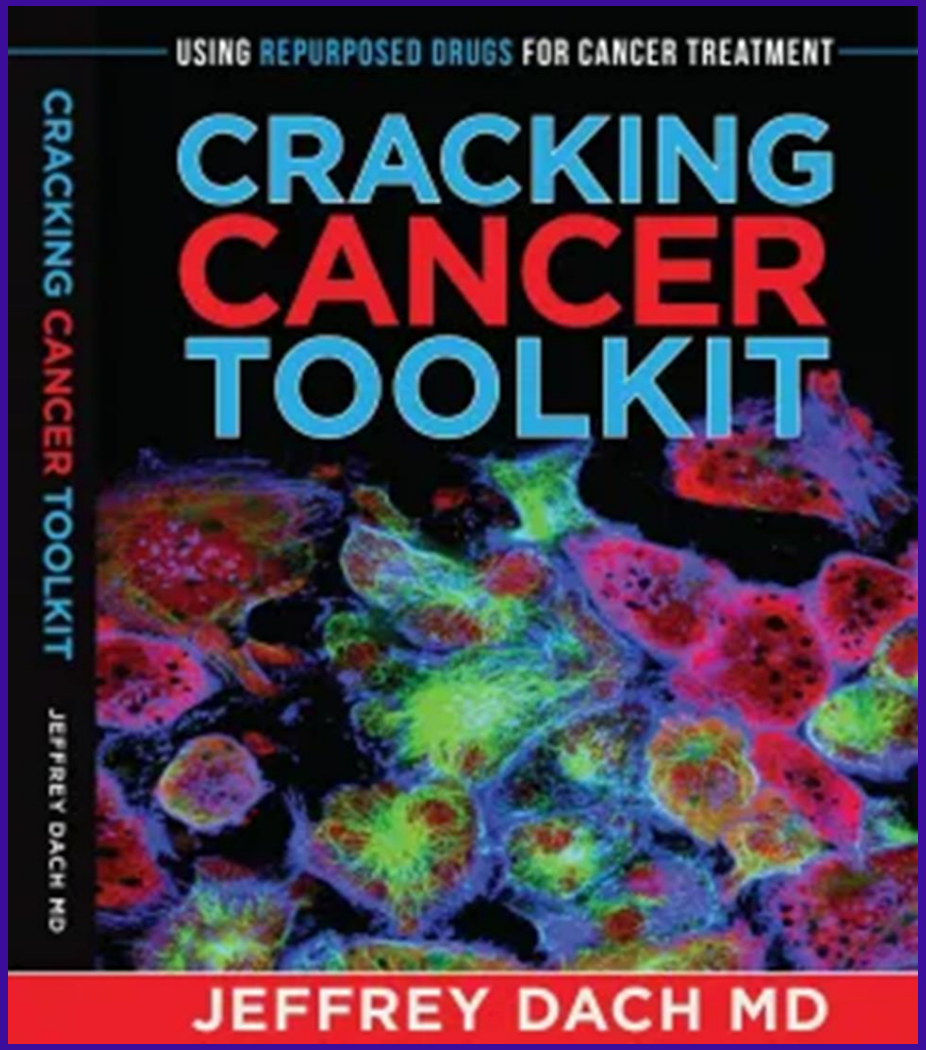
Cracking Cancer Toolkit: Using Repurposed Drugs for Cancer Treatment



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The Chemotherapy Paradigm

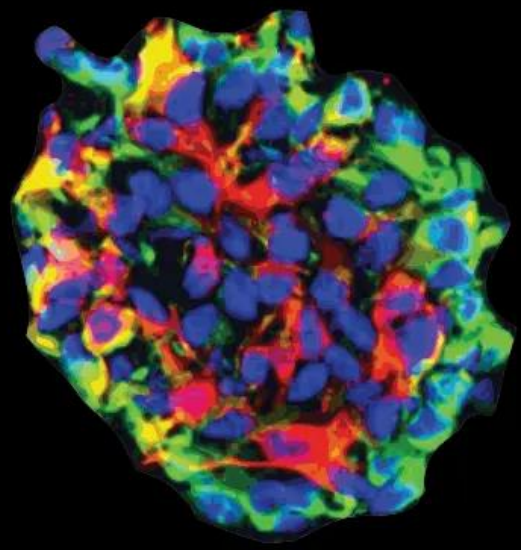
- **Old Paradigm: Chemotherapy**
- **New Paradigm: Cancer as a Metabolic Disease.**
- **Chemotherapy Can Not Eradicate Cancer Stem Cells. We Need New Therapies that can.**

- Chemo Causes Massive Inflammation, via Activation of NF-kB, and COX-2.
- Worsens Cancer Induced Immunosuppression

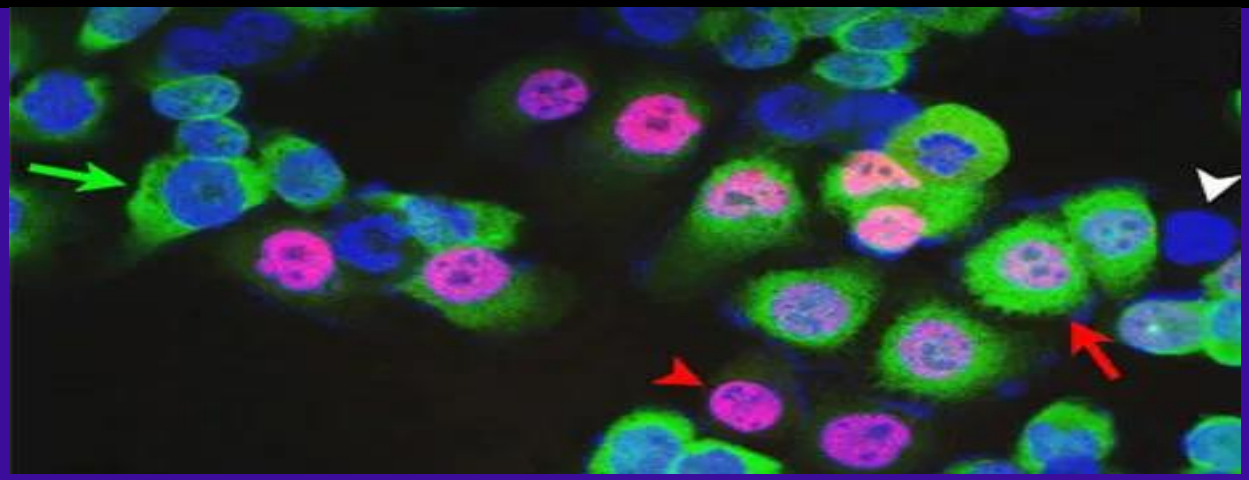
Pecqueur, Claire, et al. “Targeting metabolism to induce cell death in cancer cells and cancer stem cells.” International journal of cell biology 2013 (2013).

Cancer Stem Cells

Cancer Stem Cell Conference



September 20-23, 2016 | Hilton Cleveland Downtown



Cancer Stem Cell Meetings

- Oncologists attend national CSC meetings, yet remain oblivious upon returning to the hospital, continuing old chemotherapy protocols as if nothing has changed.

Cancer Stem Cells - Quote

- “CSCs are responsible for **clinical failure** of currently available oncological therapies because they survive treatment with hormones, radiation, chemotherapy, and molecularly targeted drugs. **How to eliminate CSCs has become a research focus in recent years.**” (Jiang,2020)

Jiang, Lin-Li, and Lei Liu. "Effect of metformin on stem cells: Molecular mechanism and clinical prospect." World Journal of Stem Cells 12.12 (2020): 1455.

"The Successful Elimination of Cancer

requires anti-cancer therapy affecting 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).

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.

New Technologies Driving the New Paradigm

- Automated High Thru-Put Drug Screening
- PET Scan Imaging with 18 FDG isotope
- Internet Message Groups. (Social Media)

Flobak, Åsmund, et al. "A high-throughput drug combination screen of targeted small molecule inhibitors in cancer cell lines." Scientific data 6.1 (2019): 1-10.
Gupta, Piyush B., et al. "Identification of selective inhibitors of cancer stem cells by high-throughput screening." Cell 138.4 (2009): 645-659.
Harvey, Alan L., and Ian A. Cree. "High-throughput screening of natural products for cancer therapy." Planta medica 76.11 (2010): 1080-1086.

