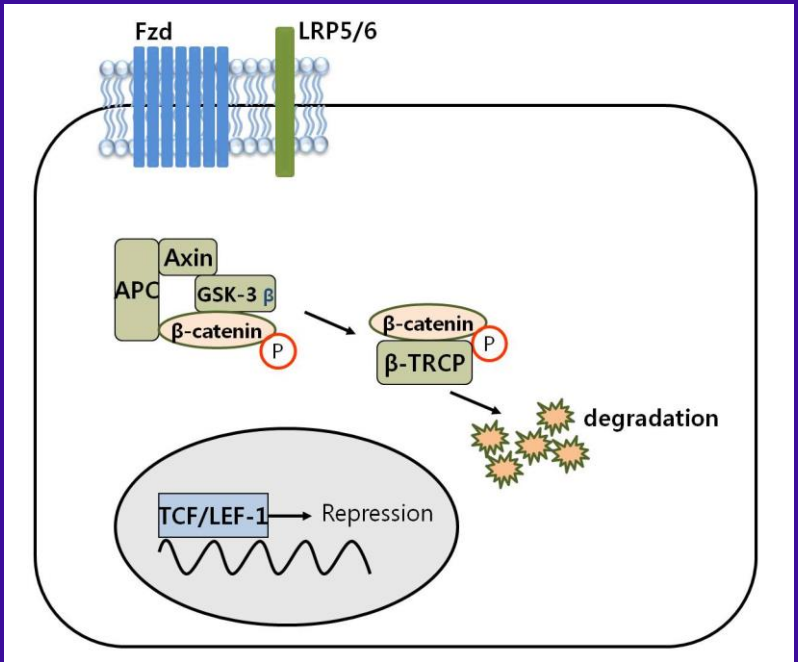
Wnt Cancer Stem Cell Pathway



Han, Jae-Ik, and Ki-Jeong Na. "Wnt/β-Catenin signaling pathway in canine skin melanoma and a possibility as a cancer model for human skin melanoma." Melanoma in the Clinic-Diagnosis, Management and Complications of Malignancy. IntechOpen, 2011.

Wnt Cancer Stem Cell Pathway

Wnt OFF



Wnt OFF: In the absence of Wnt signals, a cellular complex degrades β-catenin, so there is no entry of the β-catenin protein into the nucleus, the gene TCF/LEF is suppressed, and no nuclear transcription of Cyclin D1 or other growth signals takes place.

Han, Jae-Ik, and Ki-Jeong Na. "Wnt/β-Catenin signaling pathway in melanoma." Melanoma in the Clinic-Diagnosis, Management of Malignancy. IntechOpen, 2011.

Repurposed Drugs Targeting Wnt Signaling

- Ivermectin (Specific WNT-TCF Blocker at low micromolar concentrations.)
- Metformin (Diabetic Drug)
- Niclosamide, Pyrvinium (hook,pin, antiparasitics)
- Mefloquine/Chloroquine (antimalarial)
- Doxycycline/ Clarithromycin/Azithromycin
- Sulfasalazine (Rheumatology, Xct inhibitor)
- VIT A, Fenretinde, ATRA, (Pro Myleo Leukemia)

Melotti, Alice, et al. “The river blindness drug Ivermectin and related macrocyclic lactones inhibit WNT-TCF pathway responses in human cancer.” EMBO molecular medicine (2014): e201404084.

Ivermectin Top Candidate, Blocks TCF Gene

- Alice Melotti et al. used a transcriptional reporter assay for TCF activity driven by ß-catenin to test a collection of 1,040 drugs. Only one agent**, ivermectin**, perfectly tracked the profile induced by blocking the TCF gene, blocks the Wnt pathway, and kills cancer stem cells…!!!! (2014)
- Sharmeen et al. at the University of Toronto screened a library of 100 drugs for activity against a leukemic cell line. They reported ivermectin as the top candidate for inducing leukemic cell death at low micromolar concentrations. (2010)

Sharmeen, et al. “Antiparasitic ivermectin induces hyperpolarization and cell death in leukemia cells.” Blood 116.18 (2010): 3593-3603
Melotti, Alice, et al. “The river blindness drug Ivermectin inhibit WNT-TCF pathway responses in human cancer.” EMBO molecular medicine (2014): e201404084.

Pyrvinium Oxphos Inhibitor

- Pyrvinium binds to and activates casein kinase 1 (CK-1), thus degrading cytosolic Beta-Catenin, resulting in potent inhibition of Wnt signaling at low concentrations (10 nanoMolar). (Thorne 2010)
- OXPHOS inhibitor Accumulates in mitochondria with inhibition of complex I and II in the electron transport chain.
- Inhibits Glutathione Uptake from TME
- Potent Androgen Receptor Blocker (BPH)

Thorne, Curtis A., et al. “Small-molecule inhibition of Wnt signaling through activation of casein kinase 1α.” Nature chemical biology 6.11 (2010): 829.

Niclosamide

- Antiparasitic for Hookworm
- Targets CSC, Wnt and Notch inhibitor
- Downregulates NF-Kb
- Inhibits antegrade lysosomal trafficking
- Inhibits OXPHOS-mito ETC uncoupler.
- Effective for Ovarian CA w/wo chemo
- Effective for P53 deficient/mutated cell types
- Reverses EMT Epithelial to Mesenchymal Trans
- Blocks Late Stage Autophagy

Thorne,

Metformin Oxphos Inhibitor

- First Line Diabetic Drug (French Lilac plant)
- Accumulates in Mitochondria
- Inhibits Complex I ETC.
- Docks in the hexokinase 2 binding site, effectively blocking its function, resulting in separation of hexokinase 2 from the VDAC on the outer mitochondrial membrane.
- Activates AMPk, Inhibits mTOR, induces "Protective autophagy", synergy wth chloroquine

Salani, Barbara, et al. "Metformin impairs glucose consumption and survival in Calu-1 cells by direct inhibition of hexokinase-II." Scientific reports 3 (2013).

Niclosamide for MM

- "At clinically achievable nontoxic concentrations, [Niclosamide] killed Multiple Myeloma cell lines as efficiently or better than chemotherapy and anti-myeloma drugs with little impact on normal cells. More importantly there was rapid reduction in light chain production [the clonal antibodies which cause amyloid deposits and renal impairment]." (Khanim, 2011)

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.

