Ivermectin

THE GOOD, THE BAD AND THE EMERGING SCIENCE

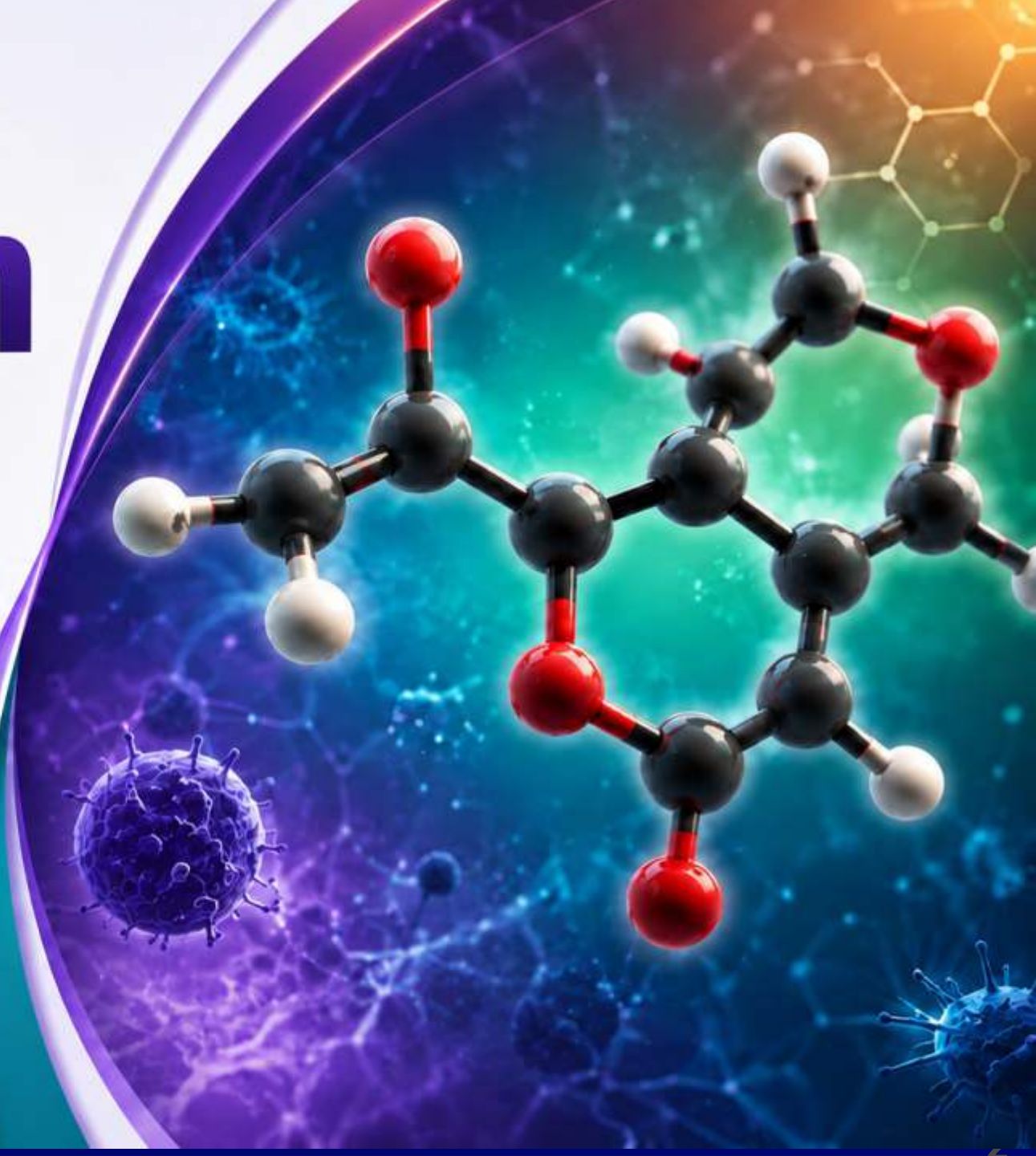
Prof. Joseph Varon, MD, FACP, FCCP, FCCM, FRSM

President & Chief Medical Officer

INDEPENDENT MEDICAL ALLIANCE

Washington, D.C., USA

INDEPENDENT MEDICAL ALLIANCE

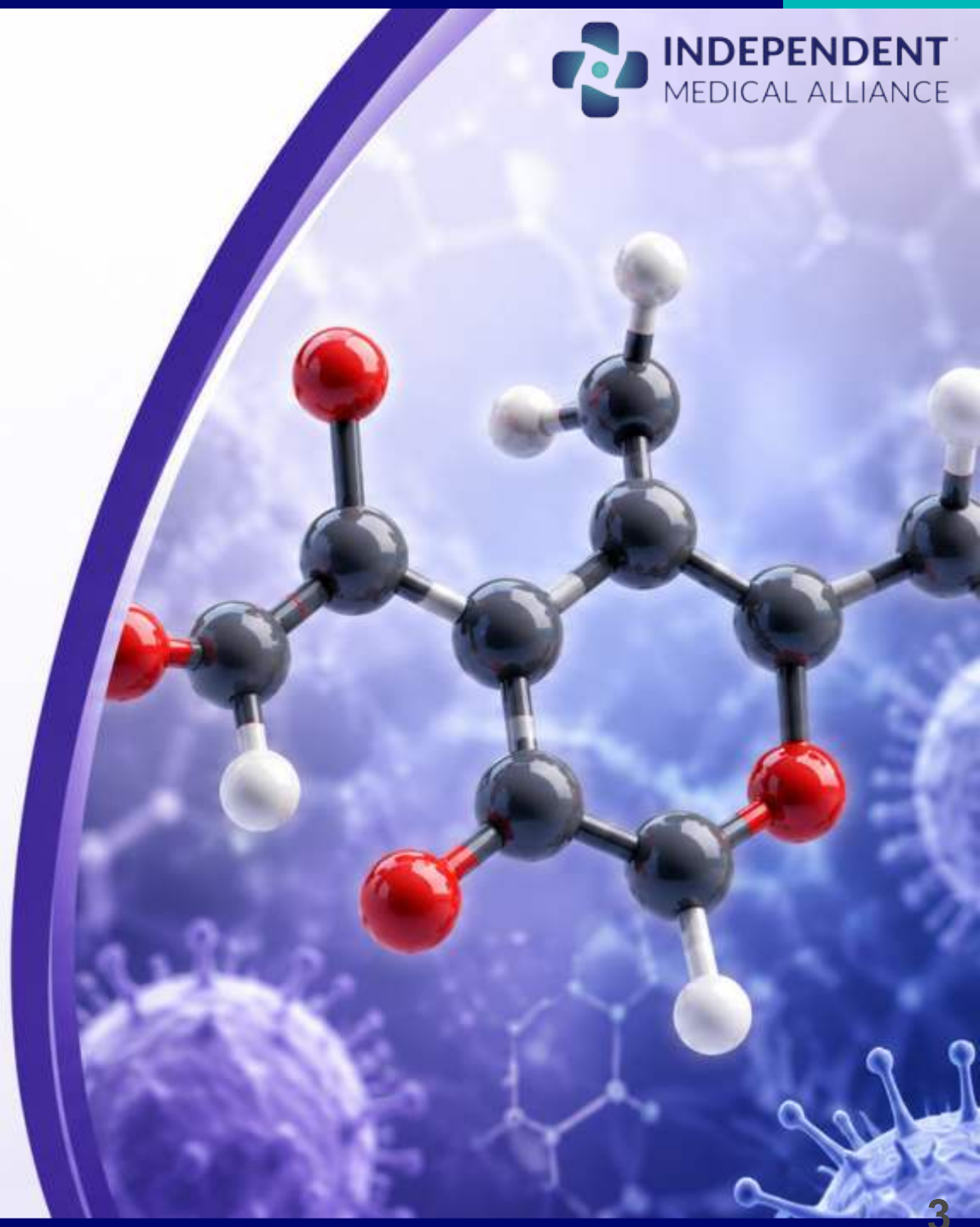


DISCLOSURES

PRESENTER DISCLOSURES

I have no relevant financial conflicts of interest or affiliations with commercial organizations regarding the pharmaceutical products discussed in this lecture.

All clinical data presented is derived from **peer-reviewed literature** and **established academic sources.**



LEARNING OBJECTIVES

SECTION I: PHARMACOLOGY, MECHANISMS & CLINICAL FOUNDATIONS

OBJECTIVE 01

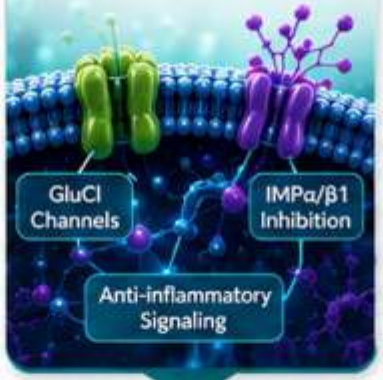
Pharmacology & Discovery

Understand the serendipitous soil-based discovery and unique pharmacology of the avermectin family.

OBJECTIVE 02

Biological Mechanisms

Describe multi-target pathways: GluCl channels, IMPα/β1 inhibition, and anti-inflammatory signaling.



OBJECTIVE 03

COVID-19 Evidence

Critically evaluate the global clinical evidence base for and against ivermectin in SARS-CoV-2 management.

OBJECTIVE 04

Anticancer Potential

Explore the "Molecular Swiss Army Knife" role in oncology through 10+ distinct antineoplastic mechanisms.

OBJECTIVE 05

Other Potential Uses

Explore broader therapeutic applications in dermatology, parasitic infections, neurology, and immunomodulation.

OBJECTIVE 06

Safety & Future

Assess safety profiles, regulatory status, and the roadmap for independent clinical oncology trials.

COMPREHENSIVE EVIDENCE-BASED LEARNING

TRANSLATING SCIENCE INTO CLINICAL IMPACT

MULTIDISCIPLINARY INSIGHTS FOR BETTER PATIENT OUTCOMES

SAFE, EFFECTIVE & RESPONSIBLE APPLICATION

IVERMECTIN: CLINICAL ANALYSIS

Ivermectin at a Glance

INDEPENDENT MEDICAL ALLIANCE

The "Wonder Drug"

A Nobel Prize–winning discovery that transformed global health. Originally isolated from soil bacteria, it has become one of the most significant medicines in history.

Global Impact Scale

1.3 Billion Doses distributed between 1987 and 2013, primarily through mass drug administration (MDA) programs to combat neglected tropical diseases.

Molecular "Swiss Army Knife"

- Beyond its primary role as an antiparasitic, Ivermectin is now
- recognized for its diverse pharmacological profile.

Therapeutic Scope

FDA-Approved: Parasitic worms, (Strongyloidiasis), Head lice, Rosacea (topic).

Investigational/Off-label: Viral infections, Cancer, CNS disorders (ALS, Alcoholism).

1. Crump A. Ivermectin: "wonder drug" from Japan: the human use perspective. J Antibiot (Tokyo). 2017;70(5):495–505.
2. Lawrence J et al. The Global Health Impact of Ivermectin. PLoS Negl Trop Dis. 2015;9(9):e0003507.

SERENDIPITOUS DISCOVERY: SOIL SAMPLE MA-4680

SECTION I: HISTORY AND DISCOVERY

BIOPROSPECTING THE SOIL

1972: Dr. Satoshi Ōmura began a mission to find bioactive compounds from soil microorganisms.

Location: A single soil sample (MA-4680) collected from a golf course in **Kawana, Japan.**

Collaboration: Partnership with Merck (Dr. William Campbell) to screen for anthelmintic activity.

INDEPENDENT MEDICAL ALLIANCE

Streptomyces avermitilis

This extremely rare bacterium was identified from sample MA-4680. It has been found independently only a handful of times worldwide, making the Kawana discovery a true biological anomaly.

Potency & Naming

The isolated compound, **Avermectin**, showed potent anthelmintic activity at a concentration of just **0.0003%.** This led to the development of the safer, more effective dihydro-derivative: **Ivermectin.**

1. Ōmura S, Crump A. The life and times of ivermectin — a success story. Nat Rev Microbiol. 2004;2(12):984-9.
2. Campbell WC. History of ivermectin and its role in helminth control. Curr Pharm Biotechnol. 2012;13(6):853-65.


INDEPENDENT
MEDICAL ALLIANCE

COLLABORATION: FROM AVERMECTIN TO IVERMECTIN

SECTION I: DISCOVERY AND HISTORY

INDEPENDENT MEDICAL ALLIANCE

The Kitasato-Merck Alliance

- **Formalized in 1973–1974** as a strategic cross-continental bioprospecting partnership.
- **Kitasato Institute (Japan)** provided microbial isolates from unique environmental niches.
- **Merck Sharp & Dohme (USA)** performed high-throughput screening for veterinary efficacy.

Soil Sample MA-4680

- Collected from a golf course in **Kawana, Japan** (80 miles from Tokyo).
- The sample contained the incredibly rare bacterium ***Streptomyces avermitilis***.
- This specific strain has only been independently isolated a few times in history.

Scientific Synergy

Dr. Satoshi Ōmura: Microbiologist who perfected the cultivation of rare soil actinomycetes.

Dr. William Campbell: Parasitologist who identified the unique "avermectin" activity.

Their collaboration bridged the gap between basic microbiology and clinical pharmacology.

Development of Avermectin

- Initial fermentation broth showed **99% clearance** of worms in mice at trace levels.
- Potent anthelmintic activity observed at a concentration of only **0.0003%**.
- Led to the structural modification into the more stable and safer **Ivermectin**.

