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STOPPING THE 10 DEADLIEST CANCERS

EGCG and Curcumin Emerge as AI Targets of the Warburg Effect

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Please note: This is a complementary guide on understanding and interrupting the Warburg effect—a powerful strategy in treating some of the world's deadliest cancers. The full guide, 'Cancer Care: The Role of Repurposed Drugs and Metabolic Interventions in Treating Cancer,' and all scientific references, can be found here: imahealth.org/research/cancer-care

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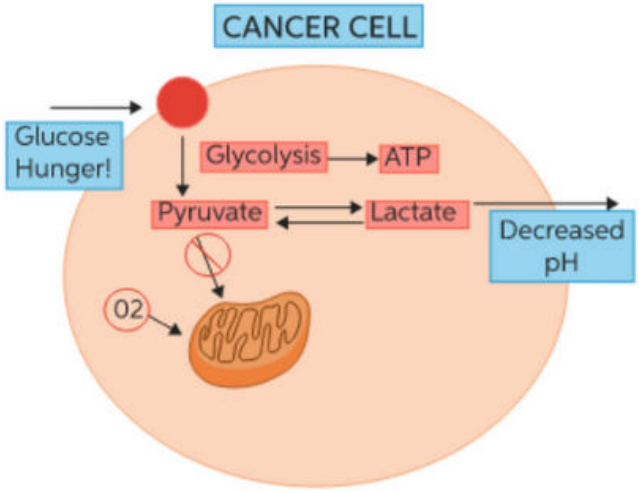
Stopping the 10 Deadliest Cancers

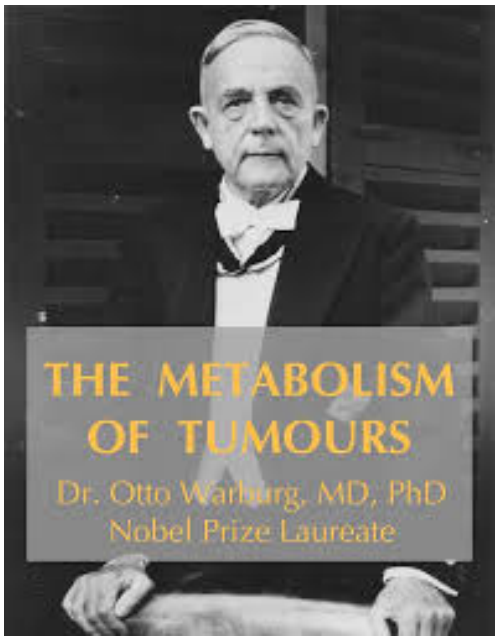
Back in 1924, a scientist named Otto Warburg noticed something strange: Cancer cells use sugar differently than normal cells do. Nearly 100 years later, his discovery might change how we think about cancer forever. Warburg discovered that the mitochondria of cancer cells switch to an "emergency mode." They start burning sugar in a primitive, inefficient way called the Warburg effect (anaerobic respiration). Instead of generating 30 energy units from each sugar molecule, cancer cells produce only 2! Even worse, this process creates lactic acid, which builds up around the cells, creating the perfect environment for cancer to grow.

Figure 1 illustrates the Warburg effect, which shows how cancer cells shift their metabolism to favor sugar fermentation even in the presence of oxygen.

Figure 1: The Warburg Effect



Aerobic Glycolysis Defective Mitochondria



Using AI, we reviewed the 10 deadliest cancers and found that they exhibit the most powerful Warburg effects, based on the heightened activity of four key molecular pathways. These pathways—HIF-1, GLUT1, c-Myc, and hexokinase 2 (HK2)—are central to the Warburg effect. Table 1 lists the 10 cancers most driven by these pathways, making them the most active Warburg effect tumors. Not surprisingly, they're also the deadliest.

Table 1. The 10 deadliest cancers by prognosis, metabolic activity, and c-Myc activation

Rank	Cancer Type	5 Year Survival Rate	Glut1 Activity	Hexokinase Activity	HIF-1 Activity	c-Myc Activity (Most-Least)
1	Pancreatic Cancer	12.5%	High (↑↑↑)	High (HK2↑↑↑)	High (↑↑↑)	High (↑↑↑)
2	Small Cell Lung Cancer	7.0%	High	High (HK2↑↑)	High (↑↑↑)	High (↑↑↑)
3	Glioblastoma (GBM)	6.8%	High (↑↑↑)	High (HK2↑↑↑)	High (↑↑↑)	High (↑↑)
4	Liver Cancer (HCC)	21.6%	High	High (HK2↑↑)	High (↑↑↑)	High (↑↑)
5	Acute Myeloid Leukemia	31.7%	Moderate-High	High (HK2↑)	Moderate (↑↑)	Moderate (↑↑)
6	Esophageal Cancer	21.7%	High	Moderate-High	High (↑↑↑)	Moderate (↑↑)
7	Stomach Cancer	35.7%	Moderate	Moderate (HK2↑)	Moderate (↑↑)	Moderate (↑)
8	Ovarian Cancer	49.7% (Late 31%)	Low-Moderate	Moderate (HK2)	High (↑↑↑)	Low-Moderate (↑)
9	Mesothelioma	10.0%	Moderate	Moderate	Moderate (↑↑)	Low (→)
10	Gallbladder Cancer	19.4%	Moderate	Moderate	Moderate (↑↑)	Low (→)

The Lactic Acid–HIF-1-VEGF Connection

The accumulation of lactic acid doesn't just create an acidic environment—it initiates a crucial molecular cascade. Research shows that lactate activates a protein called hypoxia-inducible factor-1 (HIF-1), even when oxygen is present. This is significant because HIF-1 is normally only activated when cells don't have enough oxygen.