All OxPhos Inhibitors Are Cancer Stem Cell Agents

- All OXPHOS inhibitors are Wnt pathway inhibitors and therefore may serve as valid anti-CSC agents. This is due to the "Mitochondrial-Wnt Signaling Axis" (Roberto Costa 2019)

Costa, Roberto, et al. "Impaired mitochondrial ATP production downregulates Wnt signaling via ER stress induction." Cell reports 28.8 (2019): 1949-1960.

Botanicals Targeting Wnt Pathway, Killing Cancer Stem Cells

- Sulforaphane
- Curcumin
- Berberine
- Parthenolide (feverfew)
- EGCG (green tea)
- Quercetin
- Baicalin (Chinese Skullcap)

- Resveratrol/ Pterostilbene
- Silibin (Milk Thistle)
- Diallyl trisulfide Allicin(Garlic)
- Vitamin D3
- Most are OXPHOS inhibitors

Scarpa, E. S., and P. Ninfali. “Phytochemicals as Innovative Therapeutic Tools against Cancer Stem Cells.” International journal of molecular sciences 16.7 (2014): 15727-15742.

references

(1) McCubrey, James A., et al. "Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs." Aging (Albany NY) 9.6 (2017): 1477.

Cancer Prevention

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

Haider,

Repurposed Drugs Considerations

- Drug Therapeutic Blood Levels Pharmacokinetics: Are we able to reach therapeutic blood levels using standard dosages?
- Drug Efficacy in Human Use ?
- Cancer Stem Cell Activity: Is the drug active against CSCs?
- Adverse Effects—Drug Toxicity: Is the drug too toxic for human use?
- Interactions with Other Drugs: CYP450 enzyme system?

Haider, Ahmad,

Hallmarks of Cancer Cells Hanahan and Weinberg

- Reprogrammed Energy Metabolism – The Warburg Effect (HKII-VDAC)
- Growth Signals Upregulated (VEGF, PDGF,EGF,E2)
- Evasion of Apoptosis (BCL2)
- Evasion of the Immune System (PIBF)
- Upregulated Inflammation (NF-kB)

1) Hanahan, Douglas, and Robert A. Weinberg. “The hallmarks of cancer.” cell 100.1 (2000): 57-70.
2) Hanahan, Douglas, and Robert A. Weinberg. “Hallmarks of cancer: the next generation.” cell 144.5 (2011): 646-674.

All Hallmarks Are Downstream of Metabolic Disturbance

- "All recognized hallmarks of cancer are considered downstream epiphenomena of the initial disturbance of cellular energy metabolism. The disturbances in tumor cell energy metabolism can be linked to abnormalities in the structure and function of the mitochondria. (1)"

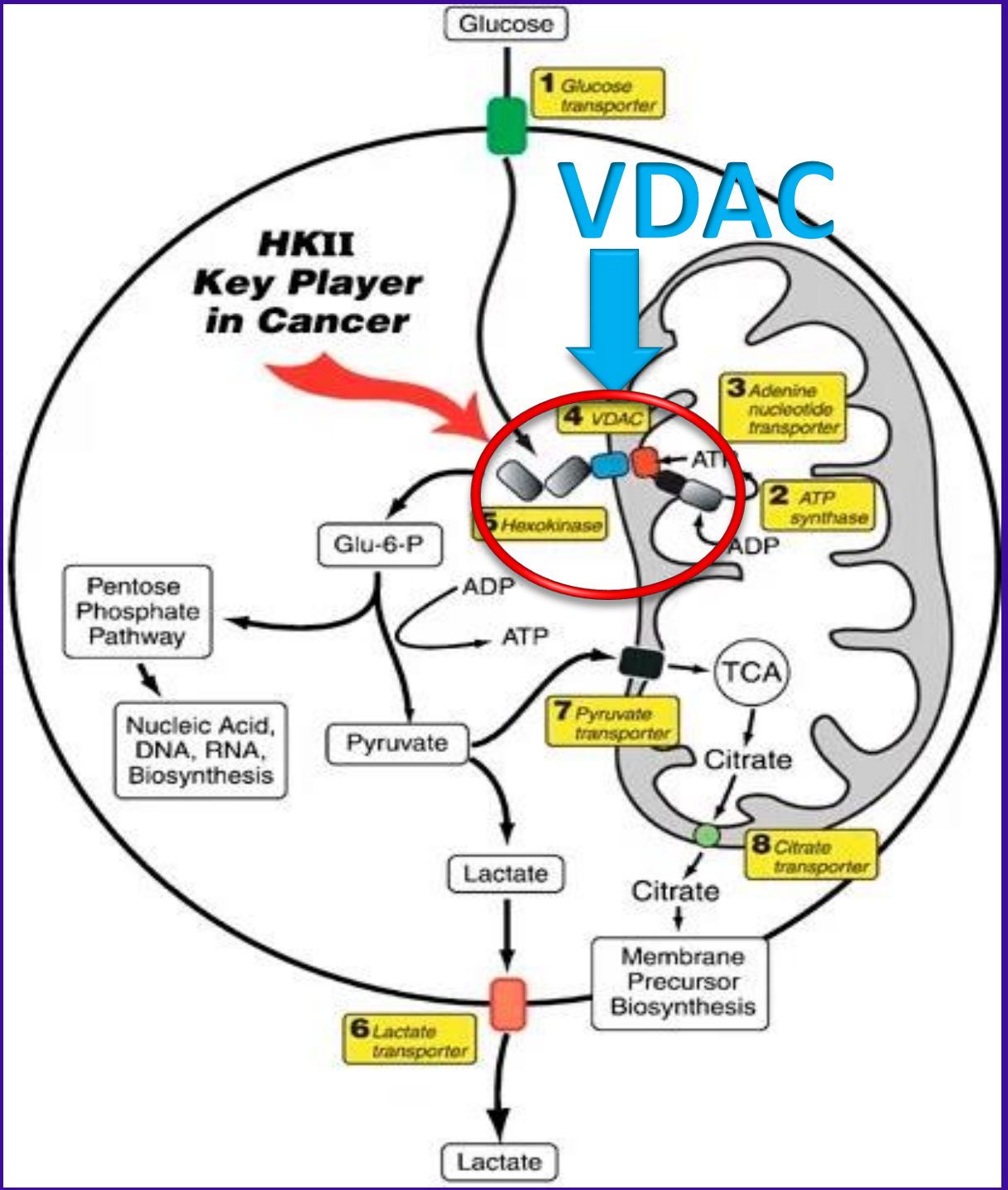
1) Seyfried, Thomas N., et al. "Cancer as a metabolic disease: implications for novel therapeutics." Carcinogenesis 35.3 (2013): 515-527.