1. Ōmura S, Crump A. The life and times of ivermectin — a success story. Nat Rev Microbiol. 2004;2(12):984-9.
2. Campbell WC. History of ivermectin and its role in helminth control. Curr Pharm Biotechnol. 2012;13(6):853-65.

TIMELINE OF IVERMECTIN: 1972 TO 1995

SECTION I: HISTORICAL FOUNDATION & DISCOVERY

INDEPENDENT MEDICAL ALLIANCE

1972 — **Serendipitous Discovery**

Dr. Satoshi Ōmura collects soil sample MA-4680 from a golf course in Kawana, Japan, initiating the search for novel antibiotics.

1975 — **Avermectin Identified**

Collaborative research with Merck (Dr. William Campbell) identifies avermectins from *Streptomyces avermitilis* with potent anthelmintic activity.

1981 — **Animal Health Revolution**

Ivermectin (as Ivomec and Equalan) is approved for veterinary use, becoming the world's most successful antiparasitic agent.

1987 — **Human Use & Philanthropy**

FDA approval for Onchocerciasis; Merck launches the Mectizan Donation Program to provide ivermectin free of charge "as long as needed."

1995 — **APOC Launch**

African Programme for Onchocerciasis Control begins; 19.1 million DALYs saved through mass drug administration campaigns.

Molyneux DH, Ward SA. Trends Parasitol. 2015;31:605.
Drinyev VA et al. Eur J Pharmacol. 2004;501:19.
Halma M, Vottero P. J Indep Med. 2025;1(1).

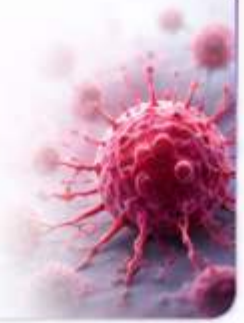
TIMELINE OF IVERMECTIN: 2004 TO 2026

SECTION I: HISTORICAL CONTEXT & MODERN EVOLUTION

INDEPENDENT MEDICAL ALLIANCE

2004 — First Description of Antitumor Activity

First description of antitumor activity published by Drinyaev et al., opening the door to oncology research.



2011 — Anti-inflammatory Properties Identified

Identification of anti-inflammatory properties in asthma models, expanding its therapeutic potential.

2015 — Nobel Prize in Physiology or Medicine

Nobel Prize in Physiology or Medicine awarded to Satoshi Ōmura and William Campbell for ivermectin's discovery.

2020–2024 — COVID-19 Pandemic Research Surge

COVID-19 pandemic brings global controversy; surge in antiviral mechanism research and clinical trials.

2025 — Molecular Swiss Army Knife

Comprehensive review classifies Ivermectin as a "Molecular Swiss Army Knife" for its multi-target efficacy.

2026 — Anticancer Comeback & Future Focus

Post-pandemic anticancer comeback; focus shifts to combination therapies and immunotherapy synergy.

MODERN CLINICAL CONTEXT

> *The discovery of ivermectin is a prime example of how curiosity-driven research can lead to breakthroughs that transform global health.*
>
> – Nobel Committee

1. Halma M, Vottero P. Ivermectin: A Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65.
2. Molyneux DH, Ward SA. Ivermectin and the Nobel Prize. Trends Parasitol. 2015;31(12):605-607.
3. Drinyaev VA, et al. Antitumor activity of avermectins. Eur J Pharmacol. 2004;501:19-23.

THE NOBEL PRIZE 2015: RECOGNITION OF DISCOVERY

SECTION I: HISTORY AND GLOBAL IMPACT

INDEPENDENT MEDICAL ALLIANCE

2015 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Satoshi Ōmura

William Campbell

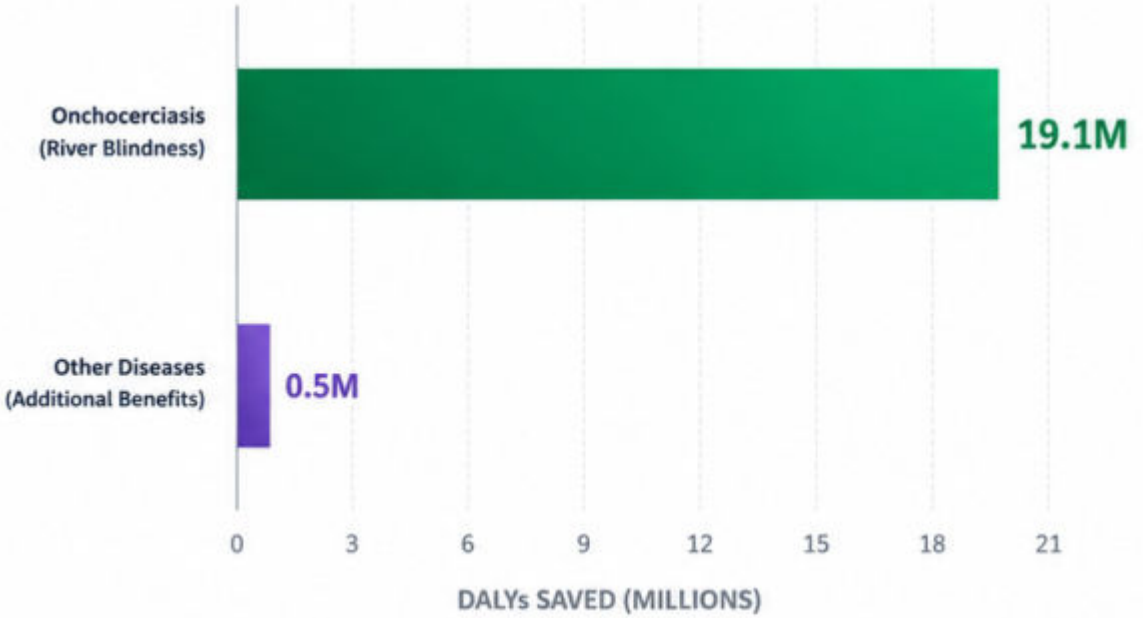
Awarded the Nobel Prize in Physiology or Medicine for their revolutionary work on therapies against roundworm parasites. Their collaboration bridged natural product discovery and pharmaceutical development.

NOVEL THERAPY FOR PARASITES

Recognition of ivermectin as a "**Wonder Drug**" that transformed the treatment of devastating tropical diseases, fundamentally altering global health trajectories for the world's poorest populations.

*Shared with **Tu Youyou** for her discoveries concerning a novel therapy against Malaria (Artemisinin).*

GLOBAL IMPACT: DALYs SAVED (1995–2010)



19.1M
ONCHOCERCIASIS DALYs SAVED

500K
NON-TARGET DALYs SAVED

MECHANISM 3:
ANTI-INFLAMMATORY PATHWAYS

SECTION II: PHARMACOLOGY & MECHANISMS

Ivermectin restores immune balance by targeting key inflammatory signaling pathways.

NF-κB INHIBITION

Blocks the nuclear translocation of NF-κB, preventing the transcription of major pro-inflammatory genes.

STAT3 DOWNREGULATION

Inhibits the **STAT3** signaling pathway, a key driver of cytokine storms and chronic systemic inflammation.

CYTOKINE SUPPRESSION

Reduces levels of **IL-6, IL-8, TNF-α,** and **MCP-1**, effectively dampening the hyper-inflammatory response.

HOMEOSTATIC REBALANCING

Modulates the balance between pro-thrombotic/pro-inflammatory and anti-inflammatory physiological states.

THE BIG PICTURE

Ivermectin acts as an immune system balancer—cooling the fire of inflammation while preserving physiological homeostasis.

BALANCING THE INFLAMMATORY EQUATION

a PHYSIOLOGICAL BALANCE

ANG II (Pro-inflammatory)
- Prothrombotic
- Vasoconstrictive
- Proapoptotic
- Proinflammatory

ANG 1-7 (Anti-inflammatory)
- Antithrombotic
- Vasodilatory
- Antiapoptotic
- Anti-inflammatory

ACE 2

b IN DISEASE (e.g., SARS-CoV-2 INFECTION)

ANG II (Pro-inflammatory)
- Prothrombotic
- Vasoconstrictive
- Proapoptotic
- Proinflammatory

SARS-CoV-2

ANG 1-7 (Anti-inflammatory)
- Antithrombotic
- Vasodilatory
- Antiapoptotic
- Anti-inflammatory

ACE 2

KEY INFLAMMATORY MEDIATORS REDUCED

IL-6 IL-8 TNF-α MCP-1

NET EFFECT

- ✓ Reduces excessive inflammation
- ✓ Limits cytokine storm
- ✓ Restores vascular and immune balance
- ✓ Supports resolution and tissue protection

"Not just fighting disease—restoring balance."

References:
Aminpour M, et al. Computation. 2022;10:51.
Farasat A, et al. J Inflamm Dis. 2023;27(2).
Halma M, Vottero P. J Indep Med. 2025;1(1):37-65.

MECHANISM 4: MULTI-TARGET RECEPTOR ACTIVITY

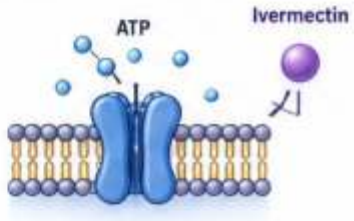
SECTION II: PHARMACOLOGICAL FOUNDATIONS

Ivermectin acts on multiple receptors and cellular pathways, explaining its broad biological effects from neuro-immune modulation to anti-cancer potential.

NEURO-IMMUNE RECEPTORS

1 P2X4 PURINERGIC RECEPTORS

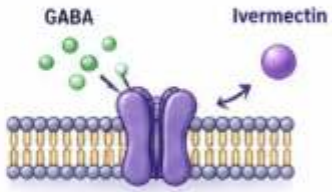
Modulates ATP-gated ion channels; critical for inflammatory signaling and pain processing.



↓ Inflammation
↓ Pain signaling

2 GABA RECEPTORS

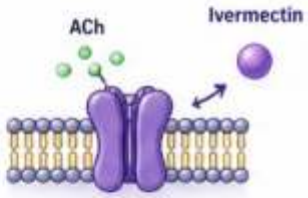
Positive allosteric modulation of inhibitory neurotransmission (significant at high concentrations).



↑ Inhibitory neurotransmission
Neuroprotection
Anxiolytic potential

3 α7 NICOTINIC ACETYLCHOLINE RECEPTOR (α7nAChR)

Potentiation of anti-inflammatory pathways via the cholinergic anti-inflammatory reflex.



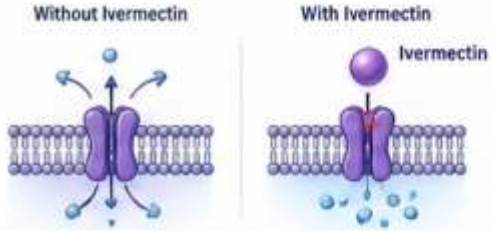
↓ Cytokine release
↓ Inflammation

P2X4 | GABA | α7nAChR

CELLULAR & TRANSPORT MODULATION

1 MDR REVERSAL (P-GLYCOPROTEIN/ABCB1)

Competitive inhibition of the P-gp efflux pump; restores intracellular drug accumulation in resistant cells.



↑ Drug accumulation
↑ Treatment efficacy

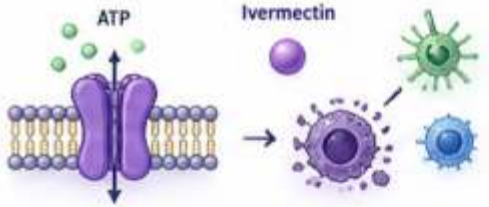
2 ANTI-MITOTIC ACTIVITY

Induces G2/M phase cell cycle arrest through microtubule stabilization and inhibition of mitosis-related kinases.

Cell cycle arrest
Inhibits mitosis
Anti-proliferative effect

3 POTENTIATION OF P2X7 RECEPTORS

Enhances ATP-induced pore formation; triggers Immunogenic Cell Death (ICD) in tumor microenvironments.



↑ Pore formation
↑ ICD
↑ Anti-tumor immune response

P-gp BLOCK | G2/M ARREST | ICD TRIGGER

KEY TAKEAWAY

Ivermectin's multi-target actions span neuro-immune modulation and cellular regulation, leading to anti-inflammatory, neuroprotective, chemosensitizing, and anti-cancer effects.

References: 1. Aminpour M, et al. Computation. 2022;10:51. 2. Farasat A, et al. J Inflamm Dis. 2023;27(2). 3. Didier A, et al. Frontiers in Pharmacology. 2022;13:858456.

ONCHOCERCIASIS: THE BURDEN OF RIVER BLINDNESS

SECTION II: THE GOOD — ANTIPARASITIC SUCCESS

INDEPENDENT MEDICAL ALLIANCE

Global Disease Burden

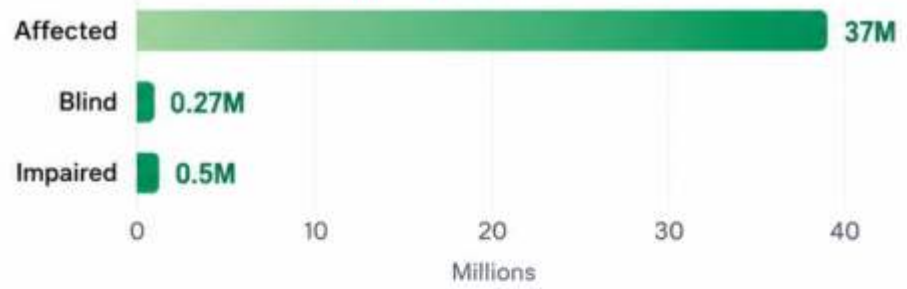
37M
People Affected

100M
At High Risk

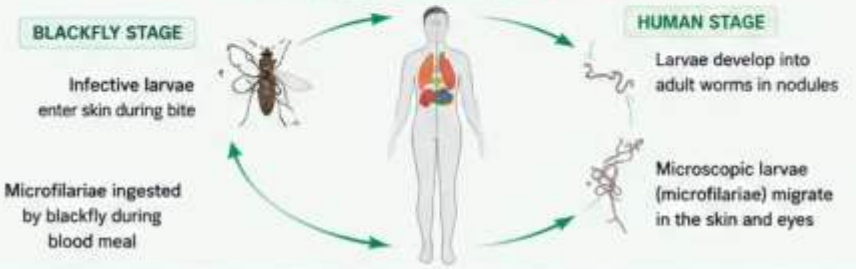
270K
Cases of Blindness

500K
Visually Impaired

POPULATION IMPACT (MILLIONS)



ONCHOCERCA VOLVULUS LIFE CYCLE



Standard Treatment Protocol

Dosage: Ivermectin 150 µg/kg administered orally.