Once activated, HIF-1 becomes a master regulator that helps cancer cells adapt to their harsh environment. It stimulates the production of vascular endothelial growth factor (VEGF) in cancer cells, which signals the body to build new blood vessels to feed the growing tumor.

This creates a powerful feedback loop: Damaged mitochondria produce lactate, activating HIF-1. That, in turn, triggers blood vessel formation and delivers more nutrients to the tumor—allowing it to grow larger, produce more lactate, and reinforce the cycle.

Several repurposed compounds are known to inhibit HIF-1 activation. Table 2 lists the most powerful HIF-1 blockers identified to date.

Table 2. Repurposed agents that block HIF-1

Rank	Agent	HIF-1α Supression	Key Mechanisms/Evidence
1	EGCG	✓ Strong	Inhibits HIF-1α stabilization via PI3K/Akt/mTOR and prevents hypoxia-induced signaling.
2	Reservatrol	✓ Strong	Activates SIRT1, promoting HIF-1α degradation; suppresses VEGF and angiogenisis.
3	Curcumin	✓ Strong	Blocks HIF-1α synthesis and nuclear translocation via NF-κB inhibition.
4	Quercetin	✓ Moderate	Inhibits HIF-1a via PI3K/Akt/mTOR pathways and ROS reduction.
5	Metformin	✓ Moderate	Suppresses HIF-1α through AMPK activation and mTOR inhibition.

The c-Myc–GLUT1 Connection

Another key player in cancer's metabolic reprogramming is c-Myc, an oncogenic transcription factor that regulates many aspects of cell growth and division. Research has shown that c-Myc directly activates the gene encoding GLUT1, a glucose transporter located on the cell surface that brings glucose into the cell.

When c-Myc is overexpressed, as it often is in cancer cells, it dramatically increases the number of GLUT1 transporters, allowing cancer cells to consume far more glucose than normal cells. Nuclear run-on studies have confirmed that c-Myc directly increases the transcription rate of the GLUT1 gene.

Table 3 lists the most powerful GLUT1 inhibitors currently recognized for limiting glucose uptake in cancer cells.

Beyond GLUT1, c-Myc activates additional genes that encode glycolytic enzymes, essentially reprogramming the cell's entire metabolic machinery to support the Warburg effect.

Table 4 highlights key compounds shown to suppress c-Myc activity in cancer cells.

Table 3. The most powerful GLUT-1 blockers

Rank	Agent	GLUT1 Supression	HK2 Supression	Key Mechanisms/Evidence
1	EGCG	✓ Strong	✓ Strong	Directly inhibits GLUT1 and HK2; disrupts glycolysis via HIF-1α/ STAT3 pathways.
2	Quercetin	✓ Strong	✓ Moderate	Inhibits GLUT1/HK2 via HIF-1α/PI3K/Akt pathways.
3	Metformin	✓ Moderate	✓ Moderate	AMPK activation downregulates GLUT1/HK2 via mTOR inhibition.
4	Reservatrol	✓ Moderate	✓ Moderate	Modulates SIRT1/AMPK, reducing GLUT1/HK2 expression.
5	Curcumin	✓ Moderate	✓ Moderate	Downregulates GLUT1/HK2 via NF-kβ/HIF-1α inhibition.

Table 4. The most powerful c-Myc blockers

Rank	Agent	c-Myc Supression	Key Mechanisms/Evidence
1	Curcumin	✓ Strong	Directly downregulates c-Myc transcription; inhibits β-catenin/TC4F binding to MYC promoter.
2	EGCG	✓ Strong	Suppresses c-Myc via PI3K/Akt/mTOR inhibition and mIRNA-34a upregulation.
3	Reservatrol	✓ Strong	Reduces c-Myc expression via SIRT1 activation and AMPK-mediated metabolic stress.
4	Quercetin	✓ Moderate	Inhibits c-Myc through JAK/STAT and PIK3/Akt pathway modulation.
5	Ivermectin	✓ Moderate	Suppresses c-Myc via PAK1 inhibition and Wnt/β-catenin pathway disruption.

The PI3K/AKT/mTOR Pathway: Master Regulator of Warburg

The PI3K/AKT/mTOR pathway is a critical signaling cascade that regulates numerous cellular processes, including metabolism, growth, proliferation, and survival. In many human cancers—particularly prostate, ovarian, and other aggressive types—the pathway becomes dysregulated because of various oncogenic events. Inhibiting this pathway offers promising strategies for cancer prevention and treatment.