Reprogrammed Energy Metabolism

- The Warburg Effect/Fermentation.
- Carbon Shunted Away from OXPHOS towards GLYCOLYSIS (PDK upregulated, Inhibiting PDC)
- High Lactate Accumulation
- HKII - Translocated to the VDAC
  - Provides ATP for Glycolysis Pathway
  - Prevents Mitochondrial Apoptosis.

Reprogrammed Energy Metabolism

Hexokinase-II Translocated to the VDAC

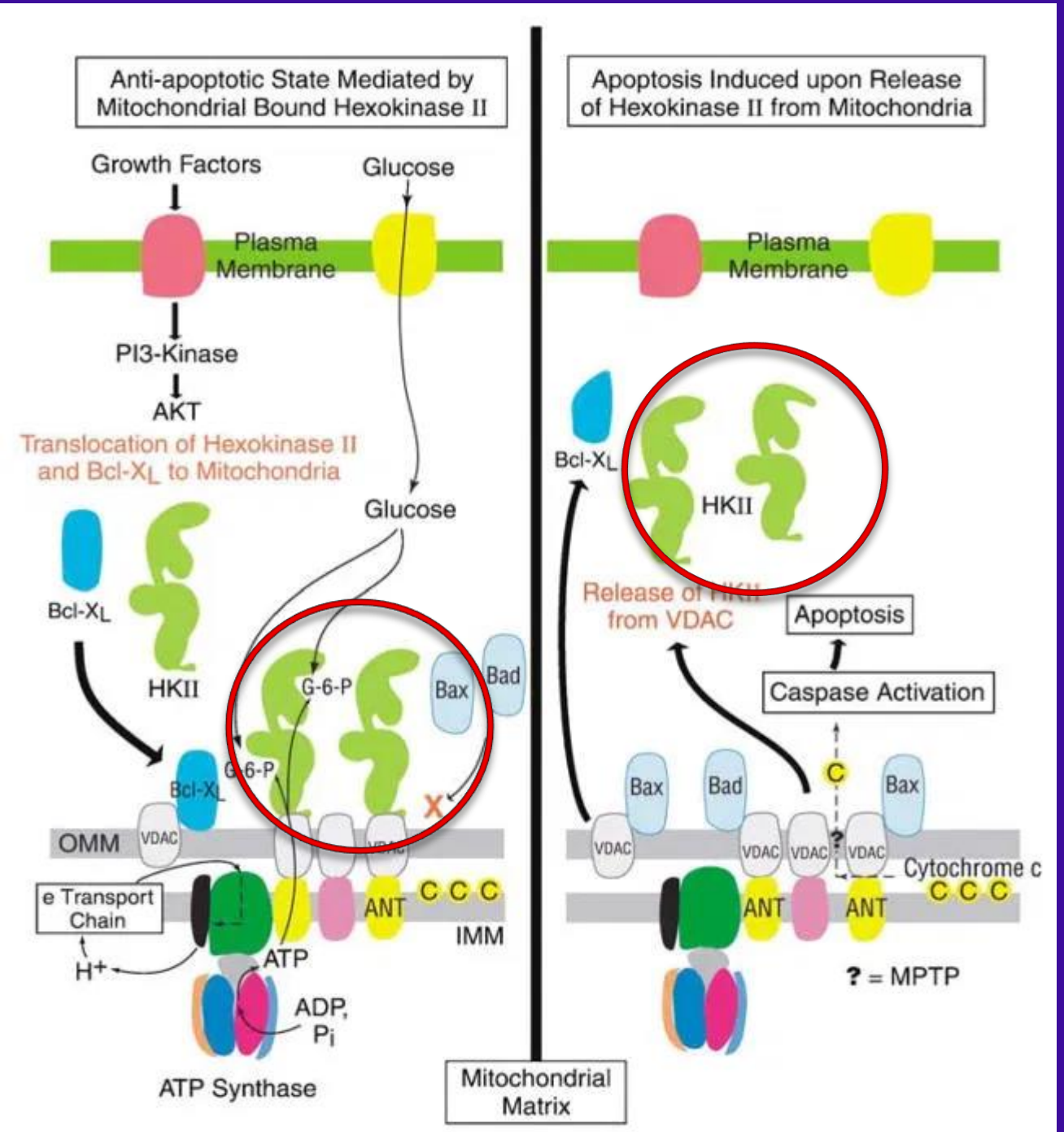


HKII-VDAC

- Hexokinase II attached to VDAC on mitochondrial membrane, utilizing ATP to convert glucose to G6-P

- Mathupala, Ko, and P. L. Pedersen. "Hexokinase II: cancer's double-edged sword when bound to mitochondria." Oncogene 25.34 (2006): 4777.

HKII-VDAC



- Apoptosis induced by release of Hexokinase II from VDAC at outer mitochondrial membrane.
- Fig 3 Mathupala, Ko, and P. L. Pedersen. "Hexokinase II: cancer's double-edged sword when bound to mitochondria." Oncogene 25.34 (2006): 4777.

Natural Substances which Detach HKII from VDAC

- Methyl Jasmonate
- Chinese Skullcap (Baicalin, Oroxylin A)
- Curcumin
- CBD (Cannabidiol)

1)

Repurposed Drugs Detach HKII from VDAC

- Metformin
- Itraconazole
- Fenofibrate
- Aspirin

Head, Sarah A., et al. “Antifungal drug itraconazole targets VDAC1 to modulate the AMPK/mTOR signaling axis in endothelial cells.” Proceedings of the National Academy of Sciences 112.52 (2015): E7276-E7285.