Cancer as Metabolic Disease

- Warburg Effect (Shift from OXPHOS to Glycolysis) High Lactate Generation.
- High Glucose Uptake Seen on PET Scan.
- 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
- Metabolic Plasticity- Switching Pathways

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
Surveillance

Fifth Pillar

Upregulation Inflammatory Pathways NF-kB, IL-6 cytokines

The Cancer Stem Cell

- Exists in Dormant State
- Negative on PET Scan
- Cancer Relapse after Chemotherapy
- Exists in Energetic State – CTC Circulating Tumor Cells

Cancer Stem Cell Pathways

- Wnt/Beta Catenin
- Hedgehog
- Notch

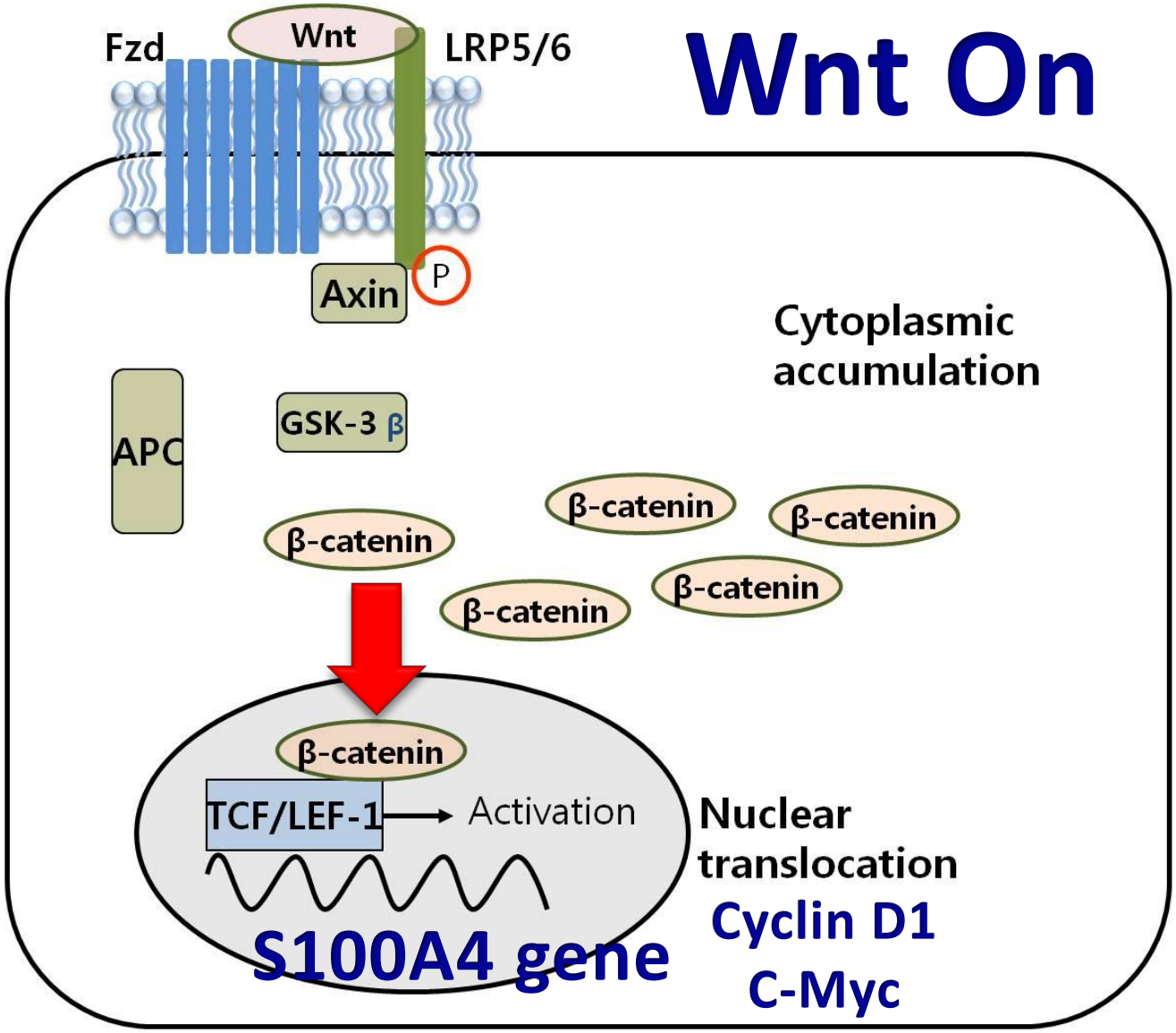
Targeting these pathways eliminates cancer stem cells