Studies of cells with hyperactive mTOR signaling have identified this pathway as a "major positive regulator of the Warburg effect." It activates key transcription factors such as HIF-1α and c-Myc, which increase the expression of glycolytic enzymes and glucose transporters.

Table 5 ranks the most effective compounds known to suppress the PI3K/AKT/mTOR pathway and reduce Warburg-driven metabolic activity.

Table 5. Compounds ranked by PI3K/AKT/mTOR pathway suppression

Rank	Agent	In Vitro Evidence	Mechanisms of Action
1	Curcumin	Strong inhibition of Akt/mTOR phosphorylation in multiple cancer cell lines; concentration and time-dependent inhibition of downstream targets.	Activates PP2A or calyculin A-sensitive protein phosphatases targeting Akt/mTOR; inhibits both mTORC1 and mTORC2; decreases phosphorylation of 4E-BP1, eIF4G, p70 S6K, and S6.
2	IV Vitamin C	Dose-dependent inhibition of mTORC1/2 in multiple cancer cell lines; reduces phosphorylation of S6K, S6, 4EBPI and AKT.	Induces intercellular ROS; promotes GSK3-FBXW7-mediated Rictor ubiquitination and degradation; upregulates HM0X1 expression.
3	EGCG	Inhibits proliferation and induces apoptosis in ovarian cancer cells; downregulates p-AKT and p-mTOR.	Upregulates PTEN expression; downregulates PDK1, p-AKT and p-mTOR expression; effects reversed by PTEN inhibitor VO-Ohpic.
4	Metformin	Inhibits mTOR signalling in various cell types.	Activates AMPK which inhibits mTOR signalling; may have AMPK-independent mechanisms.
5	Atorvastatin	Inhibits cell proliferation in ovarian cancer cells via AKT/mTOR inhibition.	Associated with induction of apoptosis, autophagy, and cell cycle arrest; Decreases P-Akt/Akt ratio in some muscle types but increases it in others.

The Warburg Effect: A Self-Reinforcing Cycle

Recent research has revealed that the Warburg effect isn't just a one-way street—it forms a negative feedback loop that amplifies itself. As cancer cells shift to aerobic glycolysis, they produce more NADH (a molecule involved in cellular energy production), which increases cell proliferation, creating a positive arm of the feedback loop.

This self-reinforcing cycle helps explain why the Warburg effect is so persistent in cancer cells and why it's so difficult to reverse once established. Interestingly, research also suggests that both aerobic glycolysis and oxidative phosphorylation work together synergistically to support cancer cell growth and survival.

In addition to targeting core Warburg-related pathways, researchers have explored repurposed agents such as ivermectin in cancers with overlapping molecular drivers, including PAK1 activation. Table 6 summarizes the 10 most common human cancers worldwide, highlighting their PAK1 activation status and emerging ivermectin-related treatment implications based on recent studies.

Table 6. Top 10 most common human cancers by global incidence and ivermectin treatment implications (2022–2025)

Integrated analysis of epidemiology and repurposed therapeutics

Rank	Cancer Type	New Cases (2022)	% Total	PAK1 Activation Status	Ivermectin Treatment Implications (Per Recent Studies)
1	Lung	2,480,675	12.4%	Activated	Synergizes with EGFR TKIs to restore gefitinib sensitivity; inhibits WNT-TCF targets (AXIN2 LEF1) in xenografts at 10 mg/kg.
2	Breast	2,296,840	11.5%	Activated	Induces immunogenic cell death (ICD) and T-cell infiltration; combines with anti-PD1 for complete responses in 2025 trials ($p<0.01$).
3	Colorectal	1,926,425	9.6%	Activated	Inhibits Wnt/β-catenin via PP2A activation (5μM); synergises with vincristine (58%migration reduction).
4	Prostate	1,467, 854	7.3%	Activated	Overcomes docetaxel resistance via PAK1 inhibition; phase II trials ongoing with cyclophosphamide combos.
5	Stomach	968,784	4.8%	Activated	Targets PAK1-MORC2 axis to reverse chemo resistance; reduces oxidative stress in DMH-induced models (1 mg/kg).
6	Liver	830,180	4.3%	Activated	Blocks metastasis via integrin β1FAK suppression (3 mg/kg); synergizes with sorafenib in HCC models.
7	Cervix Uteri	662,301	3.3%	Activated	Disrupts HPV E6/E7-PAK1 synergy, enhances cisplatin efficacy via Akt/mTOR inhibition in phase 1 trials.
8	Thyroid	614,729	3.1%	Activated	Inhibits BRAF phosphorylation at invasive fronts; FRAX597 reduces anaplastic cancer motility by 72% in preclinical models.
9	Bladder	573,278	2.9%	Activated	Suppresses EMT via E-cadherin restoration; shRNA knockdown reduces Transwell invasion by 41%.
10	Non-Hodgkin Lymphoma	510,576	2.8%	Activated	Overcomes PI3K inhibitor resistance via ERK pathway modulation; IPA-3 synergizes with BKM120 (75% tumor reduction).

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