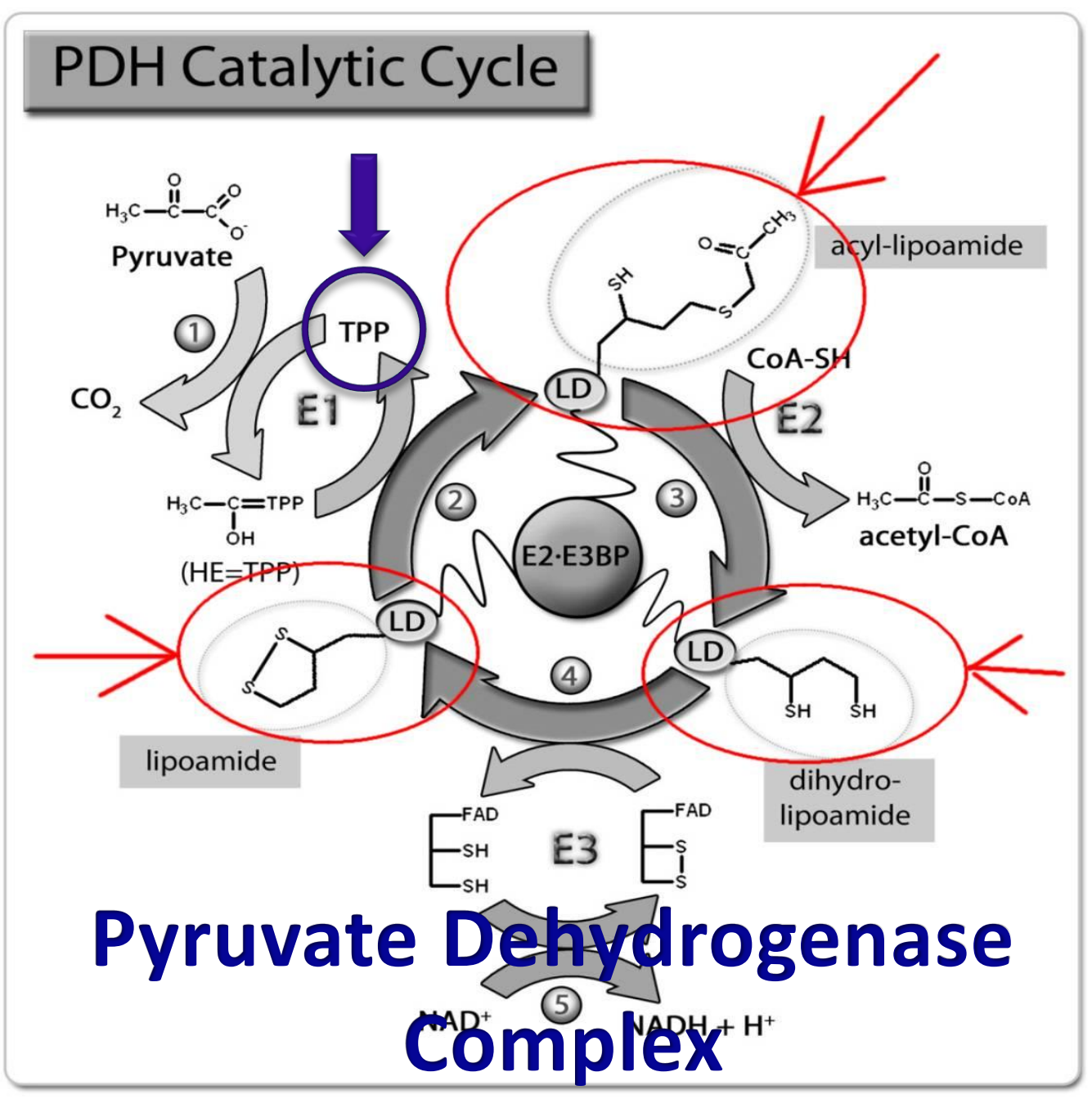
Three Pillars of Cancer Cell Metabolism

Aerobic GLYCOLYSIS

Metabolic Reprogramming in Cancer Cells

- "Inhibition of PDC activity by pyruvate dehydrogenase kinase [PDK]–mediated phosphorylation has been associated with the pathobiology of many disorders of metabolic integration, including cancer. Consequently, the PDC/PDK axis has long been a therapeutic target." (Stacpoole, Peter 2017)
- Reprogram from Mitochondrial Glucose Oxidation to Glycolysis in Cytoplasm.

Stacpoole, Peter W. "Therapeutic targeting of the pyruvate dehydrogenase complex/pyruvate dehydrogenase kinase (PDC/PDK) axis in cancer." JNCI: Journal of the National Cancer Institute 109.11 (2017).



Pyruvate Dehydrogenase Complex

ALA and Thiamine in PDH Cycle

The Pyruvate Dehydrogenase Complex in Cancer. Paul M. Bingham and Zuzana Zachar in Biochemistry, Genetics and Molecular Biology edited by Rosa Angela Canuto, Published: November 14, 2012. (15)

Alpha Lipoic Acid

- BH3 Mimetic , Inhibits BCL2, Restores Apoptosis
- Increases PDC activity,
- Shunts Away from Glycolysis to OXPHOS
- Thiamine and Carnitine co-factors
- Synergy with Melatonin (Glycolysis Inhibitor- reverses Warburg Effect)

Stacpoole, Peter W. “Therapeutic targeting of the pyruvate dehydrogenase complex/pyruvate dehydrogenase kinase (PDC/PDK) axis in cancer.” JNCI: Journal of the National Cancer Institute 109.11 (2017).

Glycolysis Inhibitor
DCA Dichloroacetic Acid

- "The combined use of DCA and Poly-MVA has been one of the truly big advances in integrative cancer therapies in the past 20 years. (Paul Anderson, 2018)"

- Poly-MVA is Alpha Lipoic Acid, Thiamine and Palladium, Liquid Polymer.

1) Stengler, Mark and Anderson Paul. Outside the Box Cancer Therapies: Alternative Therapies that Treat and Prevent Cancer. Hay House, Inc, 2018.

DCA Dichloroacetic Acid

- DCA (dichloroacetate) non-metabolizable pyruvate analog that strongly inhibits PDK function, exactly what we are looking for.
- "PDK1 inhibition leads to pyruvate dehydrogenase [PDH] activation and forces cells to use mitochondria as the main ATP generator. As a result, glycolysis is vastly diminished."
- Thiamine and R-Alpha Lipoic Acid Support Metablic Activities of DCA

Villalba, Martin, et al. "Chemical metabolic inhibitors for the treatment of blood-borne cancers." Anti-Cancer Agents in Medicinal Chemistry 14.2 (2014): 223-232.

Metabolic Reprogramming in Cancer Cells

- "Inhibition of PDC activity by pyruvate dehydrogenase kinase [PDK]–mediated phosphorylation has been associated with the pathobiology of many disorders of metabolic integration, including cancer. Consequently, the PDC/PDK axis has long been a therapeutic target." (Stacpoole, Peter 2017)
- Switches from Mitochondrial Glucose Oxidation to Glycolysis in Cytoplasm.