Cancer Stem Cell Pathway 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

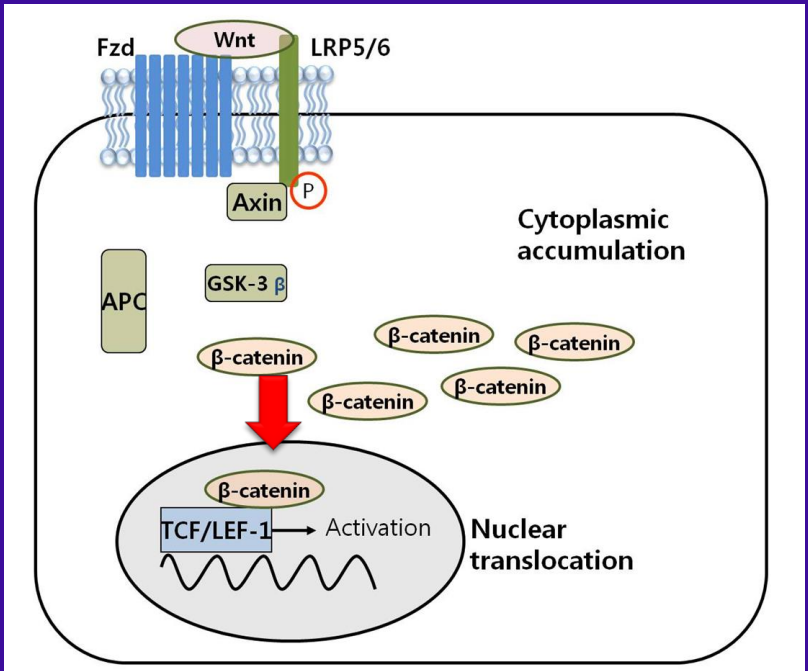
Wnt Cancer Stem Cell Pathway



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

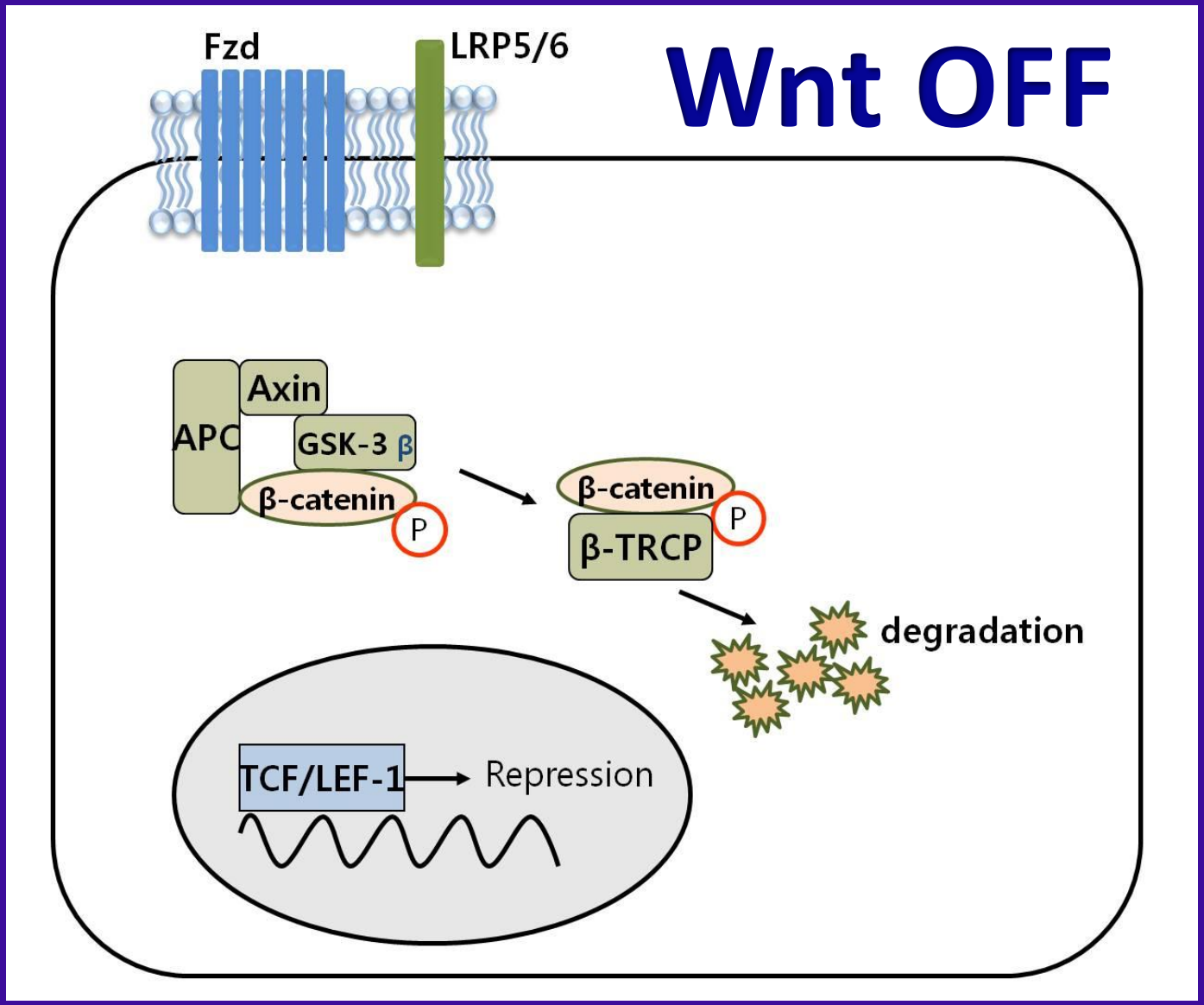
Wnt On



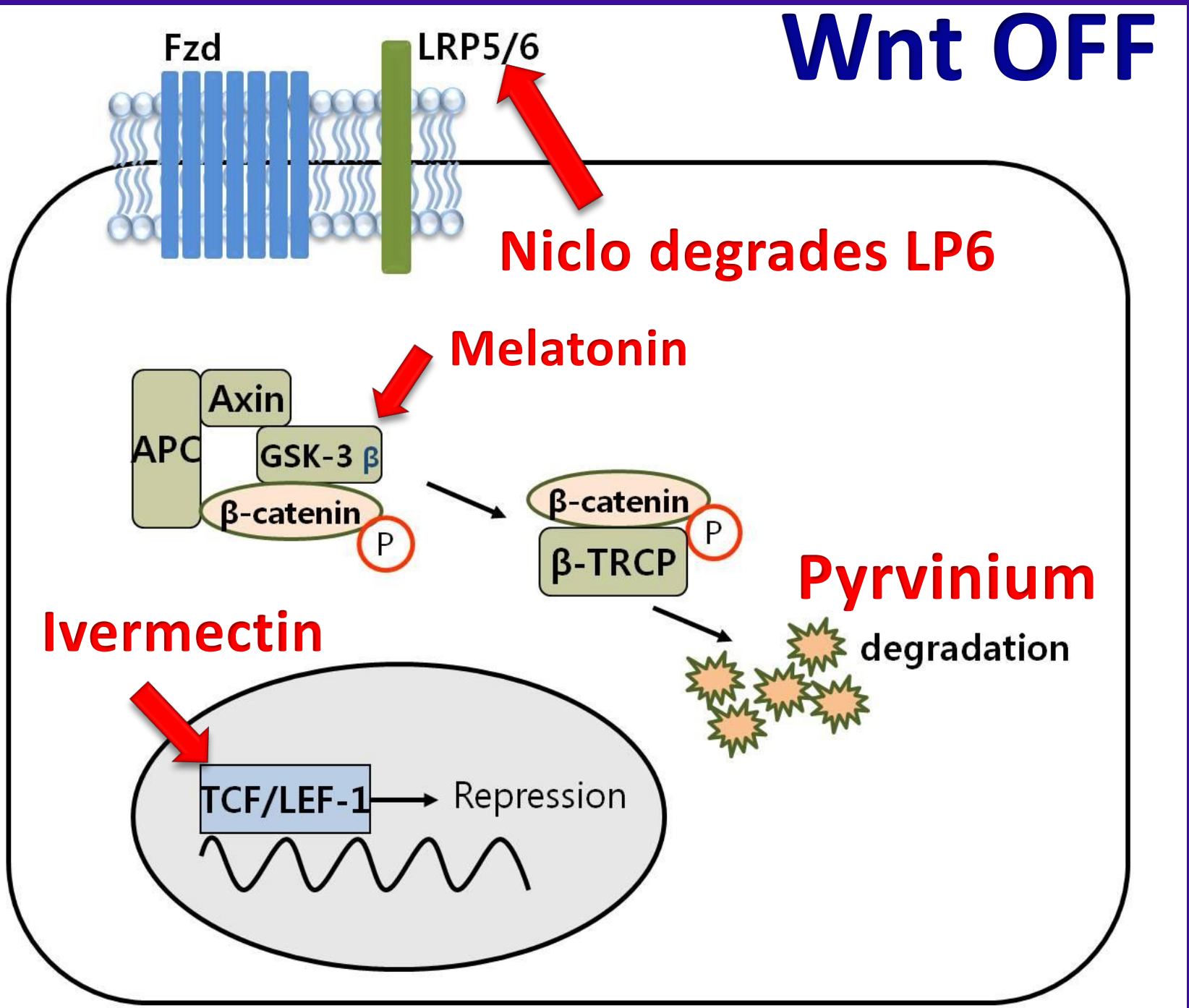
Wnt ON: βeta-catenin is NOT degraded, and instead the accumulated β-catenin enters the nucleus and activates the target gene TCF/LEF, and c-Myc and Cyclin D1.

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

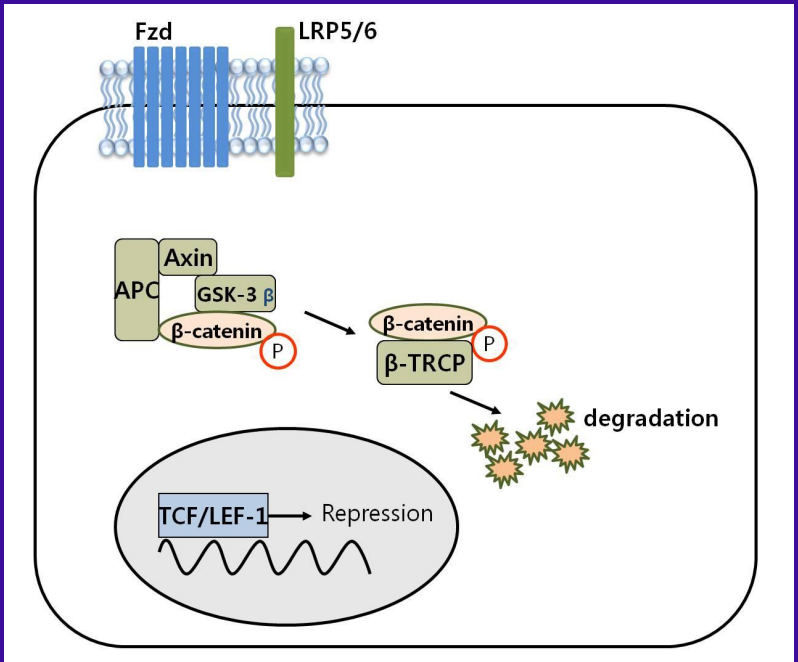


Han, Jae-Ik, and Ki-Jeong Na. "Wnt/β-Catenin signaling pathway in canine skin melanoma and a possibility as a cancer model for human skin melanoma." Melanoma in the Clinic-Diagnosis, Management and Complications of Malignancy. IntechOpen, 2011.


Wnt 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

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

- Metformin (Anti-Diabetic Drug, OXPHOS inhibitor)
- Ivermectin (Specific WNT-TCF Blocker at low micromolar concentrations.)
- Niclosamide (Hookworm, OXPHOS Uncoupler)
- Pyrvinium (hookworm,pinworm)
- Mefloquine/Chloroquine (Antimalarial, Autophagy Inhibitors)
- 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.

Metformin Oxphos Inhibitor

- First Line Diabetic Drug (French Lilac plant)
- Targets Cancer Stem Cells.
- Docks in the HK II binding site, blocks function, separates HK II from VDAC on the outer mitochondrial membrane.
- Accumulates in Mito, Inhibits Complex I ETC.
- 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).
Rattan, Ramandeep et al. "Metformin: an emerging new therapeutic option for targeting cancer stem cells." Journal of oncology 2012 (2012).

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)

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

Niclosamide

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

Pan, Jing-Xuan, Ke Ding, and Cheng-Yan Wang. “Niclosamide, an old antihelminthic agent, demonstrates antitumor activity by blocking multiple signaling pathways of cancer stem cells.” Chinese journal of cancer 31.4 (2012): 178.

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.

Pyrvinium Oxphos Inhibitor

- Pyrvinium degrades 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.

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 Cancer Stem Cells Wnt Pathway Inhibitors

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

- Resveratrol/ Pterostilbene
- Silibin (Milk Thistle)
- (Garlic) Diallyl trisulfide Allicin
- 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.

Repurposed Drugs Considerations

- Are we able to reach therapeutic blood levels using standard dosages?
- The Drug is Effective in animal models, but is the Drug Effective in Humans?
- Is the drug active against CSCs?
- Drug Toxicity: What are adverse effects? Is the drug too toxic for human use?
- Drug Interactions: CYP450 enzyme system?

More References

(1) Liskova, Alena, et al. “Dietary Phytochemicals Targeting Cancer Stem Cells.” Molecules 24.5 (2019):899.

(2) Das, Plabon K., et al. “Natural Compounds Targeting Cancer Stem Cells: A Promising Resource for Chemotherapy.” Anti-Cancer Agents in Medicinal Chemistry (2019).

(3) Chan, Marion et al “Targeting cancer stem cells with dietary phytochemical-Repositioned drug combinations.” Cancer Letters 433 (2018): 53-64.

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

(5) Ortiz, Luis Miguel Guamán, et al. “Berberine, an epiphany against cancer.” Molecules 19.8 (2014):12349-12367.

(6) Mokhtari, Reza Bayat, et al. “The role of Sulforaphane in cancer chemoprevention and health benefits: a mini-review.” J of Cell Comm and Signaling 12.1 (2018): 91-101.

(7) Papandreou, Ioanna, et al. “Plant stilbenes induce endoplasmic reticulum stress and anti-cancer activity enhanced by inhibitors of autophagy.” Exp Cell Res 339.1 (2015): 147-153.

(8) Steele, A. J., et al. “Parthenolide (feverfew) induces selective apoptosis of B-chronic lymphocytic leukemia cells in vitro.” Leukemia 20.6 (2006): 1073-1079.

(9) Eo, Hyun Ji, Gwang Hun Park, and Jin Boo Jeong.“Inhibition of Wnt signaling by silymarin in human colorectal cancer cells.” Biomolecules & Therapeutics

(10) Haghi, Atousa, et al. “A comprehensive review on curcumin, quercetin, and allicin, in the treatment of gastric cancer.” Journal of Gastrointestinal Cancer 48.4 (2017): 314-320.

Hallmarks of Cancer Cells Hanahan and Weinberg

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

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**." (Thomas Seyfried 2013).