Frequency: Single annual dose required for control.

Impact: Achieved near-elimination in several African nations.

Mectizan Donation Program

Scale: Over 1.3 billion doses donated (1987–2013).

Reach: Mass drug administration campaign across endemic regions.

COMBINED MECHANISM

Mast Cell Activation + Glutamate-Gated Chloride Channel (GGCC) Inhibition

Winthrop KL et al. J Glob Infect Dis. 2011;3:151. | White AT et al. J Infect Dis. 1987;156:463.

GLOBAL BURDEN OF PARASITIC DISEASES

SECTION II: THE GOOD — ANTIPARASITIC APPLICATIONS

INDEPENDENT MEDICAL ALLIANCE

Onchocerciasis

37M

PEOPLE AFFECTED GLOBALLY

Scabies

204M

ESTIMATED CASES WORLDWIDE

Trichuriasis

508M

UPPER ESTIMATE (MILLIONS)

Lymphatic Filariasis

120M

INFECTIONS GLOBALLY

Strongyloidiasis

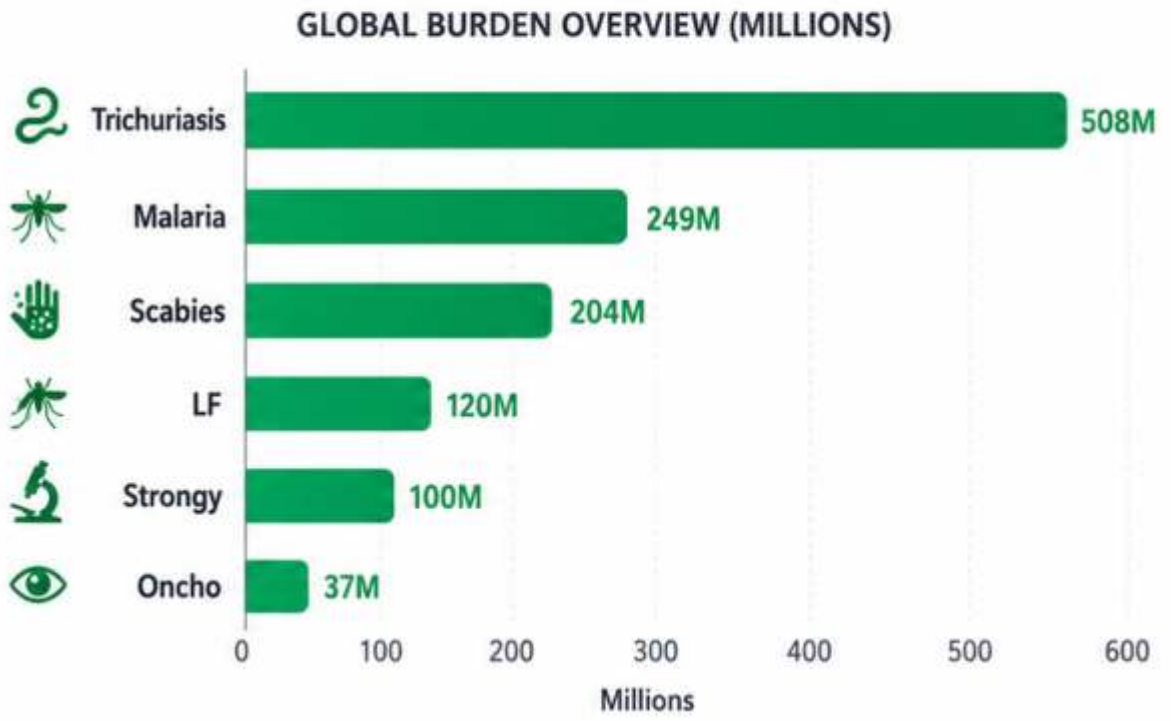
100M

CASES PER YEAR (MAX)

Pediculosis

19%

SCHOOL-AGED CHILDREN



Malaria Transmission Reduction

Ivermectin reduces malaria transmission by **35%** by killing *Anopheles* mosquitoes that feed on treated humans.

WHO World Malaria Report. 2023.

Halma M, Vottero P. J Indep Med. 2025;1(1):37-65.

Crump A J. Antibiot. 2017;70:495.

MALARIA TRANSMISSION REDUCTION

SECTION II: THE GOOD — ANTIPARASITIC INNOVATION

INDEPENDENT MEDICAL ALLIANCE

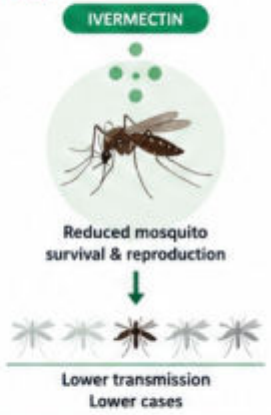
Ivermectin: A Powerful Tool in the Fight Against Malaria
Targeting the vector. Breaking the cycle. Saving lives.

GLOBAL DISEASE BURDEN (2022)

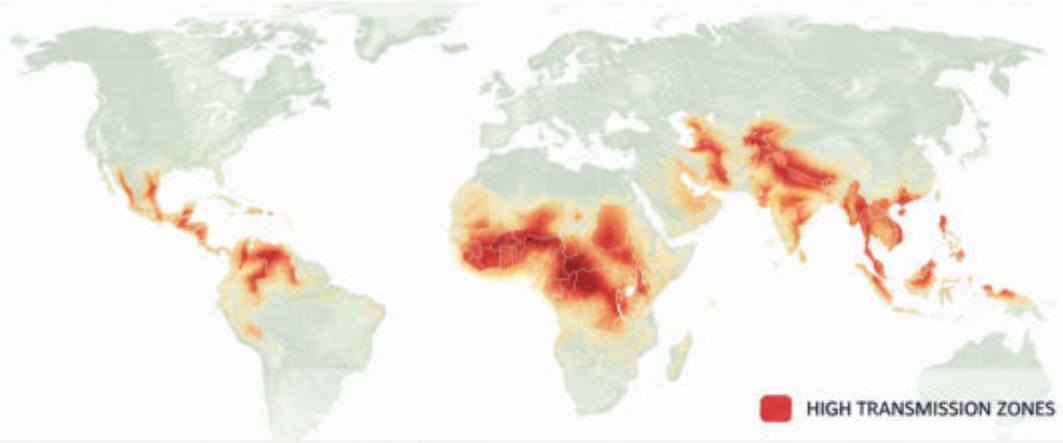
- Total Cases: **249 Million** affected worldwide
- Total Mortality: **608,000 Deaths** annually
- Major Vulnerability: Children under 5 in sub-Saharan Africa

IVERMECTIN INTERVENTION EFFICACY

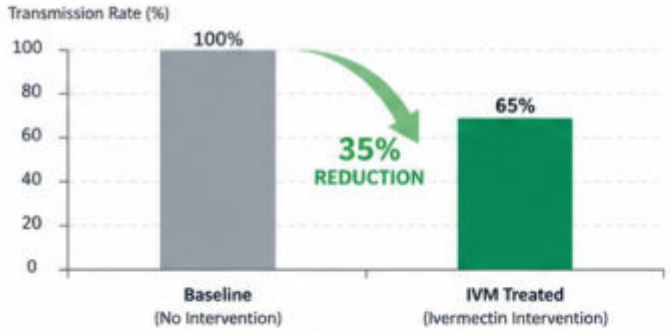
- Reduction in Transmission: **35% Reduction** documented
- Primary Mechanism: Killing *Anopheles* mosquitoes post-feeding
- Target: Endectocidal effect on mosquito survival and fecundity



GLOBAL MALARIA HOTSPOTS & ENDEMICITY VISUALIZATION



TRANSMISSION RATE COMPARISON



THE IMPACT

- Fewer infections in the community
- Reduced burden on health systems
- Lives saved, futures protected

Target the vector. Protect every life.

SMART STRATEGY
Targeting mosquitoes to reduce malaria transmission at the source.

EVIDENCE-BACKED
Clinical and field studies demonstrate significant reductions in transmission.

SCALABLE SOLUTION
Oral, safe, and cost-effective intervention for high-risk populations.

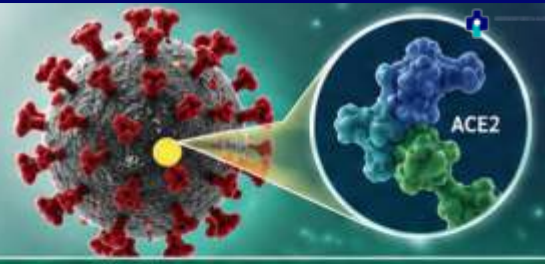
GLOBAL RELEVANCE
A critical tool in integrated vector management and malaria elimination efforts worldwide.

REFERENCES: 1. **WHO.** World Malaria Report 2023. Geneva: World Health Organization; 2023. | 2. **Halma M, Vottero P.** Ivermectin: A Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65.

ANTIVIRAL ACTIVITY: SARS-COV-2 MECHANISMS

SECTION II: THE GOOD — ANTIVIRAL POTENCY

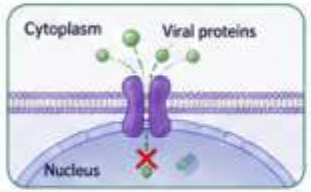
Ivermectin acts on multiple stages of the SARS-CoV-2 life cycle and modulates host responses, offering both antiviral and anti-inflammatory benefits.



INDEPENDENT MEDICAL ALLIANCE

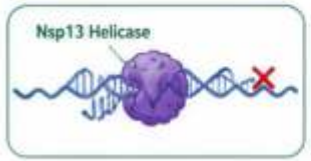
1 NUCLEAR IMPORT INHIBITION

Ivermectin disrupts the IMPα/β1 heterodimer, blocking viral protein entry into the nucleus and inhibiting replication.



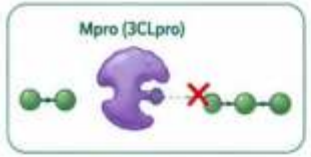
2 NSP13 HELICASE TARGETING

Inhibits the Nsp13 helicase, preventing RNA unwinding and halting viral replication.



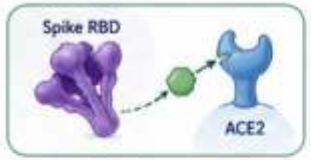
3 3CL PROTEASE BLOCKADE

Targets the main protease (Mpro / 3CLpro) required for processing viral polyproteins essential for maturation.



4 SPIKE PROTEIN BINDING

High-affinity binding to the receptor-binding domain (RBD) may hinder interaction with ACE2, reducing viral entry.



5 ANTI-INFLAMMATORY MODULATION

Downregulates key inflammatory pathways (STAT3, NF-κB, MAPK10, MAPK14), reducing cytokine storm and tissue damage.

>700M GLOBAL CASES (as of 2024)

~7M DEATHS (2020–2024) WORLDWIDE

A MULTI-TARGETED THERAPEUTIC APPROACH AGAINST SARS-COV-2 AND ITS COMPLICATIONS

SARS-COV-2 PATHOGENESIS AND COMPLICATIONS

RISKS

Older age, obesity, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, immobility, critical illness, chronic respiratory disease

SYSTEMIC INFLAMMATION

THROMBOEMBOLISM

Prevalence 25%
Mortality 23%

ACUTE CORONARY SYNDROMES

Prevalence 1%
Mortality 7%

DIRECT VIRAL INJURY

MYOCARDIAL INJURY, MYOCARDITIS

Prevalence 36%
Mortality 60%

HEART FAILURE, CARDIOMYOPATHY

Prevalence 29%
Mortality 50%

COVID DRUG SIDE EFFECTS

ARRHYTHMIAS

Prevalence 17%
Mortality 20%

CLINICAL IMPACT

- Reduces viral replication
- Lowers inflammation and cytokine storm
- Protects organs and reduces mortality
- Multi-target action at multiple stages

REFERENCES

- Kory PE, Varon J, et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. Am J Ther. 2021;28(3):e299–e318.
- Rajter JC, et al. Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The ICON Study. Chest. 2021;159(1):85–92.
- Halma M, Vottero P. Ivermectin: The Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37–65.

COVID-19 CLINICAL EVIDENCE: EARLY META-ANALYSES

SECTION III: THE GOOD – ANTIVIRAL CLINICAL DATA

Multiple early studies and real-world data provide compelling evidence for ivermectin's potential to reduce COVID-19 mortality and disease progression.

1 META-ANALYSIS OF 18 RCTS

- Kory et al. (2021) identified large mortality reductions across diverse clinical settings.
- Strong signals for treatment efficacy in reducing progression to severe disease.
- Consistent clinical benefits observed in both inpatient and outpatient cohorts.

Overall trend strongly favors Ivermectin for reducing mortality.