Stacpoole, Peter W. "Therapeutic targeting of the pyruvate dehydrogenase complex/pyruvate dehydrogenase kinase (PDC/PDK) axis in cancer." JNCI: Journal of the National Cancer Institute 109.11 (2017).

DCA Synergy with OXPHOS and Autophagy Inhibitors

- DCA (Glycolysis Inhibitor) Plus Propranolol (OXPHOS Inhibitor and Autophagy Inhibitor)
- DCA (Glycolysis Inhibitor) Plus Metformin (OXPHOS Inhibitor)
- DCA (Glycolysis Inhibitor) Plus Omaprazole (PPI) Autophagy Inhibitor

Stacpoole

Propranolol Beta Blocker "Most Striking Discovery to Date."

- Reduced tumor proliferation
- Decreased mortality,
- Decreased Metastases,
- Longer survival
- Reduced cancer recurrence.
- Anti-angiogenic effects

- Reduces HK2 protein levels,
- Inhibits OXPHOS.
- Inhibits Autophagy (chloroquine)
- Activates GLYCOLYSIS
- Restores anti-tumor immune function.

Pantziarka, Pan, et al. "Repurposing Drugs in Oncology (ReDO)—Propranolol as an anti-cancer agent." ecancermedicalscience 10 (2016).

Propranolol Beta Blocker "most striking discovery to date."

- Synergy with DCA
- With DCA, Blocks All Three Pathways.
- Synergy with Metformin –leads to Skewed shift to Glucose Metabolsim.

Pantziarka, Pan, et al. "Repurposing Drugs in Oncology (ReDO)—Propranolol as an anti-cancer agent." ecancermedicalscience 10 (2016).

LDN Low Dose Naltrexone

- Opiate Receptor Blocker
- Inhibits Tumor Growth

Stacpoole

Melatonin Glycolysis Inhibitor

- Sleep Hormone from Pineal gland
- Bacteria and Mitochondria Make Melatonin Acetyl-CoA
- Reverses Warburg Effect via PDK inhibition.
- 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 causing 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 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.

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.

DCA Synergy with OXPHOS Inhibitors

- DCA (Glycolysis Inhibitor) Plus Metformin (OXPHOS Inhibitor)

- DCA (Glycolysis Inhibitor) Plus Propranolol (OXPHOS Inhibitor and Autophagy Inhibitor)

- Metformin Oxphos Inhibitor
- Propranolol Oxphos and Autophagy
- Omaprazole (PPI) Autophagy Inhibitor

Stacpoole, Peter W. “Therapeutic targeting of the pyruvate dehydrogenase complex/pyruvate dehydrogenase kinase (PDC/PDK) axis in cancer.” JNCI: Journal of the National Cancer Institute 109.11 (2017).

DCA Immune System Effects

- DCA restores host anti-cancer immunity by decreasing acidic lactate in the micro-environment,
- and by increasing IL-12 and “modulating cytokines toward T-helper 1 (TH1) lymphocyte function.”

- Badr, Mujtaba M., et al. “Dichloroacetate modulates cytokines toward T helper 1 function via induction of the interleukin-12–interferon-gamma pathway.” OncoTargets and therapy 7 (2014): 193.

Three Pillars of Cancer Cell Metabolism

OXPHOS

Metformin – OXPHOS Inhibitor

- Diabetic Drug from French Lilac Plant
- 30–50 per cent reduction in risk for cancer in metformin users.
- Inhibits Complex I of ETC, activates AMP-kinase (AMPK), inhibits the mTOR signaling.
- Shifts cancer cells toward a glycolytic phenotype with increased glucose consumption and lactate production.
- metformin docks in the HKII binding site, blocking its function, separates HKII from VDAC membrane.
- Badr,

Metformin – OXPHOS/Wnt Inhibitor

- "perturbation of mitochondrial function using a number of inhibitors can cause decreased Wnt activity both in vitro and in vivo." (Costa Roberto, 2019)
- All mitochondrial OXPHOS inhibitors are also Anti-CSC agents.

- Costa, Roberto, et al. "Impaired mitochondrial ATP production downregulates Wnt signaling via ER stress induction." Cell reports 28.8 (2019): 1949-1960.
- Zhang, Xiaonan, et al. "Targeting mitochondrial function to treat quiescent tumor cells in solid tumors." International journal of molecular sciences 16.11 (2015): 27313-27326.

Metformin – Detaches HKII from VDAC

- "HK2 inhibition by metformin causes release of this enzyme [HK2] from the outer membrane of mitochondria, thus leading to the activation of apoptotic signals [cell death]." (Salani, Barbara 2013)

- Salani, Barbara, et al. "Metformin impairs glucose consumption and survival in Calu-1 cells by direct inhibition of hexokinase-II." Scientific reports 3 (2013).

Metformin – Synergy with DCA

- "These data suggest that complex I inhibition cooperates with DCA activation of oxidative glucose metabolism to promote catastrophic oxidative stress in glioblastoma cells. (Ward, 2017)

- Ward, N. P., et al. "Complex I inhibition augments dichloroacetate cytotoxicity through enhancing oxidative stress in VM-M3 glioblastoma cells." PloS one 12.6 (2017): e0180061.

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

- Fenofibrate
- Itraconazole
- Mebendazole
- Exemestane
- Doxycycline

Stacpoole,

Itraconazole Antifungal

- Itraconazole binds to VDAC and disrupts HK2 (Hexokinase 2) from mitochondria.
- Inhibits 5-LOX , Wnt and Hedgehog (Hh)
- Inhibits Akt/mTOR, induces“Protective Autophagy”
- Inhibits VEGF

- Head, Sarah A., et al. “itraconazole targets VDAC1 to modulate the AMPK/mTOR signalin.” Proc Nat Acadof Sci 112.52 (2015): E7276-E7285.
- Head, Sarah A., et al. “Simultaneous Targeting of NPC1 and VDAC1 by Itraconazole Leads to Synergistic Inhibition of mTOR Signaling and Angiogenesis.” ACS chemical biology 12.1 (2016): 174-182.