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

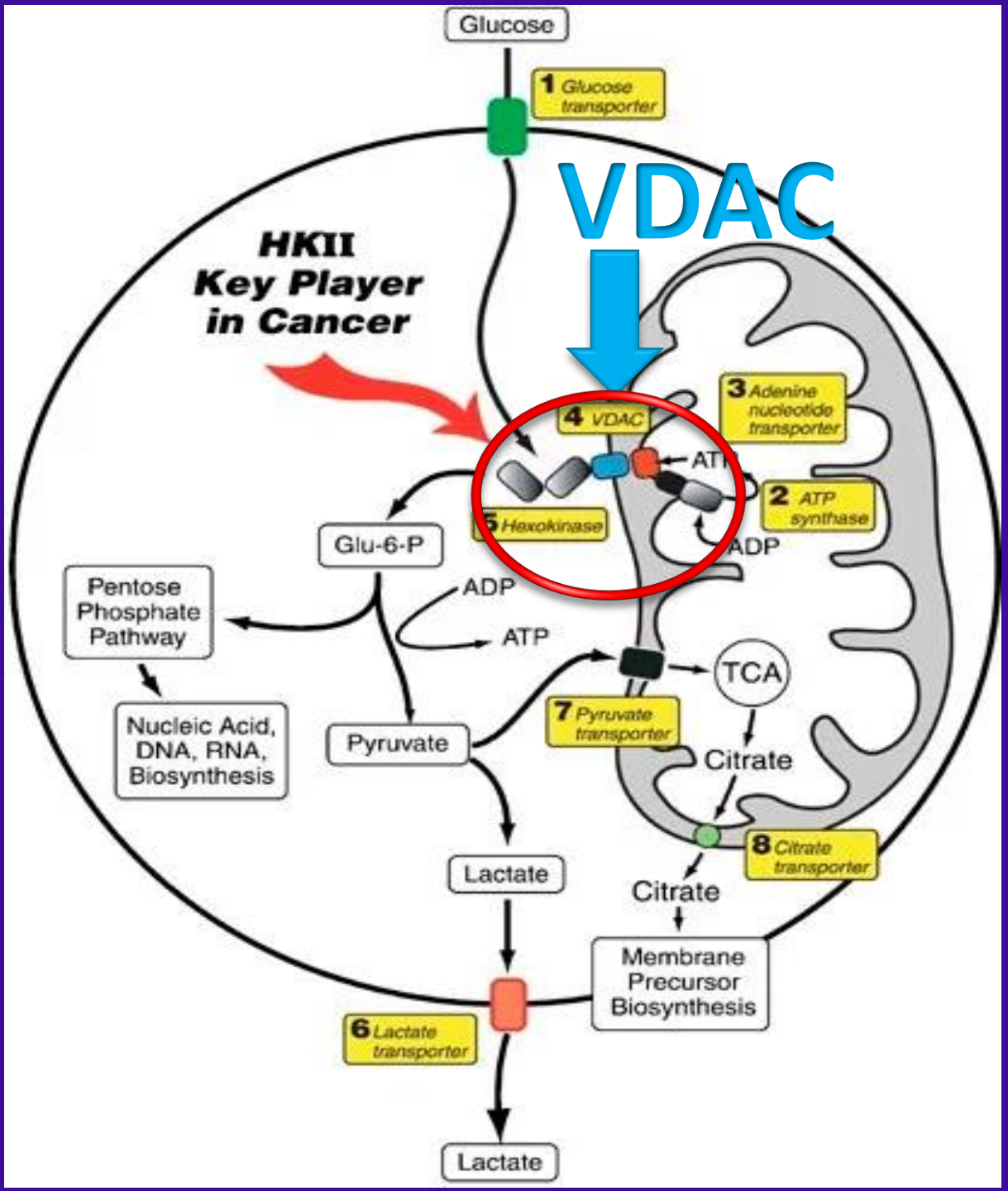
Reprogramming Energy Metabolism

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

Phan, Liem Minh, "Cancer metabolic reprogramming: importance, main features, and potentials for precise targeted anti-cancer therapies." Cancer biology & med 11.1 (2014): 1. Ward, Patrick S., and Craig B. Thompson. "Metabolic reprogramming: a cancer hallmark even warburg did not anticipate." Cancer cell 21.3 (2012): 297-308.

Reprogramming Energy Metabolism

Hexokinase-II Translocated to the VDAC

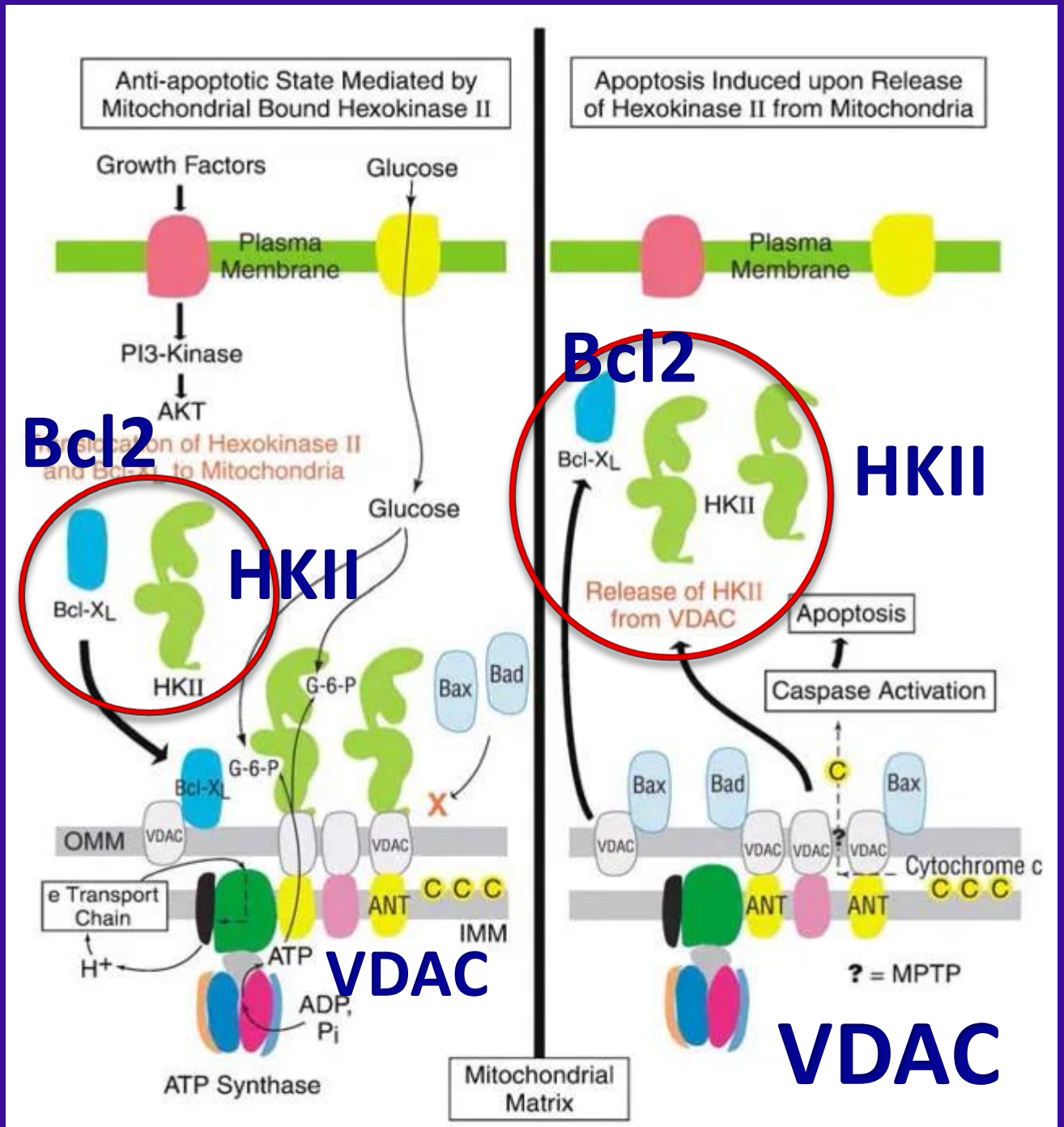


HKII-VDAC

- 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



- Release of HKII from VDAC induces Apoptosis
- BCL2 goes with it.

- Fig 3 Mathupala, Ko, and P. L. Pedersen. “Hexokinase II: cancer’s double-edged sword when bound to mitochondria.” Oncogene 25.34 (2006): 4777

Repurposed Drugs
Detach HKII from VDAC

- Itraconazole
- Fenofibrate
- Aspirin
- Metformin

Head, Sarah A., et al. “Antifungal drug itraconazole targets VDAC1 to modulate the AMPK/mTOR signaling axis in endothelial cells.” Proceedings of the National
Jan, Chia-Ing, et al. “Fenofibrate suppresses oral tumorigenesis via reprogramming metabolic processes: drug repurposing for cancer.” Int J Bio Sci 12.7 (2016): 786.
Academy of Sciences 112.52 (2015): E7276-E7285.
Tewari, Debanjan, et al. “Aspirin induces cell death by directly modulating mitochondrial voltage-dependent anion channel (VDAC).” Scientific reports 7.1 (2017): 1-9.

Itraconazole (Sporonox) Antifungal

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

- Tsubamoto, Hiroshi, et al. "Repurposing itraconazole as an anticancer agent." Oncology letters 14.2 (2017): 1240-1246.
- 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

- 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),
- Activates PPAR-alpha
- Potentiated by vitamin A derivatives.
- Dual GLYCOLYSIS and OXPHOS inhibitor

Lian, Xin, et al. "Anticancer properties of fenofibrate: a repurposing use." Journal of Cancer 9.9 (2018): 1527.