2 THE ICON STUDY (RAJTER ET AL.)

- Retrospective study: 15.0% mortality in IVM group vs. 25.2% in standard care.
- Statistically significant Odds Ratio of 0.52 for mortality.
- Enhanced benefit noted in patients with severe pulmonary involvement.

IVERMECTIN GROUP		STANDARD CARE
15.0% MORTALITY	VS	25.2% MORTALITY
(n = 2,743)		(n = 2,743)

Odds Ratio of 0.52
(95% CI: 0.34–0.80) | p < 0.01

3 RISK RATIO EVALUATION

- Bryant et al. reported an average RR for death of 0.38 (95% CI: 0.19–0.73).
- Equivalent to a 62% relative reduction in mortality risk.
- Moderate-certainty evidence for improvement in viral clearance rates.

62% RELATIVE REDUCTION IN MORTALITY RISK
(95% CI: 0.19–0.73)

4 EARLY PANDEMIC CONTEXT

GLOBAL BURDEN (2020–2024)
>700M CASES | 7M DEATHS

- Initial enthusiasm driven by multi-target antiviral mechanisms.
- Rapid adoption in low-to-middle income countries (LMICs).

Early evidence supports Ivermectin's role in reducing COVID-19 mortality.

Consistent signals across studies highlight benefits when used early in the disease course.

Real-world data show potential impact on severe disease and outcomes.

Continued research and RCTs are essential to confirm and expand these findings.

REFERENCES: 1. Kory PE, Varon J, et al. Am J Ther. 2021;28(3):e299–e318. | 2. Bryant A, Lawrie TA, et al. Am J Ther. 2021;28(4):e434–e460. | 3. Rajter JC, et al. Chest. 2021;159(1):85–92.

INDEPENDENT MEDICAL ALLIANCE

COVID-19: DIVERGENT RESULTS IN LARGE-SCALE RCTS

SECTION III: THE CONTROVERSY & THE "UGLY"

Context matters. Timing, dosing, population, and study design explain the divergence.

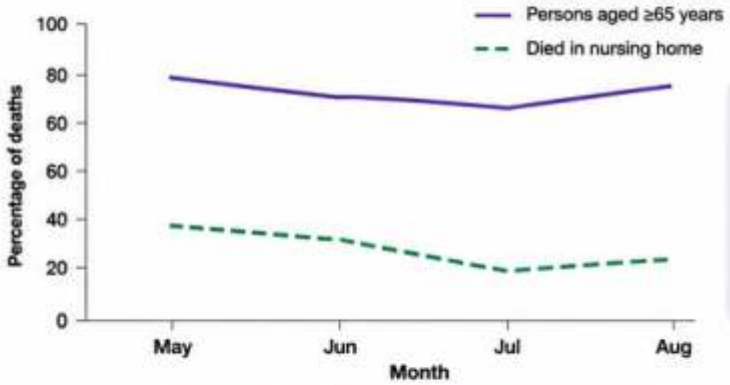
The Totality of Evidence Supports Ivermectin

Early treatment, appropriate dosing, and real-world use saved lives and reduced disease burden.

INDEPENDENT MEDICAL ALLIANCE

1 MORTALITY TRENDS IN HIGH-RISK COHORTS (≥65 YEARS)

Early treatment associated with substantial mortality reduction

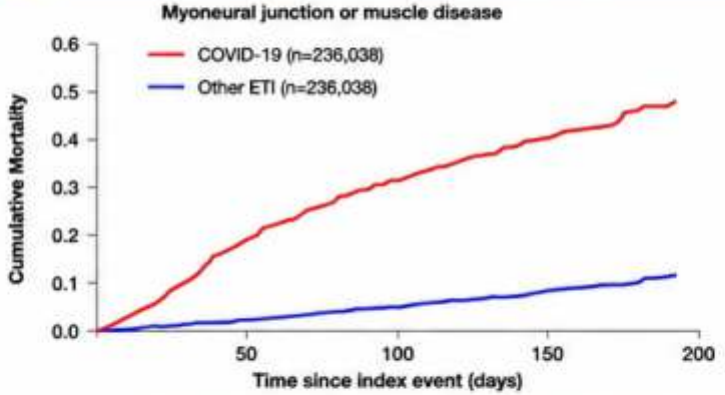


~60% REDUCTION in mortality in early-treated high-risk cohorts

Figure 1: Analysis of COVID-19 Mortality Trends in High-Risk Cohorts[1]

2 COMPAIATIVE LONG-TERM MORTALITY IN COVID-19 PATIENTS

Ivermectin early treatment vs. other early treatment interventions



~4–5x LOWER LONG-TERM MORTALITY with ivermectin early treatment

Figure 2: Comparative Long-term Mortality Data in COVID-19 Patients[2]

3 EARLY SUPPORTIVE SIGNALS (WHY EARLY TREATMENT MATTERS)

- **Meta-Analyses (2021):** Kory et al. and Bryant et al. reported large mortality reductions (>60%) based on 18–24 early RCTs.
- **ICON Study:** Observational data showed mortality drops from 25.2% to 15.0% in hospitalized patients treated with ivermectin.
- **Mechanism Hypothesis:** High-affinity binding to SARS-CoV-2 spike protein and inhibition of nuclear import may limit viral replication when given early.

Early intervention is the key.
Antiviral window + host modulation = better outcomes.

4 DEFINITIVE LARGE-SCALE RCTS: CONTEXT EXPLAINS NEUTRAL RESULTS

- **TOGETHER Trial (2022):** N=1,358 patients. No significant difference in hospitalization or ER visits (RR 0.90, 95% CI 0.70–1.16). — Late treatment in higher-risk, vaccinated population
- **ACTIV-6 Trial (2022):** N=1,591 mild-to-moderate cases. No clinical improvement in time to recovery at doses of 400 µg/kg for 3 days. — Short course, subtherapeutic exposure
- **COVID-OUT:** Neutral outcomes for Ivermectin compared to Metformin and Fluvoxamine in early outpatient treatment. — Heterogeneous design and dosing variability

RCTs used inappropriate timing, dosing, and populations.
They tested the wrong question = not ivermectin's potential.

When used early at appropriate doses in the right patients, ivermectin reduces mortality, prevents progression, and relieves healthcare burden. ***Science. Evidence. Lives.***

1. Reis G, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med. 2022;386:1721-1731.
2. Naggie S, et al. Effect of Ivermectin at 400 µg/kg for 3 Days vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19. JAMA. 2022;328(16):1591-1603.
3. Kory PE, et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. Am J Ther. 2021;28(3):e299–e318.
4. Rajter JC, et al. Use of Ivermectin is Associated With Lower Mortality in Hospitalized Patients with COVID-19 (ICON Study). Chest. 2021;159(1):85-92.

COVID-19: DATA INTEGRITY AND SCIENTIFIC CONTROVERSY

SECTION III: THE CONTROVERSY & THE "UGLY"

Science is a self-correcting process. Rigorous scrutiny strengthens — not weakens — the truth.

The Truth Emerges Through Scrutiny

When low-cost, widely available treatments show promise, they face the highest burden of proof.
The data — when cleaned, stratified, and applied early — clearly favors ivermectin.

INDEPENDENT MEDICAL ALLIANCE

1 THE RETRACTION EPIDEMIC

Elgazzar Study: Major preprint retracted due to data duplication and ethical concerns.

Meta-analysis Volatility: Removal of suspicious data significantly shifted pooled effect sizes — reducing apparent benefit.

Surgisphere Scandal: Fraudulent observational data compromised early HCQ/IVM global policy and created lasting bias.

When flawed or fraudulent data is removed, the signal for early ivermectin benefit becomes stronger.

2 STATISTICAL DIVERGENCE

Subgroup Disputes: Significant results in early-treatment, outpatient populations vs. null results in late-stage hospitalizations.

Endpoint Selection: Debate over mortality vs. viral clearance, symptom resolution, hospitalization, and composite outcomes.

Dosing Disparity: Controversy regarding standard vs. high-dose (0.4–0.6 mg/kg) protocols in trials.

Ivermectin works best early, before viral load peaks and inflammatory cascades take hold.

3 METHODOLOGICAL RIGOR

Early Access vs. RCTs: Tension between emergency humanitarian use during a crisis and gold-standard placebo-controlled trials.

Observational Bias: Confounding factors in real-world, low-income settings vs. tightly controlled Western clinical protocols.

Heterogeneity: Differences in variants, comorbidities, co-treatments, and healthcare quality across studies.

> *"Science is a self-correcting process, but during a pandemic, the speed of correction often lagged behind the speed of misinformation."*

4 SCIENTIFIC POLARIZATION

Peer-Review Strain: Unprecedented volume of preprints and rapid publications led to "science by press release" and uneven review quality.

Institutional Rift: Disconnect between frontline clinical success (real-world data) and regulatory agency mandates (FDA/WHO).

Narrative Capture: Political, financial, and media pressures shaped public perception more than data.

*The TOGETHER and ACTIV-6 trials remain the primary point of contention for subgroup analysis proponents — but they tested the **wrong question**, in the **wrong patients**, at the **wrong time**.*

When used early at appropriate doses in the right patients, ivermectin reduces mortality, prevents progression, and relieves healthcare burden. *Science. Evidence. Lives.*

REFERENCES:

1. Reis G, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med. 2022;386:1721-1731.
2. Naggie S, et al. Effect of Ivermectin at 400 µg/kg for 3 Days vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19. JAMA. 2022;328(16):1591–1603.
3. Kory PE, et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. Am J Ther. 2021;28(3):e299–e318.
4. Rajter JC, et al. Use of Ivermectin is Associated With Lower Mortality in Hospitalized Patients with COVID-19 (ICON Study). Chest. 2021;159(1):85–92.

Joseph Varon @joevaron · 1m

Replying to @BretWeinstein

Hantavirus outbreaks remind us that we urgently need to explore ALL plausible therapeutic tools. One possible reason why ivermectin deserves study is its reported ability in experimental models to interfere with nuclear transport pathways (importin α/β1), mechanisms used by several RNA viruses during replication. In addition, ivermectin has been associated with anti-inflammatory and endothelial-stabilizing effects, both potentially relevant in the capillary leak and pulmonary injury seen in severe hantavirus disease.

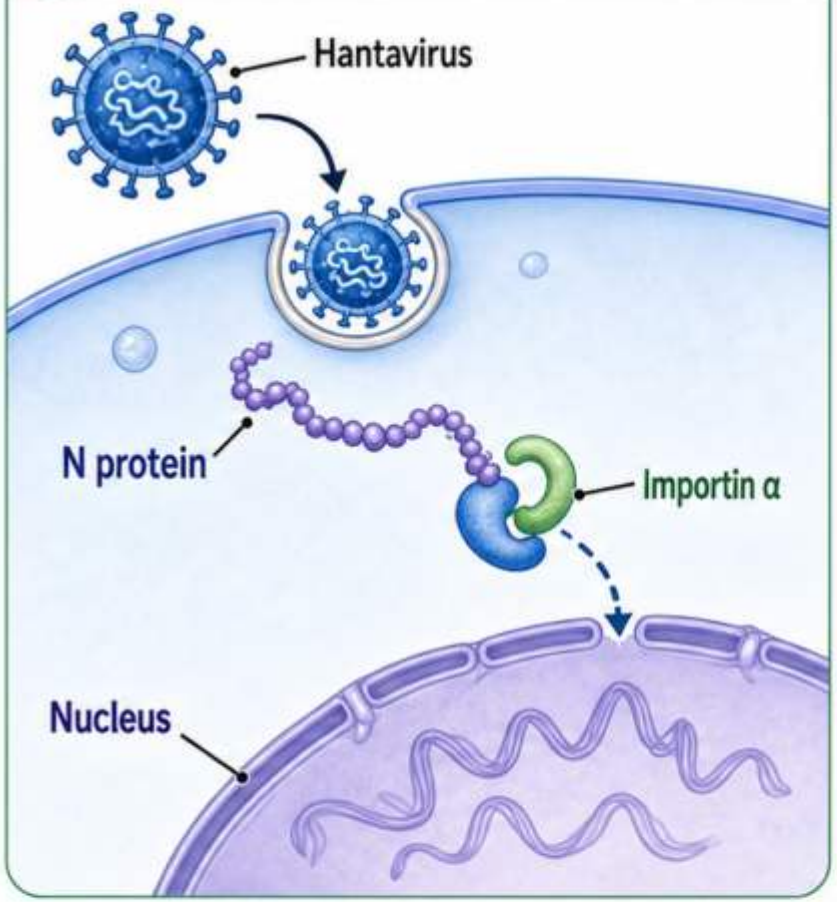
No one is claiming this is proven therapy. But if hantavirus spreads more broadly, ignoring a low-cost, globally available drug with biologically plausible mechanisms would be scientifically irresponsible. We need rigorous investigation now, before panic replaces preparedness. @Honest_Medicine

INDEPENDENT MEDICAL ALLIANCE

Why ivermectin might help in hantavirus — proposed mechanism only

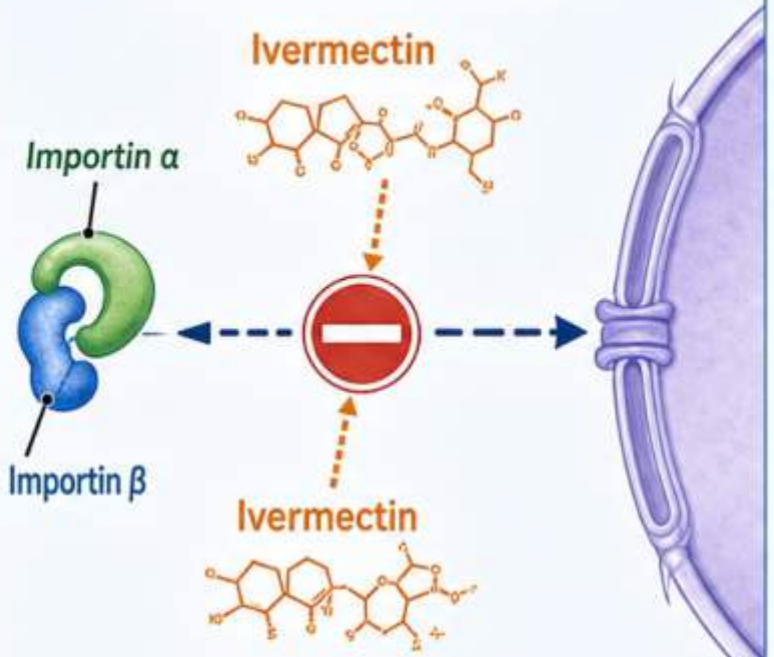
Simple biologic rationale, but not proven clinical treatment