Fenofibrate Lipid Drug

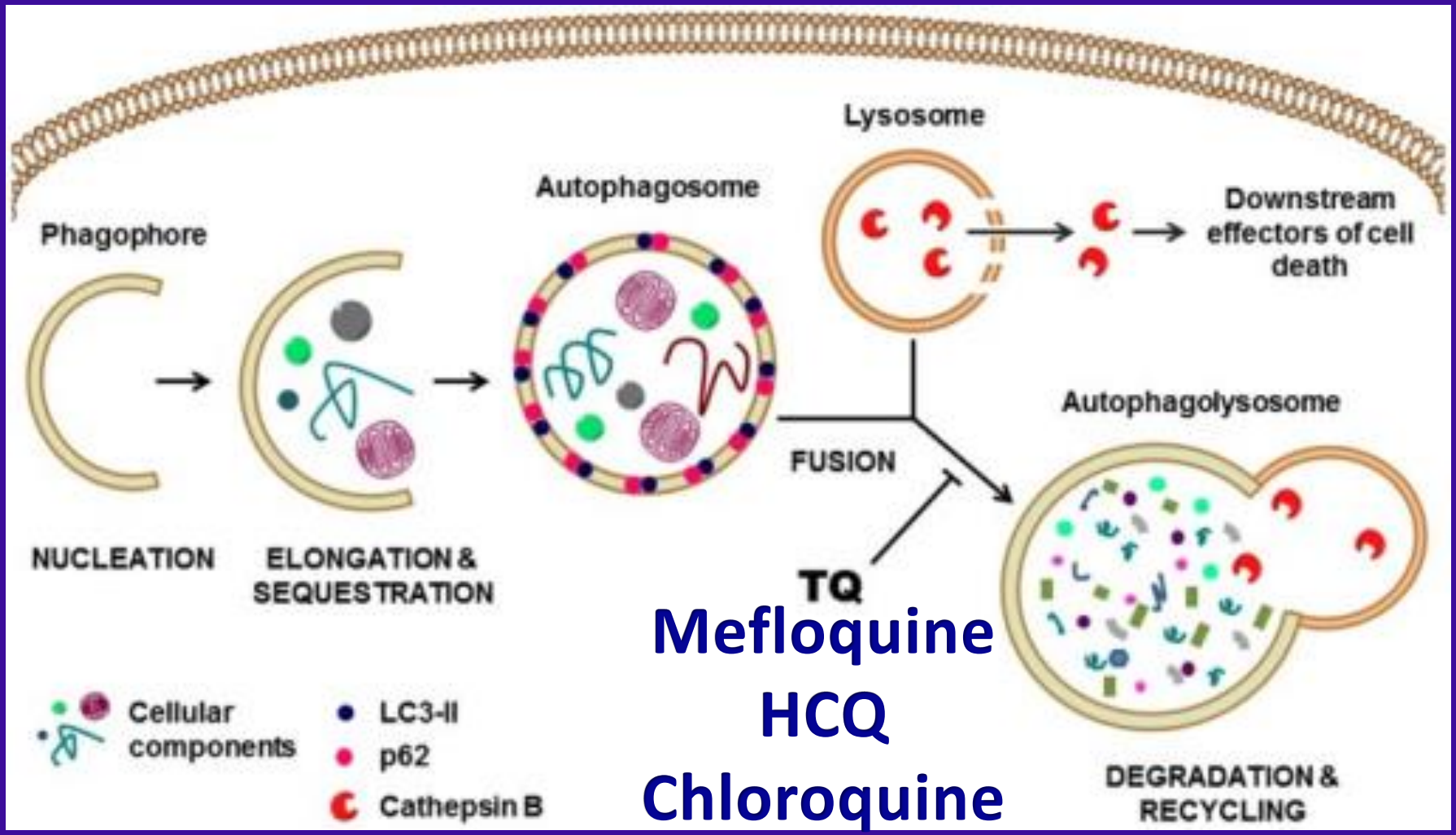
- Activates PPAR-alpha
- Potentiated by vitamin A derivatives.
- Dual GLYCOLYSIS and OXPHOS inhibitor
- Accumulates in mitochondria, inhibits Complex One of the ETC.
- Interrupts the Warburg Effect
- Disrupts HK-2 from the VDAC,
- Destroys BCL-2, and restores apoptosis.
- Blocks FASN (Fatty Acid Synthetase),

- WP

Three Pillars of Cancer Cell Metabolism

Autophagy

Autophagy



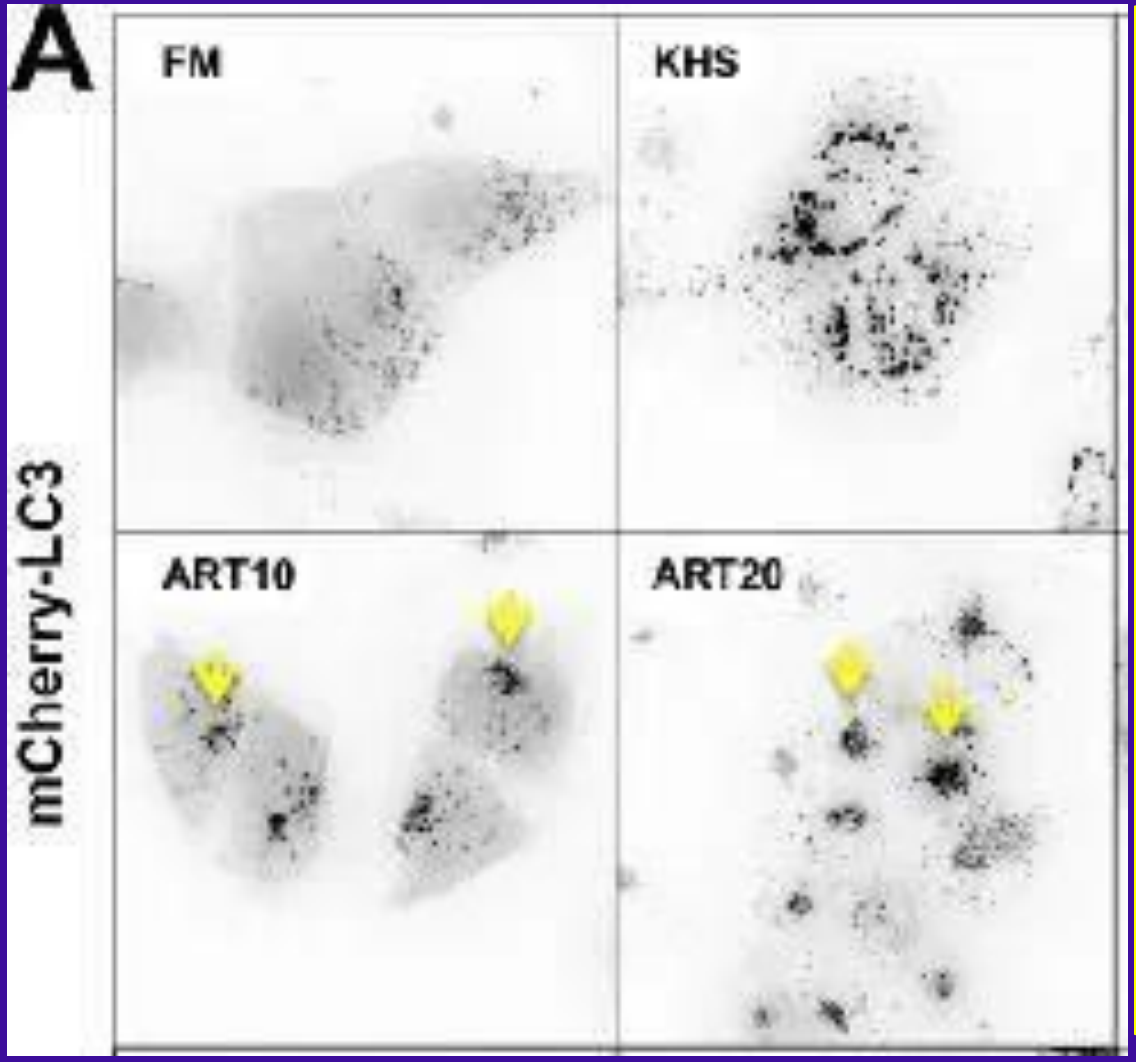
- Racoma, Ira O., et al. "Thymoquinone inhibits autophagy and induces cathepsin-mediated, caspase-independent cell death in glioblastoma cells." PLoS One 8.9 (2013): e72882.