Aspirin - Glycolysis Inhibitor

- Targets VDAC, Detaches HK2 from the VDAC.
- Glycolysis Inhibitor, Reduces Glycolytic CSC.
- Aspirin/Metformin Combination Striking synergy.
- Combined with EGFR-TKIs shows considerable synergy, overcomes TKI drug resistance.
- Combined with chemotherapy reduces inflammation, NF-kB, reducing numbers of cancer stem cells.
- Inhibit platelets and modifies the genetic expression of the cancer cell.

Yue, Wen, et al. “Metformin combined with aspirin significantly inhibit pancreatic cancer in vitro and in vivo by suppressing anti-apoptotic proteins Bcl-2.” Oncotarget 6.25 (2015
Abdelmonsif, Doaa Ali, et al. “Targeting AMPK, mTOR and β-catenin by combined metformin and aspirin therapy in HCC.” Molecular diag & ther 22.1 (2018): 115-127.

Natural Substances Bind to and Detaches HKII from VDAC

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

Goldin, N., et al. “Methyl jasmonate binds to and detaches mitochondria-bound hexokinase.” Oncogene 27.34 (2008): 4636-4643

Wei, L., et al. “Oroxylin A induces dissociation of hexokinase II from the mitochondria and inhibits in breast carcinoma.” Cell death & disease 4.4 (2013): e601.

Tewari, Debanjan, et al. “Modulation of the mitochondrial voltage dependent anion channel (VDAC) by curcumin.” Biochimica et Biophysica Acta (BBA)- Biomembranes 1848.1 (2015): 151-158.

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.

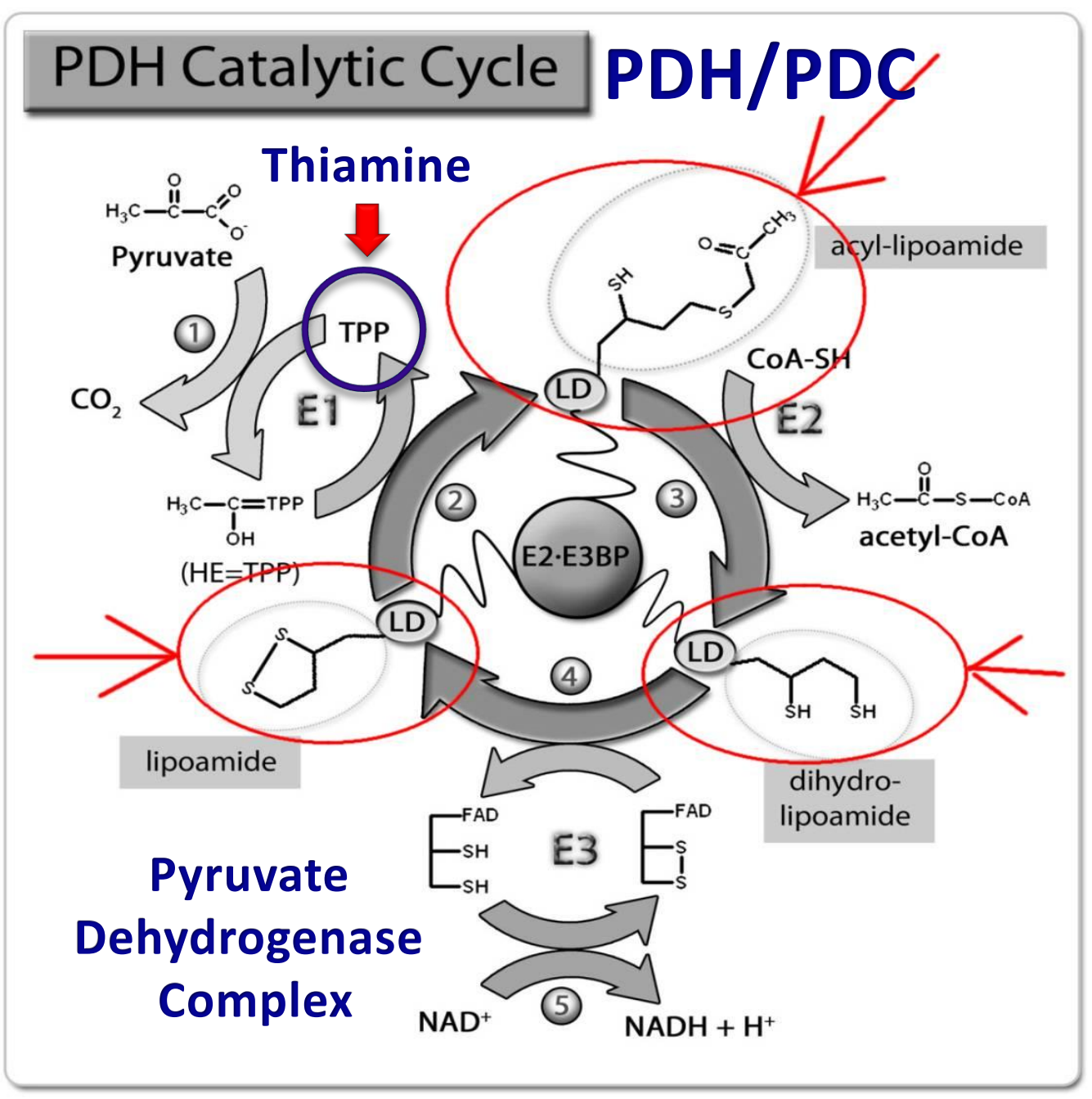
Three Pillars of Cancer Cell Metabolism

GLYCOLYSIS
Warburg Effect

Metabolic Reprogramming in Cancer Cells

- "**Inhibition of PDC activity by pyruvate dehydrogenase kinase [PDK]–mediated phosphorylation** has been associated with the pathobiology of …**cancer**. Consequently, the **PDC/PDK axis** has long been a therapeutic target." (Stacpoole, Peter 2017)
- Inhibition of PDC Reprograms from Mitochondrial OXPHOS 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).



PDH Cycle

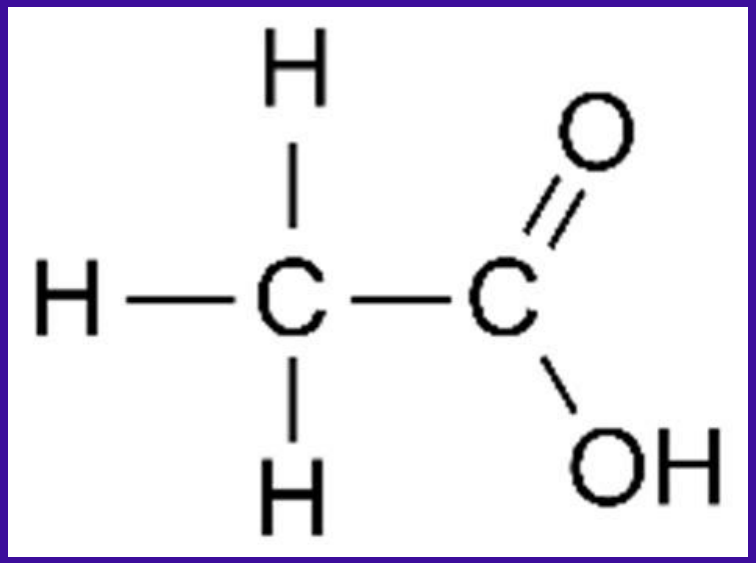
PDC- The Pyruvate Dehydrogenase Complex in Cancer. Paul M. Bingham and Zuzana Zachar in Biochemistry, Genetics and Molecular Biology edited by Rosa Angela Canuto, Published: November 14, 2012. (15)

DCA Dichloroacetic Acid

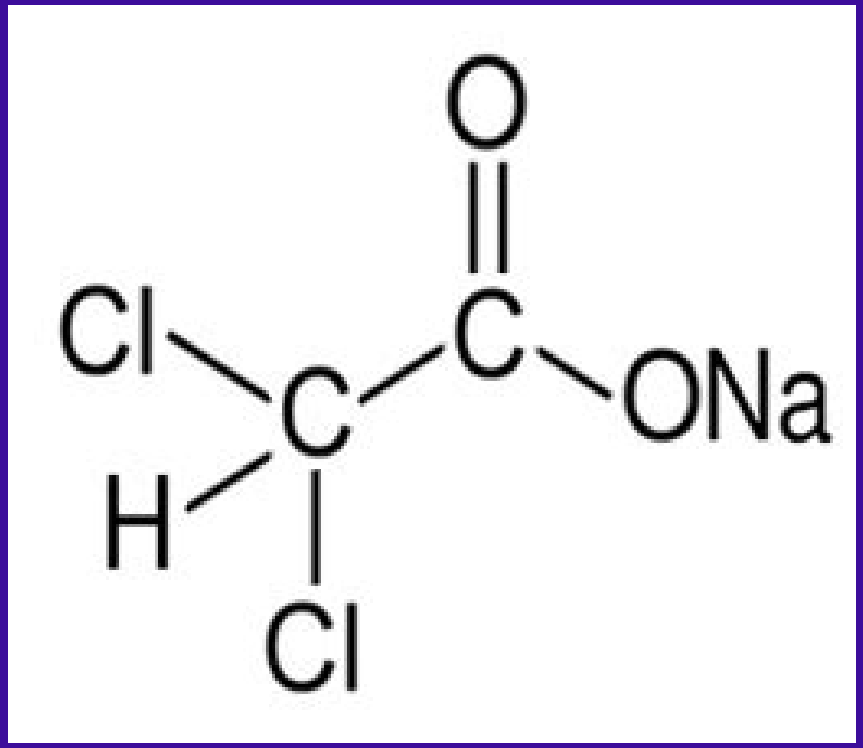
- DCA (Dichloroacetate) - Pyruvate Analog, Not Metabolized.
- Strongly Inhibits PDK Function, and Activates PDH (Pyruvate Dehydrogenase), which Activates Mitochondrial OXPHOS, and Inhibits Glycolysis in Cytoplasm (Warburg Effect)
- Thiamine and R-Alpha Lipoic Acid (Poly MVA) - Co-factors needed to prevent DCA INDUCED Neuropathy.