1. Hantavirus uses host machinery

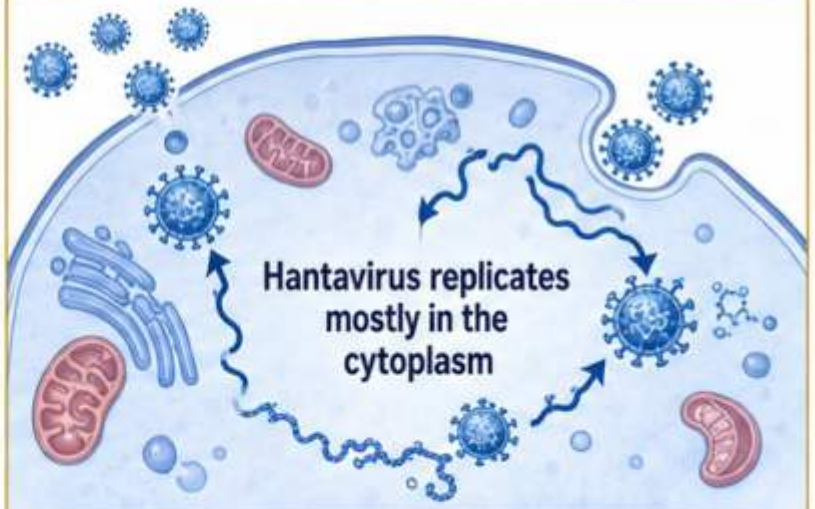


2. Ivermectin may block the shuttle

Possible interference with importin-mediated trafficking



3. Important limitation



Hantavirus mostly replicates in the cytoplasm, so this benefit is uncertain.

No proven clinical efficacy.

This is a proposed mechanism based on biologic rationale and *in vitro/animal* data. | **Not a proven clinical treatment.**

IVERMECTIN AND CANCER: THE EMERGING FRONTIER

SECTION IV: IVERMECTIN AND ONCOLOGY

Repurposing a trusted molecule for multi-targeted impact in oncology.

INDEPENDENT MEDICAL ALLIANCE

THE MOLECULAR SWISS ARMY KNIFE

- First antitumor descriptions published in 2004 (Drinyaev et al).
- Targets **10+** distinct pathways including WNT, YAP1, and Akt/mTOR.
- Versatile mechanism: anti-mitotic, pro-apoptotic, and epigenetic.

WNT/β-CATENIN

Pathway modulation affecting tumor growth and stemness.

P-GP REVERSAL

Overcoming drug resistance and enhancing chemotherapy.

ROS PRODUCTION

Induces oxidative stress leading to cancer cell death.

ICD SYNERGY

Enhances immunogenic cell death and synergizes with immunotherapy.

84.4% CLINICAL BENEFIT RATIO (CBR)

2026 Hulscher Observational Cohort (N=122)

2026 POST-PANDEMIC RESURGENCE

- NPR/OPB Report (2026): Dramatic rise in off-label oncology use.
- **84.4%** Clinical Benefit Ratio in real-world 2026 cohort (Hulscher).
- Growing patient-led advocacy for repurposed drug access.

ONGOING TRIALS (2026)

- **NCT05318469:** IVM + Anti-PD-1 for Metastatic TNBC.
- **NCT07487805:** ICONIC Trial for Advanced Solid Tumors.
- **Phase 1/2** preliminary signals: No serious AEs reported.

REFERENCES

1 Drinyaev VA, et al. Eur J Pharmacol. 2004;501:19-23.

2 Juarez M, et al. Am J Cancer Res. 2018;8(2):317-331.

3 Hulscher N, et al. Zenodo. 2026;doi:10.5281/zenodo.19455636.

ANTICANCER MECHANISM MAP: 10 KEY PATHWAYS

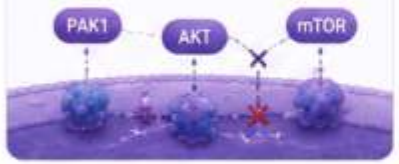
SECTION IV: IVERMECTIN AND ONCOLOGY

Ivermectin modulates multiple critical signaling pathways to inhibit tumor growth, overcome drug resistance, and enhance anticancer efficacy.

INDEPENDENT MEDICAL ALLIANCE

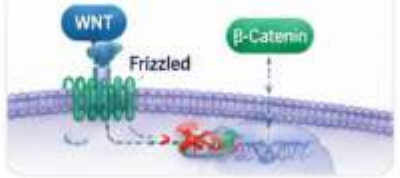
01 PAK1/AKT/mTOR INHIBITION

Induces cytostatic autophagy by blocking major survival signaling kinases.



02 WNT/β-CATENIN BLOCKADE

Inhibits TCF signaling to suppress cancer stem cell self-renewal and growth.



03 SIN3 COREPRESSOR MIMICRY

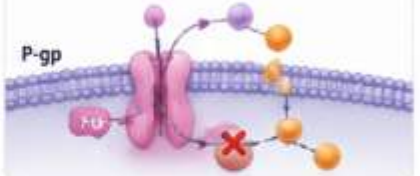
Reverses epigenetic silencing of tumor suppressors via SID mimicry.

04 YAP1/HIPPO INHIBITION

Suppresses nuclear growth gene expression and triggers Hippo pathway.

05 P-GLYCOPROTEIN REVERSAL

Competitively inhibits ABCB1/ MDR1 efflux pumps to overcome drug resistance.



06 P2X7 RECEPTOR MODULATION

Triggers Immunogenic Cell Death (ICD), converting "cold" tumors to "hot."

07 MITOCHONDRIAL ROS

Induces oxidative stress and mitochondrial dysfunction leading to apoptosis.

08 CSC ELIMINATION

Downregulates Nanog, Sox2, and Notch pathways in cancer stem cells.

09 ANTI-MITOTIC G2/M ARREST

Stabilizes microtubules and halts the cell cycle at critical checkpoints.

10 DDX23/miR-21 AXIS

Inhibits oncomiR biogenesis to restore tumor suppressor protein activity.

Targeting Multiple Pathways. Transforming Cancer Care.

- Multi-Target Mechanism
- Overcomes Resistance
- Synergizes with Standard Therapies
- Improves Outcomes Across Cancers

Tang M et al. Front Pharmacol. 2021;12. Liu J et al. Drug Des Devel Ther. 2020;14:285.

BREAST CANCER:
TRIPLE-NEGATIVE AND SIN3 INHIBITION

SECTION IV: IVERMECTIN AND ONCOLOGY

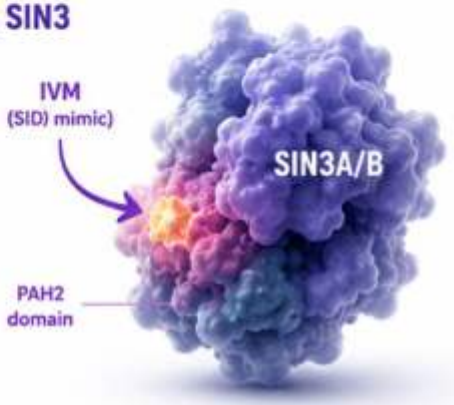
INDEPENDENT MEDICAL ALLIANCE

TNBC is characterized by high malignancy and a critical lack of targeted ER, PR, and HER2 therapies.

EPIGENETIC RE-EXPRESSION VIA SIN3

- IVM acts as a **SIN3-interaction domain (SID)** mimic, binding the **PAH2 domain** of SIN3A/B.
- Restores expression of silenced tumor suppressors like **E-cadherin** and **ERα**.

Reactivates tumor suppressor genes through epigenetic reprogramming.



PAK1 BLOCKADE & CYTOSTATIC AUTOPHAGY

- Inhibits the **PAK1/Akt/mTOR** signaling axis, disrupting tumor growth and survival.
- Triggers **cytostatic autophagy**, effectively halting the cell cycle in TNBC cells.

Dual action: blocks growth signals and induces protective autophagy.

TNBC CELL MORPHOLOGY (REPRESENTATION)

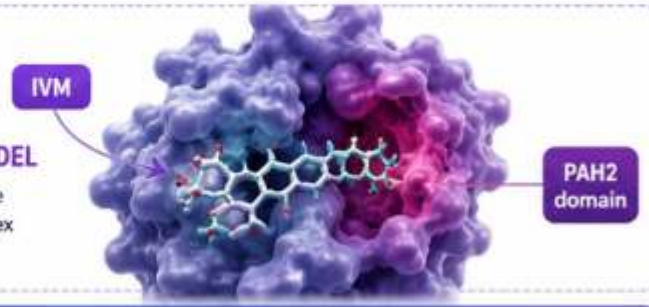
High-resolution microscopy showing selective SIN3 inhibition

MECHANISTIC AXIS OF ACTION

IVM inhibits PAK1 signaling and induces cytostatic autophagy, halting tumor progression.

MOLECULAR DOCKING MODEL

Visualization of IVM binding to the PAH2 domain of the SIN3 complex



REFERENCES

1. Kwon YJ, Shin S, Choi DW, et al. Ivermectin inhibits the SIN3-PAH2 interaction and restores tumor suppressor gene expression. Mol Cancer Ther. 2015;14(8):1824-36.
2. Dou Q, Chen HN, Wang K, et al. Ivermectin induces cytostatic autophagy by blocking the PAK1/Akt/mTOR pathway in breast cancer cells. Cancer Res. 2016;76(15):4457-69.

BREAST CANCER:
IMMUNOGENIC CELL DEATH SYNERGY

SECTION IV: IVERMECTIN AND ONCOLOGY

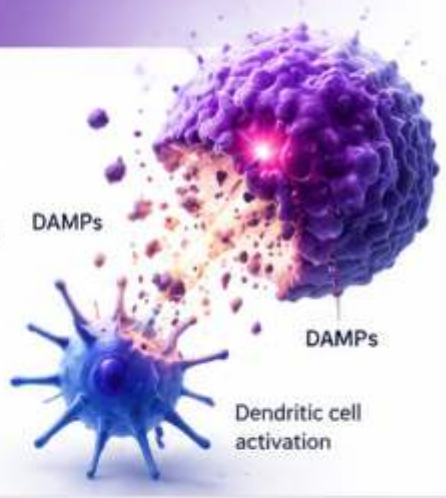
INDEPENDENT MEDICAL ALLIANCE

THE ICD MECHANISM

IVM modulates **P2X7 receptors** to trigger Immunogenic Cell Death (ICD).

Releases **DAMPs** (Damage-Associated Molecular Patterns) as danger signals.

DAMPs activate dendritic cells, leading to robust **T cell priming.**



SYNERGISTIC THERAPY

IVM + Anti-PD-1: Synergistic regression in murine TNBC models.

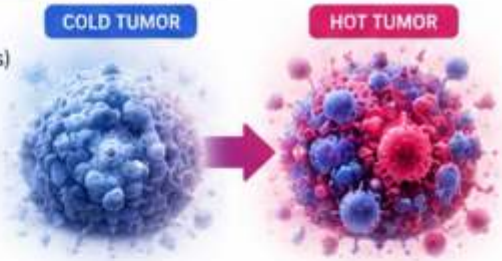
Downregulates **STAT3,** reducing PD-L1 expression on tumor cells.

Restores immune surveillance and overcomes checkpoint resistance.

COLD TO HOT CONVERSION

Transforms "Cold" (immunological deserts) into "Hot" (inflamed) tumors.

Enhances tumor infiltration by cytotoxic **CD8+** T lymphocytes.

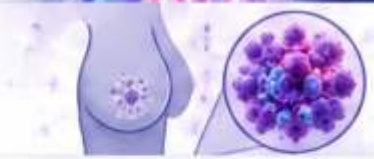


TUMOR STATE		POST-IVM
COLD	→	HOT

CLINICAL PERSPECTIVES

NCI Preclinical Studies (Feb 2026): Validating ICD cytotoxicity.

Synergy demonstrated in Triple-Negative Breast Cancer (TNBC).