Protective Autophagy

- Pro-survival mechanism in cancer cells under therapeutic stress.
- Induction of autophagy associated with resistance to chemotherapy.
- Activation AMPK/mTOR Inhibition induces protective autophagy.
- Perinuclear Clustering of Lysosomes (dormant)
- Antegrade Lysosome Trafficking (aggressive)

- Deng, Shuo, et al. "Targeting autophagy using natural compounds for cancer prevention and therapy." Cancer 125.8 (2019): 1228-1246.
- Kocaturk, Nur Mehpare, et al. "Autophagy as a molecular target for cancer treatment." European Journal of Pharmaceutical Sciences 134 (2019): 116-137.

Peri-Nuclear Clustering

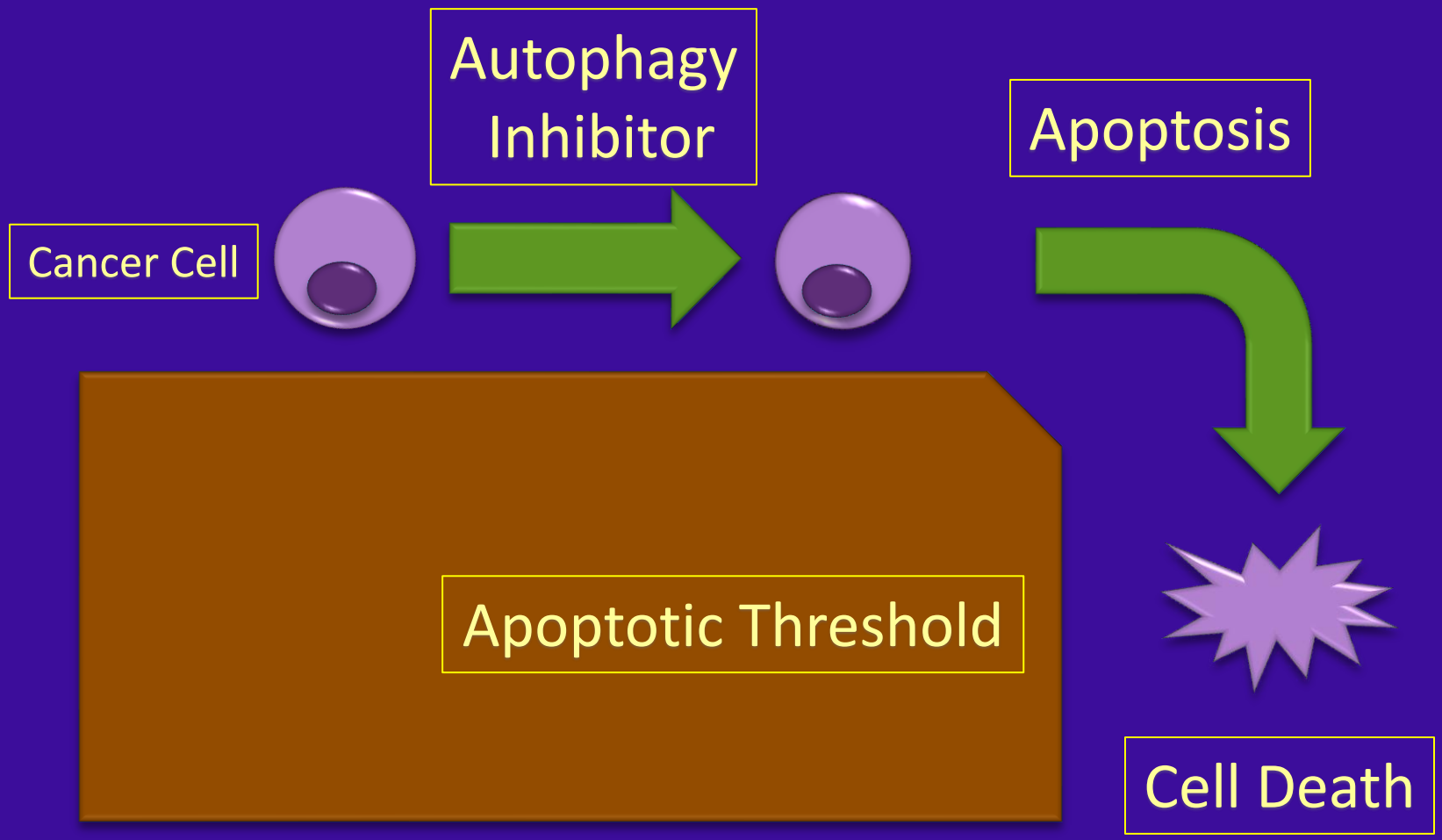


Top Row: Untreated Breast Cancer Cells showing lysosomes (dark stained particles) dispersed throughout cells.