Tataranni, Tiziana, and Claudia Piccoli. "Dichloroacetate (DCA) and cancer: an overview towards clinical applications." Oxidative medicine and cellular longevity 2019 (2019).

DCA Dichloroacetic Acid



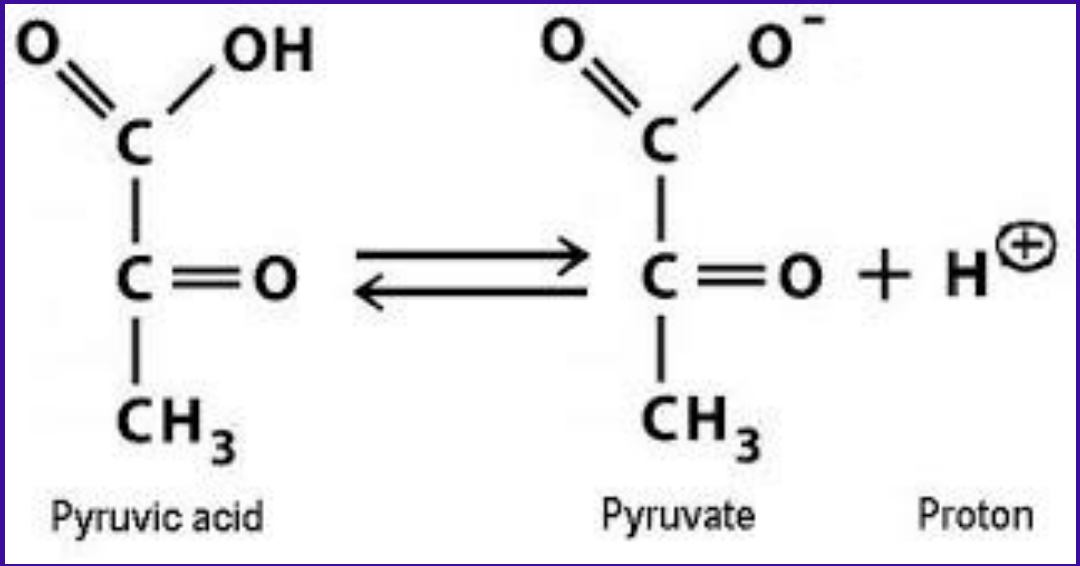
Acetic Acid

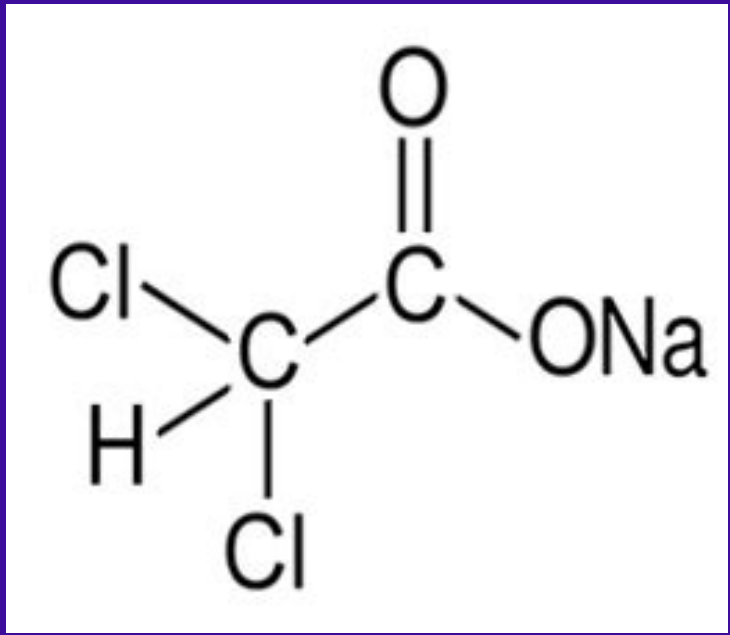


DCA

Tataranni, Tiziana, and Claudia Piccoli. "Dichloroacetate (DCA) and cancer: an overview towards clinical applications." Oxidative medicine and cellular longevity 2019 (2019).

DCA Dichloroacetic Acid





Pyruvate

DCA

Tataranni, Tiziana, and Claudia Piccoli. "Dichloroacetate (DCA) and cancer: an overview towards clinical applications." Oxidative medicine and cellular longevity 2019 (2019).

"Truly Big Advance"
DCA - Glycolysis Inhibitor

- "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.

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

DCA (GLYCOLYSIS Inhibitor) Synergy with OXPHOS and Autophagy Inhibitors

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

Villalba, Martin, et al. “Chemical metabolic inhibitors for the treatment of blood-borne cancers.” Anti-Cancer Agents in Medicinal Chemistry 4.2 (2014): 223-232.

Propranolol Beta Blocker
"Most Striking Discovery to Date."

- Inhibits OXPHOS (ATP synthase).
- Activates GLYCOLYSIS
- Reduces HK2 protein levels.
- Inhibits Autophagy (chloroquine-like)

- Reduces Tumor Proliferation.
- Anti-Angiogenic effects.
- Restores Anti-tumor Immune Function.
- Decreases mortality, metastases, recurrence.

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
- Blocks All Three Metabolic Pathways.

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

DCA Immune System Effects

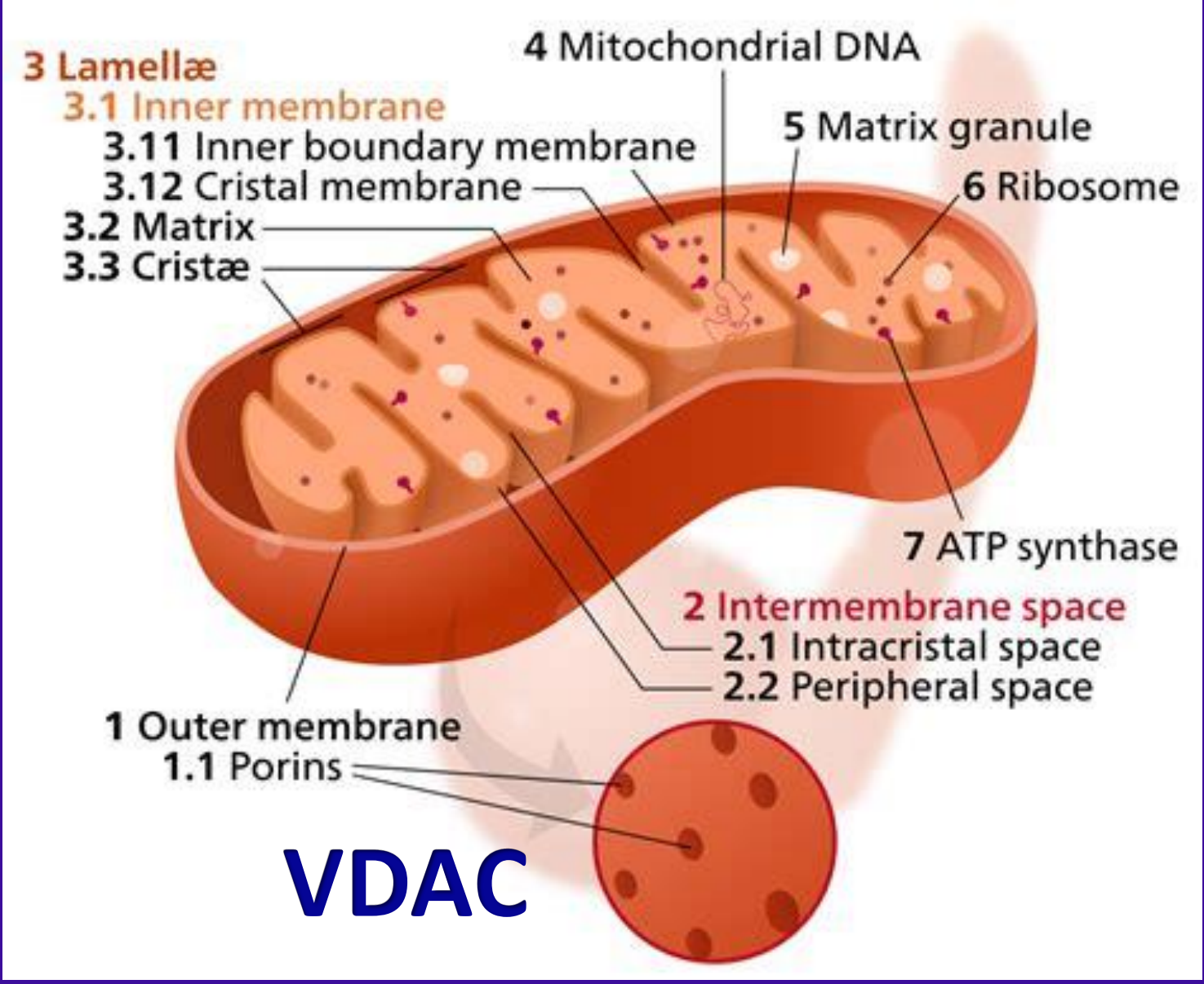
- DCA restores host anti-cancer immunity by decreasing acidic lactate in the micro-environment,
- By Increasing IL-12 and “modulating cytokines toward T-helper 1 (TH1) lymphocyte function.”