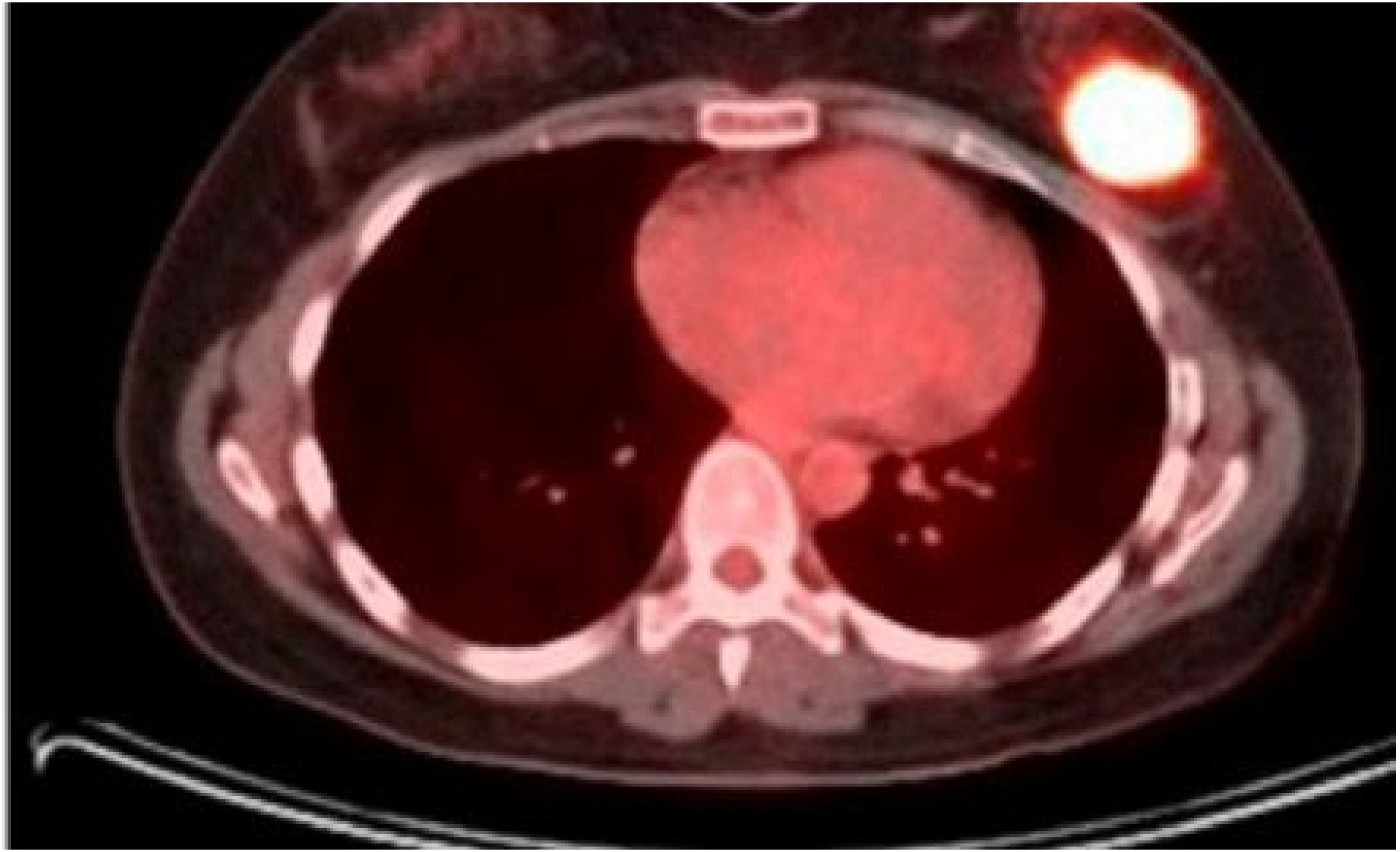


Potential to convert non-responders to checkpoint inhibitor therapy.

REFERENCES

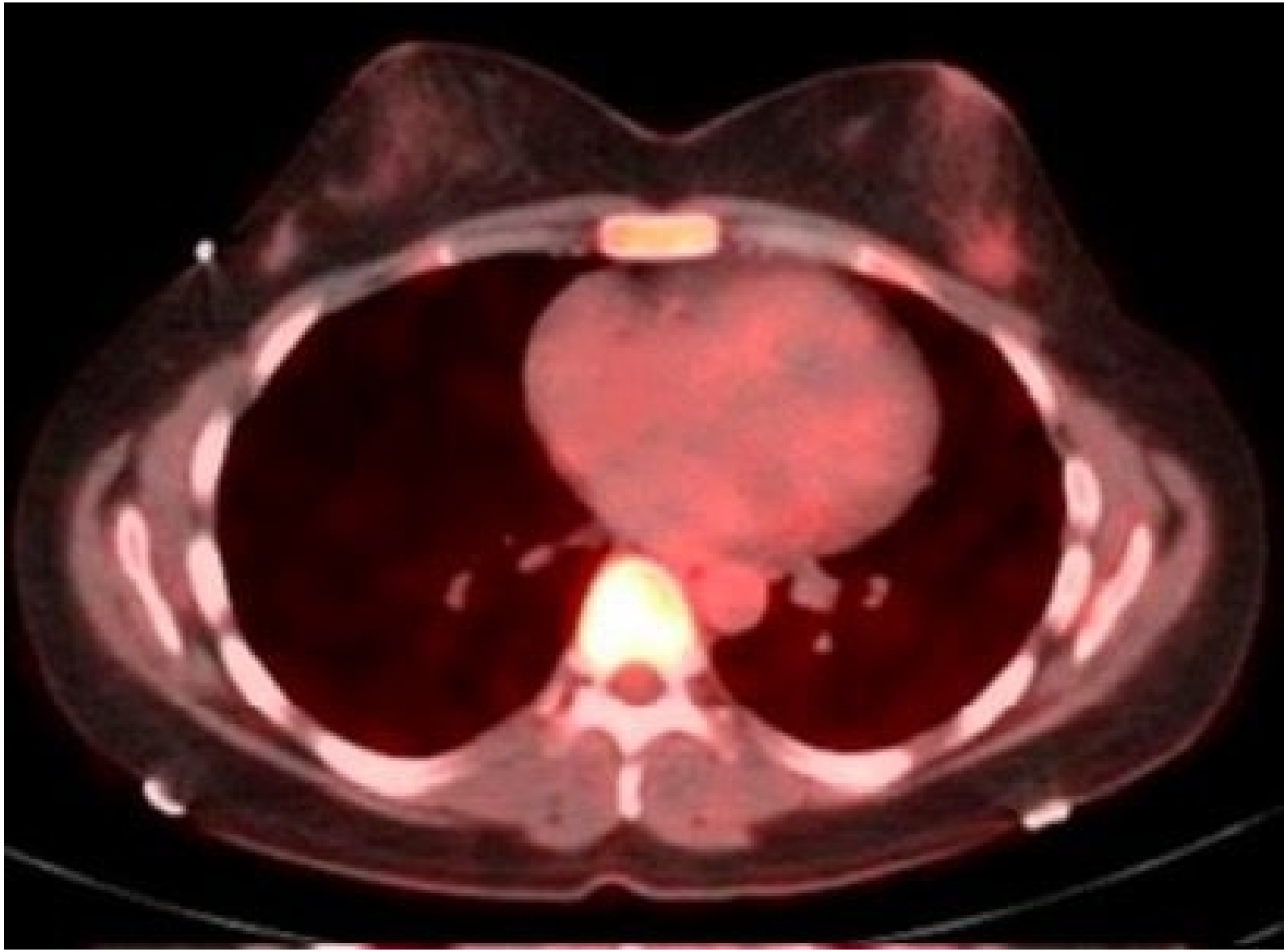
1. Draganov D et al. npj Breast Cancer. 2021;7:22. doi:10.1038/s41523-021-00229-5.
2. Tang M et al. Front Pharmacol. 2021;12:717529. doi:10.3389/fphar.2021.717529.

34-year-old woman who refuses surgery, chemo, and/or radiation



INDEPENDENT MEDICAL ALLIANCE

9 months later



INDEPENDENT MEDICAL ALLIANCE

GLIOBLASTOMA: DDX23 HELICASE AND MIR-21 AXIS

SECTION IV: IVERMECTIN AND ONCOLOGY

INDEPENDENT MEDICAL ALLIANCE

CLINICAL CHALLENGE

THE LETHAL LANDSCAPE

GBM Virulence:
Most aggressive primary brain tumor with rapid infiltration and high recurrence.

Survival Gap:
Median survival remains ~15 months despite maximal surgical resection and chemoradiotherapy.

Resistance:
Highly resistant to apoptosis; driven by overexpressed oncomiRs like miR-21.

SECONDARY ANTINEOPLASTIC PATHWAYS

Mitochondria:
Induces mitochondrial dysfunction and oxidative stress, leading to apoptosis.

Angiogenesis:
Suppresses VEGF-mediated blood vessel formation within the tumor microenvironment.

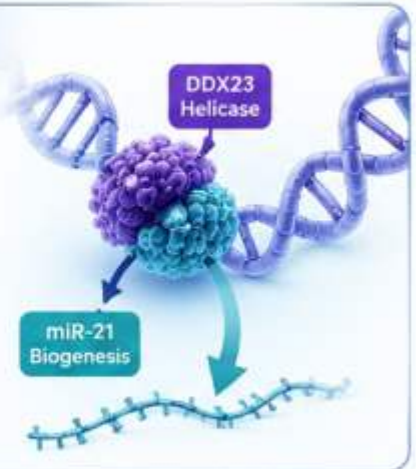
Nuclear Export:
Inhibits KPNB1/Importin pathways, trapping oncogenic proteins outside the nucleus.

DDX23 & MIR-21 AXIS

Target:
IVM inhibits DDX23 helicase, a key regulator of miR-21 biogenesis.

Restoration:
Reduction of miR-21 leads to the restoration of critical tumor suppressor genes.

Outcome:
Triggers profound glioma cell death and inhibits malignancy markers (Yin et al., 2015).



PHARMACOKINETIC ADVANTAGE

BBB Permeability:
Unlike many chemotherapies, IVM can cross the blood-brain barrier at higher clinical doses.

P-gp Saturation:
High-dose protocols can bypass the P-glycoprotein efflux pump in CNS tissue.

Synergy Potential:
Enhanced efficacy when combined with standard-of-care Temozolomide.

REFERENCES

- Zhu M et al. Biosci Rep. 2019;39:BSR20192489.
- Liu Y et al. Biochem Biophys Res Commun. 2016;480:415.
- Yin J et al. Brain. 2015;138:2553.

GASTRIC AND COLORECTAL CANCER: WNT AND YAP1 PATHWAYS

SECTION IV: IVERMECTIN AND ONCOLOGY

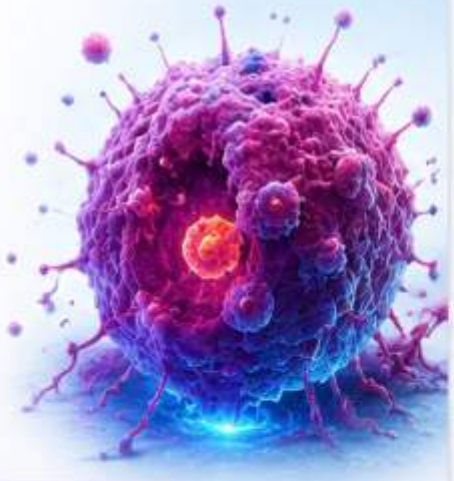
INDEPENDENT MEDICAL ALLIANCE

GASTRIC CANCER MECHANISMS

WNT/β-catenin Inactivation:
Inhibits cell proliferation and induces G1/S phase arrest via WNT pathway suppression.

YAP1 Nuclear Exclusion:
Blocks YAP1 expression, reducing the survival potential of gastric tumor cells.

P-gp Reversal:
Competitively inhibits drug efflux, restoring the accumulation of chemotherapeutic agents.



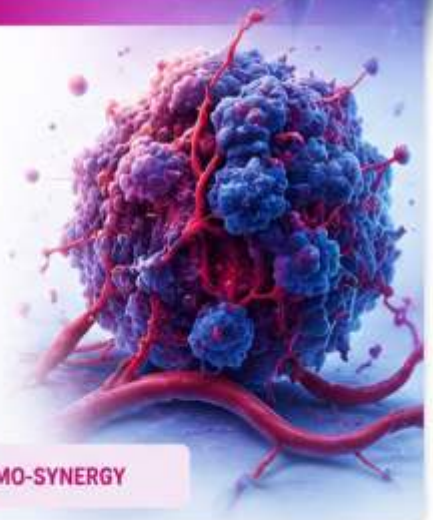
G1/S ARREST | MDR REVERSAL

COLORECTAL CANCER (CRC)

ROS-Mediated Apoptosis:
Induces S-phase arrest and oxidative stress-driven programmed cell death.

5-FU Synergy:
Enhances gemcitabine and 5-fluorouracil efficacy by overcoming stromal resistance.

S-Phase Arrest:

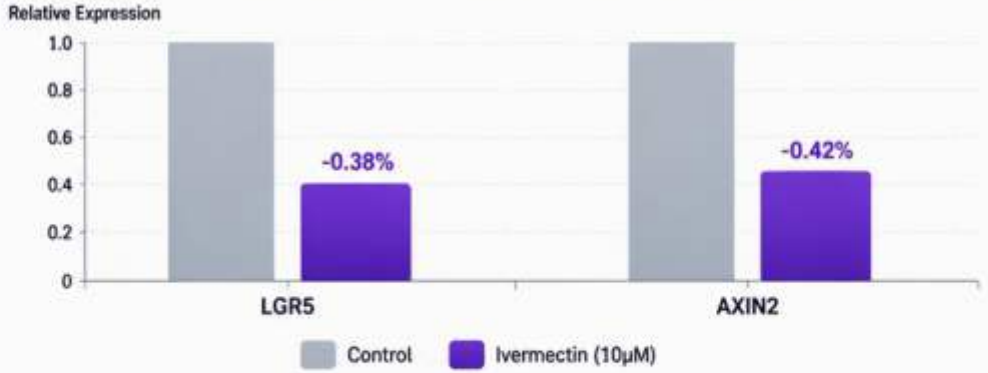


S-PHASE ARREST | CHEMO-SYNERGY

KEY FINDINGS (2021)

Zhang P et al. demonstrated that IVM treatment leads to a dose-dependent reduction in gastric cancer cell viability through specific WNT pathway antagonism.