Bottom Row, Breast cancer cells treated with Artemisinin. Yellow arrows point to peri-nuclear clustering of lysosomes.

Hamacher-Brady, Anne, et al."Artesunate Activates Mitochondrial Apoptosis in Breast Cancer Cells via Iron-catalyzed Lysosomal Reactive Oxygen Species Production." J. Biol. Chem 2011.286 (2010): 6587-6601.

Autophagy Inhibitors Push Cell Over Apoptotic Threshold



- Tompkins, K,"Focus: Death: Regulation of apoptosis by autophagy to enhance cancer therapy." Yale journal of biology and medicine 92.4 (2019): 707.

Providing the Extra "Apoptotic Push"

- "Autophagy inhibition works with many different kinds of anti-cancer agents – it doesn't matter what the other drug is so long as it is capable of providing an extra pro-apoptotic push in that cancer cell." (Tompkins,2019)

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.

Autophagy Inhibitors

- Mefloquine, Chloroquine, Hydroxy CHQ
- Azithromycin/Clarithromycin (Doxy ?)
- Propranolol
- PPI's
- Loratidine (Claritin)
- Thymoquinone (Black Seed Oil)

Stacpoole, Peter W

Fourth Pillars

Restoring
Host
Immune System

Restoring Immune Surveillance

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

PIBF Progesterone Induced Blocking Factor

- Produced by 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
- Mebendazole - microtubule-disrupting drug disturbed production of PIBF
- 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
- Use Mebendazole instead?

Cimetidine - Tagamet

- Tagamet FDA-Approved 1979 H2 Histamine Receptor blocker, antacid.
- Enhances cell-mediated immunity.
- Reverses Histamine-mediated Immunosuppression
- Cancers, Viral warts, Allergic Disorders, Burns
- induces IL-18 in monocytes- immunostimulatory cytokine with anti-tumor activity, promotes expansion of NK Cells.

AHCC Beta Glucans

- plant polysaccharides (sugars) found in edible mushrooms, baker's yeast, and cereals
- pathogen associated molecular patterns (PAMPs).
- Replacement for Coley's toxins ?
- Enhance tumor immune surveillance
- Eradication of HPV, antiviral effects

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 Upregulates Anticancer Immunity

- Antiparasitic
- Microtubule inhibitor, prevents spindle formation needed for cell replication.
- Immunomodulatory Effects – upregulates anti-cancer host immune function.
- Induces Apoptosis by inactivating BCL-2
- Induces “protective autophagy”, Synergy with Autophagy Inhibitors
- Inhibits Hedgehog CSC pathway

Fifth Pillar

Inflammation

Inhibit
NF-kB, IL-6
cytokines

Down Regulate Inflammation

- CBD Oil/Paste
- 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).

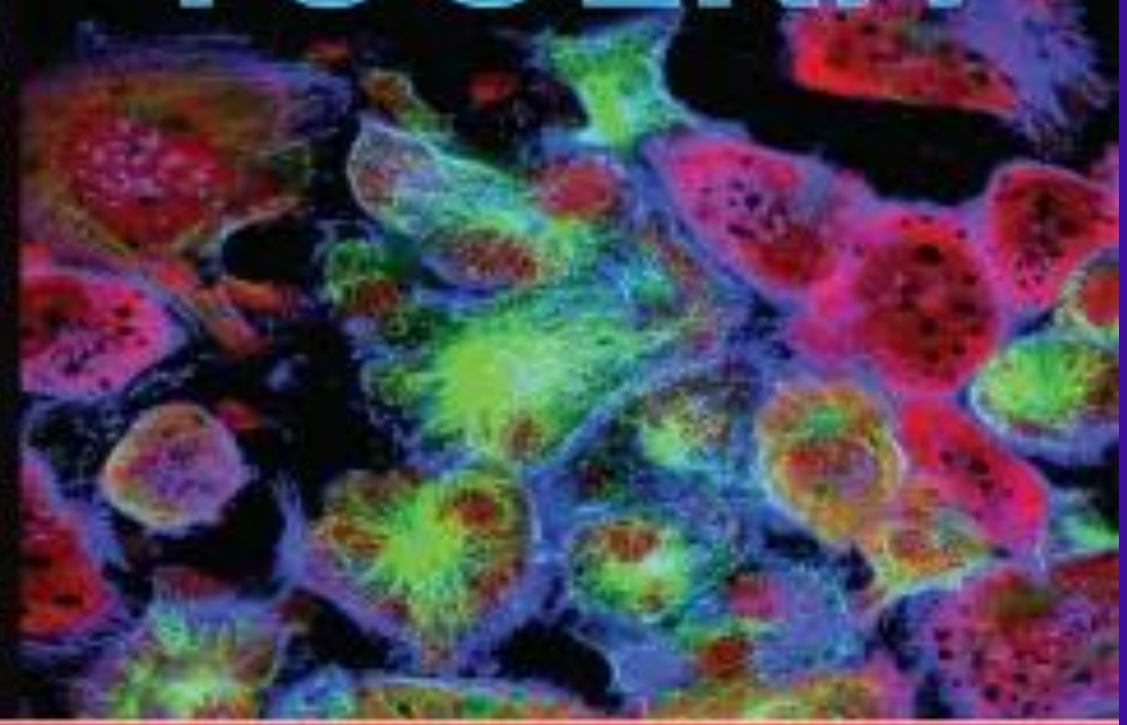
Stacpoole,

SUMMARY SLIDE

- 1) DCA Synergy with OXPHOS inhibitors (Metformin)
- 2) Eradicate Cancer Stem Cells (Melatonin)
- 3) Autophagy Inhibitor Induces Apoptosis
- 4) Detach HKII from VDAC (Itraconazole, Fenofibrate)
- 5) Three Pillars of Metabolism
- 6) Fourth Pillar - the Immune System

USING REPURPOSED DRUGS FOR CANCER TREATMENT

CRACKING CANCER TOOLKIT



JEFFREY DACH MD

CRACKING CANCER TOOLKIT JEFFREY DACH MD

Thank You – Any Questions?

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