- 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

OXPHOS -The Mitochondrion



Metformin – OXPHOS Inhibitor

- Diabetic Drug from French Lilac Plant
- Metfromin Users - 30–50 % Reduction **in cancer.**
- **Metformin Inhibits Complex I of ETC.**
- Activates AMP-kinase (AMPK)
- Inhibits mTOR signaling.
- OXPHOS Inhibitor- Shifts to Glycolytic Phenotype
- Synergy with Glycolysis Inhibitors (DCA)
- Metformin docks in the HKII binding site, blocking its function, separates HKII from VDAC membrane.

Yu, Hong, et al. "The potential effect of metformin on cancer: an umbrella review." Frontiers in endocrinology 10 (2019): 617.

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

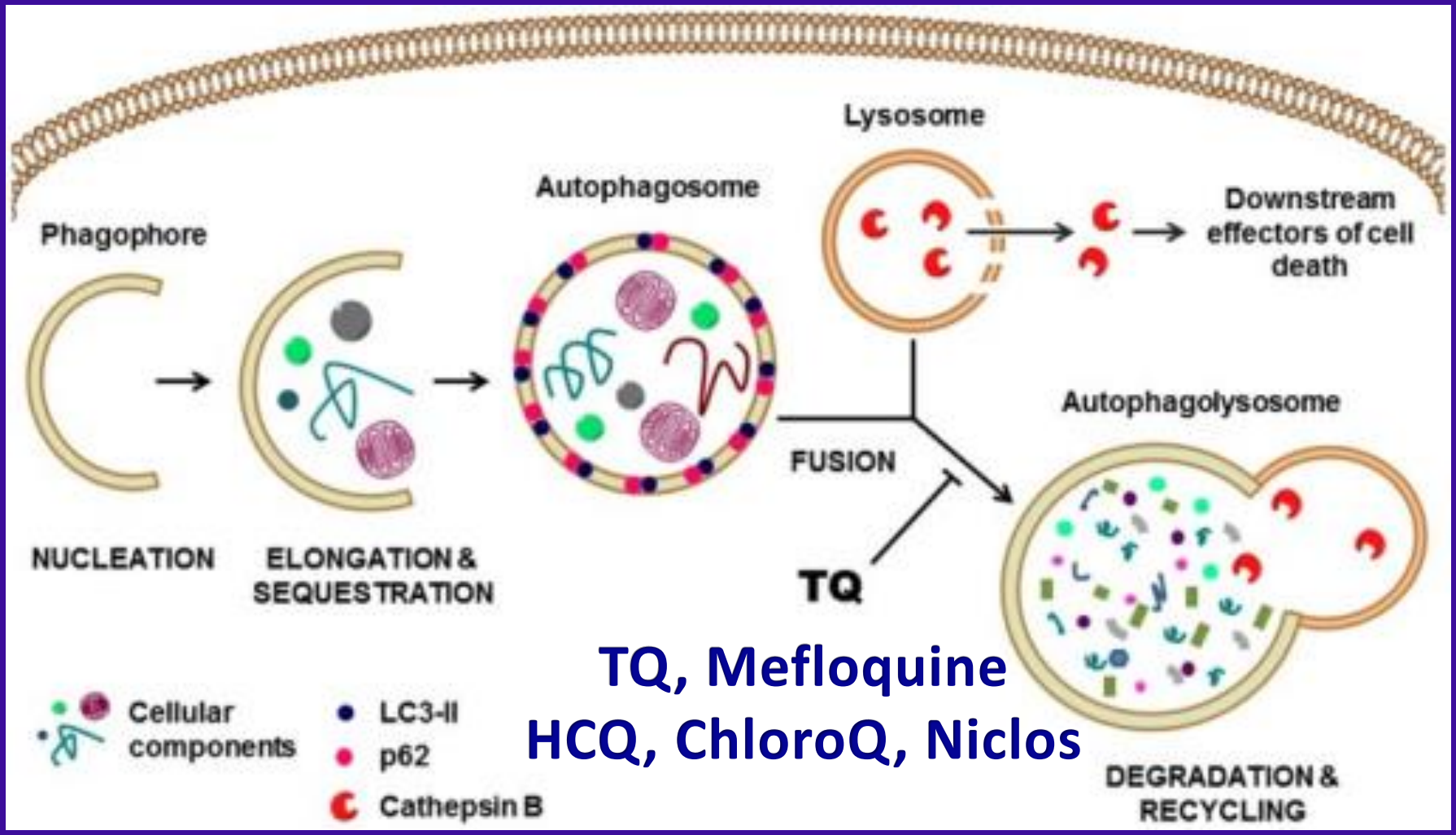
- "These data suggest that complex I inhibition cooperates with DCA activation of oxidative glucose metabolism to promote catastrophic oxidative stress in glioblastoma cells. (Ward, 2017)

- 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.

Three Pillars of Cancer Cell Metabolism

Autophagy

Autophagy



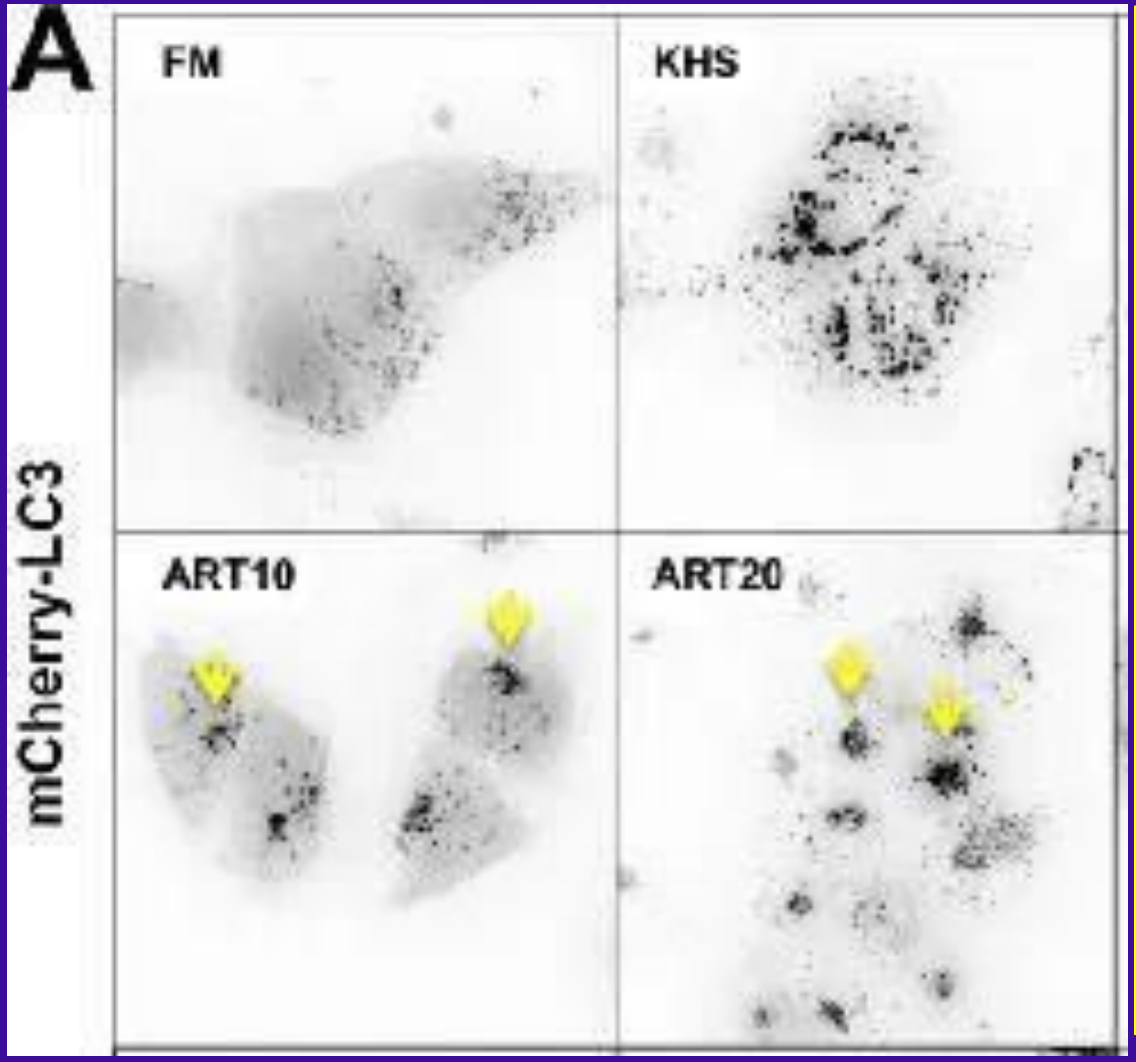
- Racoma, Ira O., et al. "Thymoquinone inhibits autophagy and induces cathepsin-mediated, caspase-independent cell death in glioblastoma cells." PLoS One 8.9 (2013): e72882.