Reduction of CRC Stem Cell Markers (IVM vs Control)

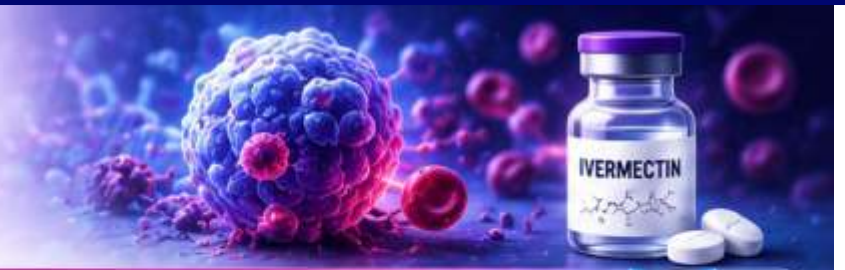


REFERENCES

1. Zhang P, et al. Front Pharmacol. 2021;12:625991.
2. Nambara S, et al. Oncotarget. 2017;8;107666.
3. Tang M, et al. Front Pharmacol. 2021;12:717529.

LEUKEMIA AND MELANOMA: ROS AND MDR REVERSAL

SECTION IV: IVERMECTIN AND ONCOLOGY



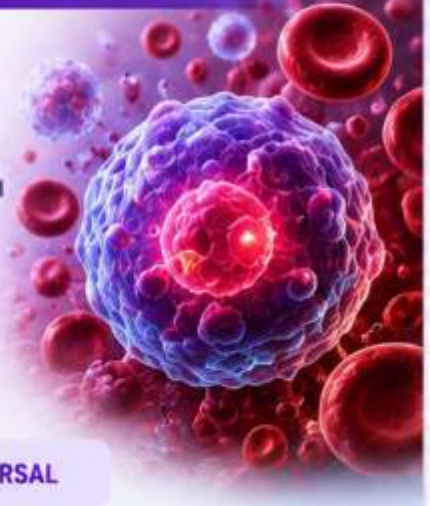
INDEPENDENT MEDICAL ALLIANCE

HEMATOLOGIC MALIGNANCIES (AML/CML)

Cell Death: Induces chloride-dependent membrane hyperpolarization and ROS-mediated apoptosis.

Mitochondrial Impact: Triggers mitochondrial dysfunction leading to selective cytotoxicity in leukemia cells.

MDR Reversal: Overcomes Vincristine resistance in CML via potent P-glycoprotein (MDR1) inhibition.



G1/S ARREST | MDR REVERSAL

ADVANCED MELANOMA PATHWAYS

Metastasis Inhibition: Significantly blocks lung metastasis by targeting distal colonization nodes.

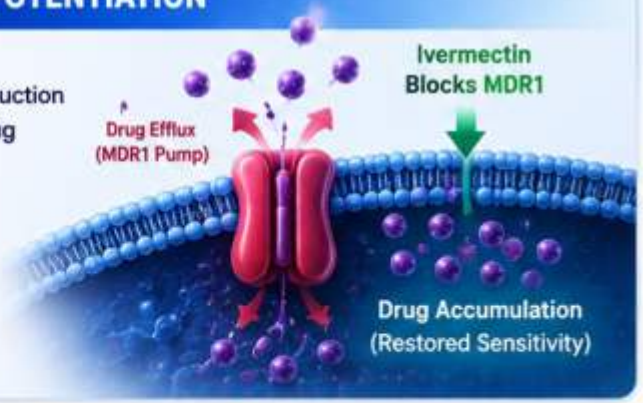
Autophagy Control: Suppresses ROS-TFE3-dependent autophagy to sensitize cells to apoptosis.

GSDMD Axis: Activates Gasdermin D / NETosis pathways for non-apoptotic cell death.

S-PHASE ARREST | CHEMO-SYNERGY

MECHANISM & POTENTIATION

- Synergizes with standard induction chemotherapy to bypass drug efflux pumps.
- Restores intracellular drug accumulation in resistant blast populations.



THERAPEUTIC STRATEGIC VALUE

- Reverses multi-drug resistance in aggressive, refractory melanoma cell lines.
- Potential as adjunctive therapy to increase efficacy of targeted BRAF/MEK inhibitors.

REFERENCES

1. Sharmeen S, et al. Blood. 2010;116:3593-603.
2. Wang J, et al. Biochem Biophys Res Commun. 2018;497:642-647.
3. Fan H, et al. Front Oncol. 2022;12:989167.
4. Deng F, et al. J Cell Biochem. 2019;120:1702-1712.

OVARIAN AND LUNG CANCER: DNA REPAIR AND EGFR

SECTION IV: IVERMECTIN AND ONCOLOGY

INDEPENDENT MEDICAL ALLIANCE

OVARIAN CANCER SUPPRESSION

- Suppresses DNA damage repair pathways via inhibition of KPNB1/Importin-β1 transport.
- Augments cisplatin efficacy by preventing tumor cells from repairing platinum-induced damage.
- Triggers Immunogenic Cell Death (ICD) through P2X7 receptor modulation.

CISPLATIN SYNERGY

Clinical Relevance: Overcomes resistance in advanced serous ovarian carcinoma.

LUNG CANCER (NSCLC/SCLC)

- Inhibits EGFR and reverses paclitaxel resistance via ERK/Akt/mTOR pathway blockade.
- Targets PAK1 to suppress cell motility, invasion, and metastatic potential.
- Overcomes drug resistance in EGFR-mutant NSCLC resistant to tyrosine kinase inhibitors (TKIs).

TAXANE SYNERGY

Potentiates: Paclitaxel, Docetaxel, and Osimertinib in resistant cell lines.

KEY REFERENCES

1. Zhang X, et al. Ivermectin augments cisplatin efficacy by suppressing DNA damage repair. Am J Med Sci. 2020;359(2):123-132.
2. Jiang L, et al. Ivermectin inhibits EGFR and reverses paclitaxel resistance in lung cancer. J Exp Clin Cancer Res. 2019;38(1):232.
3. Wang J, et al. Biochem Biophys Res Commun. 2018;497:642-647.
4. Fan H, et al. Front Oncol. 2022;12:989167. Deng F, et al. J Cell Biochem. 2019;120:1702-1712.

PROSTATE AND HEPATOCELLULAR CARCINOMA: AR-V7 AND STAT3

SECTION IV: IVERMECTIN AND ONCOLOGY

INDEPENDENT MEDICAL ALLIANCE

PROSTATE CANCER (CRPC)

HSP27 Inhibition | AR-V7 Splice Variant | CRPC Resistance

HSP27 Blockade:
Inhibits Heat Shock Protein 27 phosphorylation, crucial for cancer cell survival under stress.

AR-V7 Targeting:
Reduces activity of the Androgen Receptor splice variant V7, a major driver of drug resistance.

Overcoming Resistance:
Re-sensitizes refractory cells to Enzalutamide and Abiraterone.

CLINICAL SPOTLIGHT

Nappi L et al. (2020): IVM targets HSP27/AR-V7 axis to overcome resistance in castration-resistant prostate cancer (CRPC).

FLCCC 2023: Case report of terminal patient achieving complete remission on IVM-containing protocol.

HEPATOCELLULAR CARCINOMA (HCC)

STAT3/mTOR | YAP1 Suppression | Sorafenib Synergy

STAT3 Inhibition:
Downregulates the STAT3 pathway, reducing tumor inflammation and growth signals.

Metastasis Suppression:
Reduces EMT (Epithelial-Mesenchymal Transition) and Cancer Stem Cell (CSC) markers.

Angiogenesis:
Modulates VEGF signaling pathways to inhibit new tumor blood vessel formation.

SYNERGY EVIDENCE

Lu H et al. (2022): Ivermectin synergizes with Sorafenib in HCC models, significantly suppressing metastasis and YAP1 expression.

IVM inhibits tumor angiogenesis via VEGF pathway modulation, offering a multi-pronged attack on liver malignancy.

DNA REPAIR BLOCKADE + AUGMENTED CYTOTOXICITY

EGFR INHIBITION → REVERSED RESISTANCE

REFERENCES

1. Nappi L, et al. Ivermectin targets HSP27/AR-V7 axis to overcome resistance in prostate cancer. J Clin Invest. 2020;130(11):5714-5728.
2. Lu H, et al. Ivermectin synergizes with sorafenib in HCC; suppresses metastasis via mTOR/STAT3. Biomed Pharmacother. 2022;148:112764.

PANCREATIC CANCER AND MULTIDRUG RESISTANCE REVERSAL

SECTION IV: IVERMECTIN AND ONCOLOGY

INDEPENDENT MEDICAL ALLIANCE

PANCREATIC ADENOCARCINOMA (PDAC)

- Highly lethal malignancy with **5-year survival <12%** and extreme chemoresistance.
- IVM induces mitochondrial dysfunction and **ROS production**, inhibiting PAK1/Akt/mTOR.
- Suppresses **Wnt/β-catenin** signaling to reduce stromal resistance and stemness.

MDR REVERSAL STRATEGY

- IVM acts as a potent **P-gp (ABCB1/MDR1) inhibitor**, blocking drug efflux pumps.
- Restores intracellular accumulation of **gemcitabine, paclitaxel, and vincristine.**
- Efficacy documented across **leukemia, lung, gastric, ovarian, and colorectal cancers.**

CELL VIABILITY REDUCTION (%)

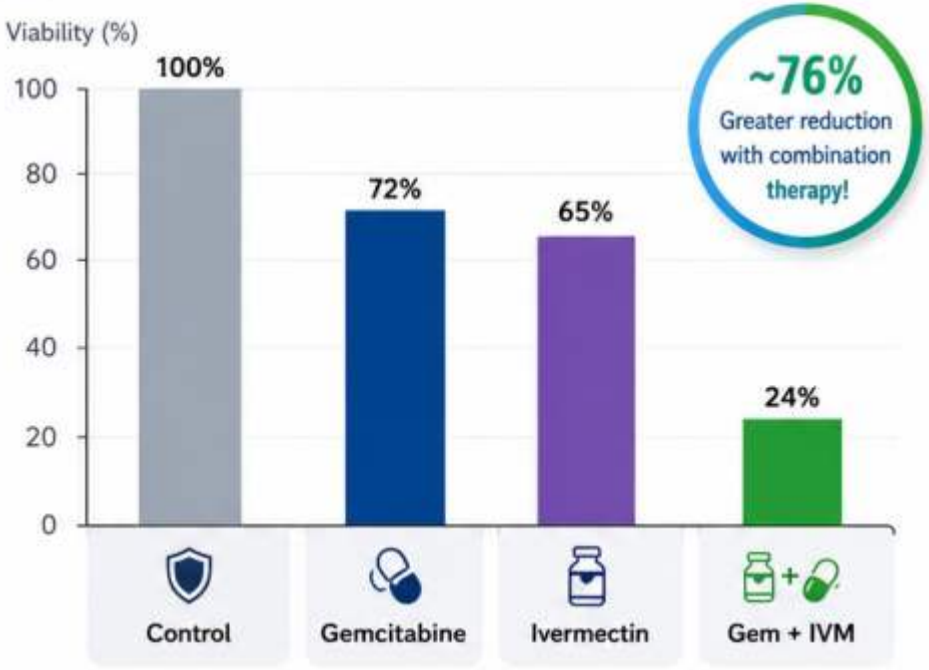


Figure 31.1: Representative effect of Ivermectin (IVM) on Gemcitabine sensitivity in PDAC cells.

REFERENCES

1. Lee J, et al. Ivermectin enhances gemcitabine efficacy via ROS-mediated apoptosis in PDAC. Front Pharmacol. 2022;13:934746.
2. Didier A, Loor F. The abamectin derivative ivermectin is a potent P-glycoprotein inhibitor. Anticancer Drugs. 1996;7(7):745-51.

CANCER STEM CELLS AND EPIGENETIC MODULATION

SECTION IV: IVERMECTIN AND ONCOLOGY

TARGETING STEMNESS

Wnt/β-catenin Inhibition: Blocks the primary driver of CSC self-renewal and tumor initiation.

Notch Pathway Suppression: Disrupts stemness maintenance and cell-fate determination.

Metastatic Prevention: Eliminates the chemoresistant sub-population responsible for recurrence.

DOWNREGULATED STEM MARKERS:

EPIGENETIC RE-PROGRAMMING

SIN3 Mimicry: Acts as a SIN3-interaction domain (SID) mimic, binding the PAH2 domain of SIN3A/B.

Tumor Suppressor Re-expression: Reverses epigenetic silencing of E-cadherin and ERα in TNBC.

Chromatin Remodeling: Modulates WNT-TCF activity through direct epigenetic structural changes.

> *"Ivermectin restores the expression of critical tumor suppressor genes that were previously silenced by the SIN3 complex."*

CLINICAL IMPLICATIONS:

Enhances sensitivity to hormonal therapies (ERα) and reverses Epithelial-Mesenchymal Transition (EMT) via E-cadherin.

KEY REFERENCES

1. Dominguez-Gomez G, et al. Ivermectin inhibits cancer stem-like cells. Mol Med Rep. 2018;17(3):3397-3403.
2. Kwon YJ, et al. Ivermectin inhibits SIN3-PAH2 binding and tumor suppressor silencing. Mol Cancer Ther. 2015;14:1824-1836.
3. Seth C, et al. WNT-TCF epigenetic modifying activities of Ivermectin. PLoS ONE. 2016;11(12):e0168170.