“Protective Autophagy”

- Many Anti-Cancer Drugs induce “Protective Autophagy”.
- Survival Mechanism. (Hibernation)
- 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

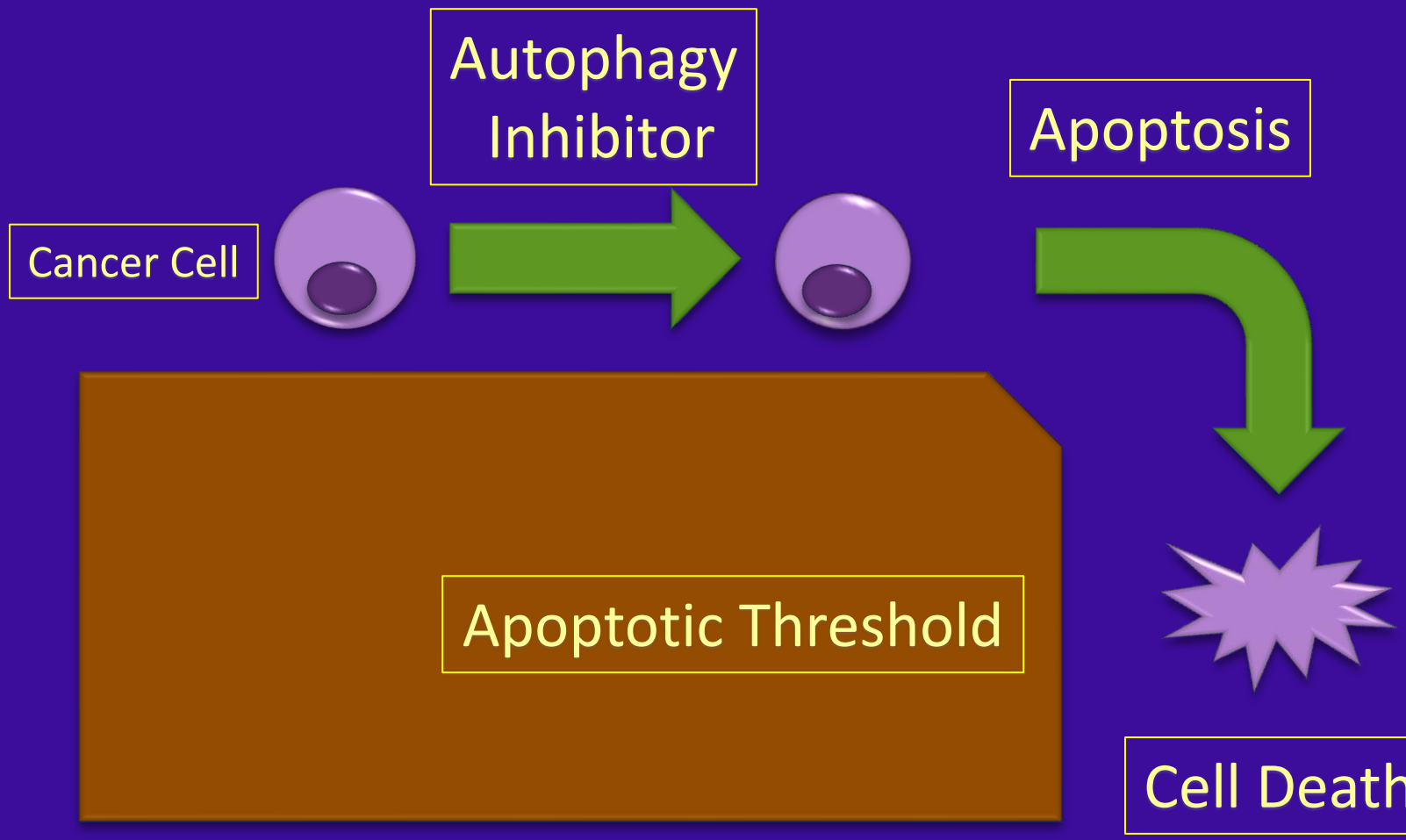


Top Row: Untreated Breast Cancer Cells showing lysosomes (dark stained particles) dispersed throughout cells.

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 ?)
- PPI's
- Loratidine (Claritin)
- Thymoquinone (Black Seed Oil)
- Propranolol (Dual OXPHOS/Autophagy)
- Niclosamide (OXPHOS/Glycolysis/Autophagy)

Levy, Jean M. Mulcahy, Christina G. Towers, and Andrew Thorburn. "Targeting autophagy in cancer." Nature Reviews Cancer 17.9 (2017): 528-542.
Deng, Shuo, et al. "Targeting autophagy using natural compounds for cancer prevention and therapy." Cancer 125.8 (2019): 1228-1246.
Amaravadi, Ravi K., Alec C. Kimmelman, and Jayanta Debnath. "Targeting autophagy in cancer: recent advances and future directions." Cancer discovery 9.9 (2019): 1167-1181.

Fourth Pillar

Restoring Host Immune Surveillance

Fifth Pillar Inflammation

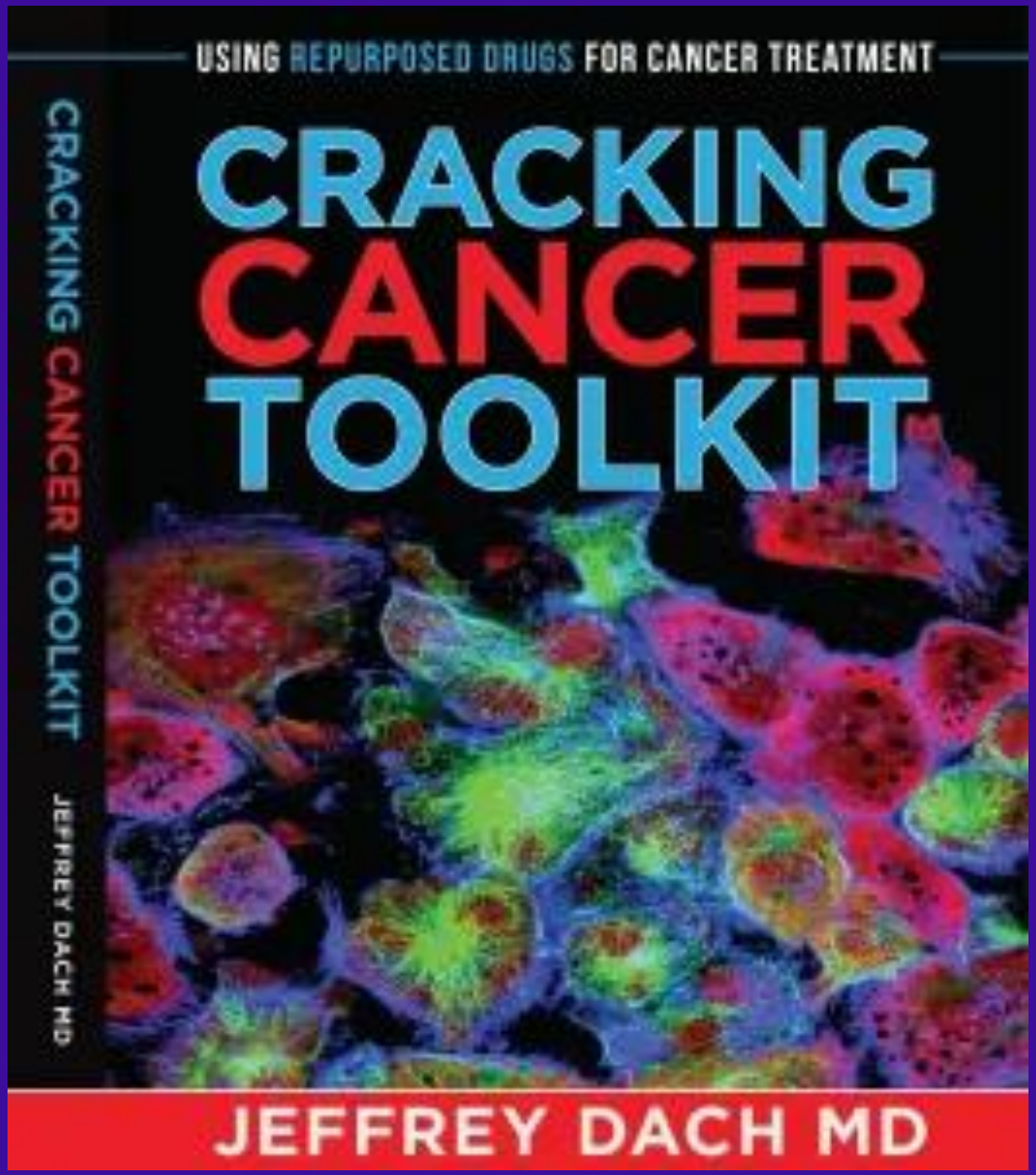
Inhibit
NF-kB, IL-6
cytokines

SUMMARY SLIDE (1)

- Eradicate Cancer Stem Cells
- Cancer as a Metabolic Disease
- Metabolic Derangements in Cancer Cells
- GLYCOLYSIS (Warburg Effect) Cytoplasm
- OXPHOS in Mitochondria
- Autophagy
- Detach HKII from VDAC (Itraconazole, Fenofibrate)
- Drugs and Supplements Targeting Pathways

SUMMARY SLIDE (2)

- DCA Synergy with OXPHOS inhibitors (Metformin) and Autophagy Inhibitors (Propranolol Both OXPHOS and Autophagy Inhibitor)
- Fourth Pillar – Restore Immune Surveillance
- Fifth Pillar - Inflammation



Thank You – Any Questions?

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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
- Metformin, etc.

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).

Fifth Pillar Inflammation

Inhibit
NF-kB, IL-6
cytokines

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,

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 Aamous Cell CA 90 year old.

- Fenofibrate
- Itraconazole
- Mebendazole
- Exemestane
- Doxycycline

Stacpoole,

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.