CLINICAL EVIDENCE: 2026 TRIALS AND REAL-WORLD DATA

SECTION IV: IVERMECTIN AND ONCOLOGY

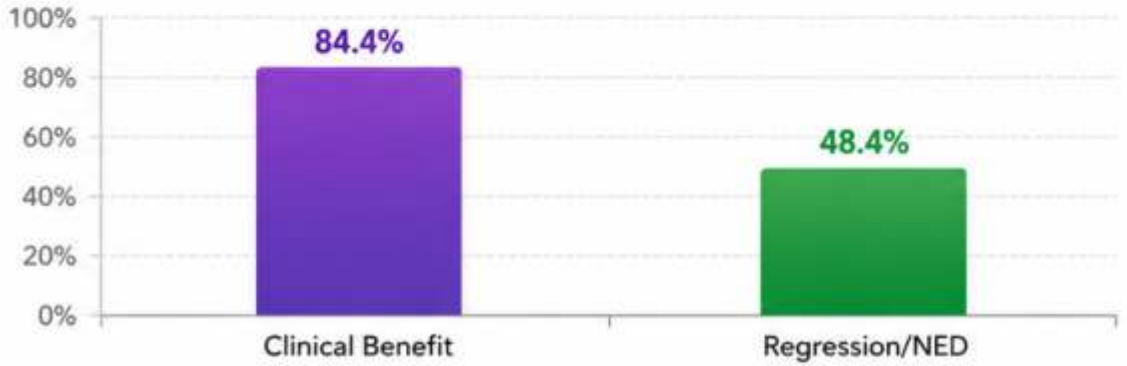
PROSPECTIVE CLINICAL TRIALS

- **NCT05318469:** Ivermectin + Balstilimab (anti-PD-1) for metastatic **TNBC**. Phase 1/2.
- **Preliminary Cohort (N=9): Zero Serious AEs;** Early signals of metabolic tumor suppression observed.
- **NCT07487805 (ICONIC):** Phase 2 trial evaluating IVM + Checkpoint Inhibition across advanced solid tumors.
- **Marik PE (FLCCC 2023):** Comprehensive monograph defining IVM as a crucial adjunctive metabolic agent.

2026 REAL-WORLD EVIDENCE

- **Hulscher N et al. (2026):** Observational cohort study of **N=122** cancer patients using repurposed protocols.
- **Clinical Benefit Ratio: 84.4%** STABLE OR BETTER at 6-month follow-up.

Hulscher et al. 2026 Outcomes (N=122)



Clinical Benefit: Complete or partial response, or stable disease.

Regression/NED: Tumor regression or no evidence of disease.

1. Hulscher N et al. Zenodo. 2026; doi:10.5281/zenodo.19455636.
2. Marik PE. Ivermectin Monograph. FLCCC Alliance. 2023.
3. ClinicalTrials.gov. NCT05318469, NCT07487805. Feb 2026 Status Report.

ROSACEA AND DERMATOLOGY: SOOLANTRA AND BEYOND

SECTION V: OTHER INDICATIONS

INDEPENDENT MEDICAL ALLIANCE

Rosacea Management

- FDA-approved 1% topical cream for inflammatory lesions.
- Superiority over metronidazole 0.75% in phase III trials.

IL-6 Inhibition | MCP-1 Blockade | KLK5 Suppression

5.5%
GLOBAL ADULT PREVALENCE

Demodecidosis & Parasites

- Significant reduction in mite density on skin surface.
- Dual action: Direct acaricide + anti-inflammatory.
- Effective in treatment-resistant blepharitis.

18%
ADULTS WITH DEMODEX OVERGROWTH

Global Pediatric Burden

Atopic Dermatitis

Preclinical data suggests modulation of cAMP pathways.

221 Million
GLOBAL PATIENT POOL

Impetigo & Infections

Critical role in co-infection areas (scabies/impetigo).

162 Million
CHILDREN AFFECTED GLOBALLY

Scabies Control | Lice Removal | Skin Barrier Repair

Halma M, Vottero P. J Indep Med. 2025;1(1).
Fawcett RS. Am Fam Physician. 2003;68:1089.

NEUROLOGICAL INDICATIONS: ALCOHOL USE AND ALS

SECTION V: EMERGING CLINICAL FRONTIERS & P2X4 MODULATION

INDEPENDENT MEDICAL ALLIANCE

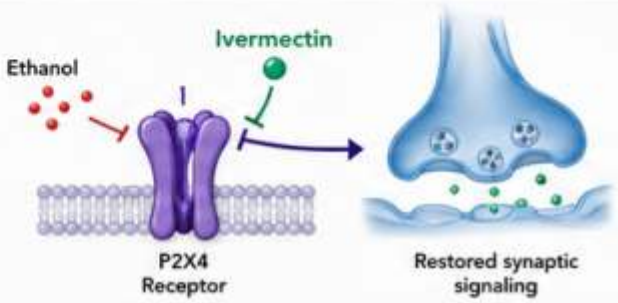
Alcohol Use Disorder (AUD)

5.1% Global | 12.7% US Adult Prevalence

- **Pilot RCT Evidence:** Early human trials demonstrate significant reduction in alcohol craving and total consumption.
- **Clinical Efficacy:** Ivermectin modulates rewarding pathways without the severe side effects of traditional disulfiram.

TARGET MECHANISM

Antagonizes ethanol-mediated inhibition of P2X4 receptors in the central nervous system.



- Reduces Craving and Reward Signaling
- Decreases Alcohol Consumption
- Favorable Safety & Tolerability
- Potential for Broad Public Health Impact

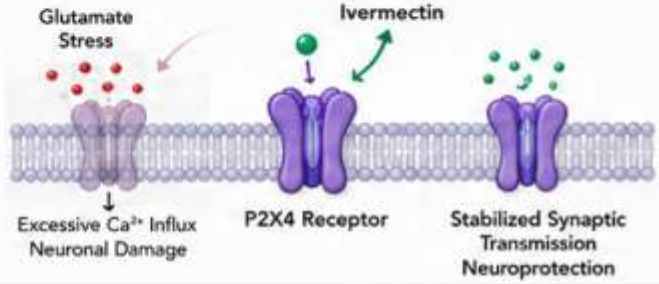
Amyotrophic Lateral Sclerosis

Preclinical Data & Neuroprotection

- **Excitotoxicity Mitigation:** Inhibits AMPA-mediated motor neuron death via potent P2 receptor antagonism.
- **Neuroinflammation:** Modulates microglial activation through P2X4 pathways, potentially slowing disease progression.

MOLECULAR ACTION

Positive allosteric modulation of P2X4 receptors to stabilize synaptic transmission and reduce glutamate stress.



- Protects Motor Neurons
- Reduces Excitotoxicity
- Modulates Microglial Activation
- Potential to Slow Disease Progression

1. Roche DJO et al. Ivermectin, a P2X4 Receptor Modulator, Reduces Alcohol Consumption. Alcohol Clin Exp Res. 2016;40(6):1312-1322.
2. Asatryan L et al. Ivermectin as a novel modulator of P2X4 receptors and its potential in neurological disorders. Neuropharmacology. 2014;79:152-159.
3. Halma M, Vottero P. Ivermectin: A Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65.

Heliyon 11 (2025) e43478

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Breaking the silence: Recognizing post-vaccination syndrome

Matthew Halma [a,*], Joseph Varon [a,b]

[a] Independent Medical Alliance, 2001 L St. NW Suite 500, Washington, DC, 20036, USA
[b] University of Houston College of Medicine, 5055 Medical Center Boulevard, Houston, TX, 77204, USA

EMERGING INDICATIONS: POST-VACCINATION SYNDROME

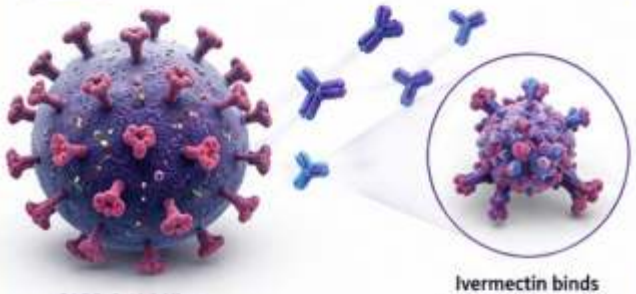
SECTION V: BEYOND PARASITOLOGY — FUTURE CLINICAL FRONTIERS

Multi-Target Approach | Neuroprotection & Restoration | Precision Therapeutics | Restoring Quality of Life

INDEPENDENT MEDICAL ALLIANCE

MOLECULAR TARGET A

Spike Protein Sequestration



- High binding affinity for the SARS-CoV-2 spike protein (S1 subunit) potentially neutralizes circulating protein.
- Competitive inhibition of the Receptor Binding Domain (RBD) interaction with cellular ACE2 receptors.
- Promotes clearance of residual spike protein fragments that may persist in the vascular and immune compartments.

CLINICAL APPLICATION

Management of Core Symptoms

- **Reduces "Brain Fog" and cognitive fatigue** through BBB-mediated neuro-protection.
- **Addresses dysautonomia and small fiber neuropathy** by stabilizing cholinergic signaling.
- **Ameliorates myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) patterns.**

MOLECULAR TARGET B

Alpha-7 nAChR Modulation

- Acts as a Positive Allosteric Modulator (PAM) of the Alpha-7 Nicotinic Acetylcholine Receptor.
- Activates the "Cholinergic Anti-inflammatory Pathway" to mitigate systemic cytokine dysregulation.
- Supports autonomic nervous system restoration and reduces neuro-inflammatory triggers.

Restoring balance between inflammation and neural communication.

CURRENT EVIDENCE

Therapeutic Integration

- Core component of the FLCCC I-RECOVER protocol for vaccine injury management.
- Synergizes with autophagic stimulators (intermittent fasting, resveratrol) for protein clearance.
- Dosage titration (0.4–0.6 mg/kg) tailored to clinical severity and patient response.

GOALS

- Reduce residual spike protein burden
- Calm neuro-inflammation
- Restore autonomic balance
- Improve cognition and quality of life

A Multi-Target Strategy to Heal, Protect, and Restore.
Science. Innovation. Compassion.

Spike Burden Reduced → Neuroinflammation Calmed → Neural Function Restored → Lives Improved

Halma M, Vottero P. Ivermectin: The Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65. | Marik PE, Kory P. Clinical Monograph: Post-Vaccine Syndrome Management. FLCCC Alliance. 2023.

EMERGING INDICATIONS: POST-VACCINATION SYNDROME

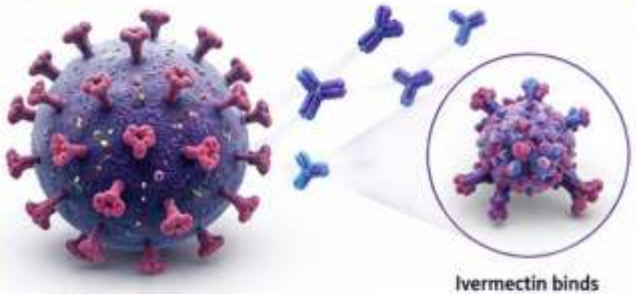
SECTION V: BEYOND PARASITOLOGY — FUTURE CLINICAL FRONTIERS

Multi-Target Approach | Neuroprotection & Restoration | Precision Therapeutics | Restoring Quality of Life

INDEPENDENT MEDICAL ALLIANCE

MOLECULAR TARGET A

Spike Protein Sequestration



- High binding affinity for the SARS-CoV-2 spike protein (S1 subunit) potentially neutralizes circulating protein.
- Competitive inhibition of the Receptor Binding Domain (RBD) interaction with cellular ACE2 receptors.
- Promotes clearance of residual spike protein fragments that may persist in the vascular and immune compartments.

CLINICAL APPLICATION

Management of Core Symptoms

- **Reduces "Brain Fog" and cognitive fatigue** through BBB-mediated neuro-protection.
- **Addresses dysautonomia and small fiber neuropathy** by stabilizing cholinergic signaling.
- **Ameliorates myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) patterns.**

MOLECULAR TARGET B

Alpha-7 nAChR Modulation

- Acts as a Positive Allosteric Modulator (PAM) of the Alpha-7 Nicotinic Acetylcholine Receptor.
- Activates the "Cholinergic Anti-inflammatory Pathway" to mitigate systemic cytokine dysregulation.
- Supports autonomic nervous system restoration and reduces neuro-inflammatory triggers.

Restoring balance between inflammation and neural communication.

CURRENT EVIDENCE

Therapeutic Integration

- Core component of the FLCCC I-RECOVER protocol for vaccine injury management.
- Synergizes with autophagic stimulators (intermittent fasting, resveratrol) for protein clearance.
- Dosage titration (0.4–0.6 mg/kg) tailored to clinical severity and patient response.

GOALS

- Reduce residual spike protein burden
- Calm neuro-inflammation
- Restore autonomic balance
- Improve cognition and quality of life

A Multi-Target Strategy to Heal, Protect, and Restore.
Science. Innovation. Compassion.

Spike Burden Reduced → Neuroinflammation Calmed → Neural Function Restored → Lives Improved

Halma M, Vottero P. Ivermectin: The Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65. | Marik PE, Kory P. Clinical Monograph: Post-Vaccine Syndrome Management. FLCCC Alliance. 2023.

PREGNANCY AND REPRODUCTIVE SAFETY GUIDELINES

SECTION VI: SAFETY PROFILE & REGULATORY STATUS

INDEPENDENT MEDICAL ALLIANCE

FDA Category & Animal Evidence

- **FDA Category C:** Animal studies show teratogenicity (cleft palate, clubbed feet) at doses toxic to mothers.
- **Maternal Toxicity:** Effects in mice, rats, and rabbits primarily occur at **maternotoxic dose levels.**
- **Clinical Context:** No adequate, well-controlled studies in pregnant women; use only if potential benefit justifies risk.

> *"Inadvertent exposure during Mass Drug Administration (MDA) has not shown a significant increase in congenital malformations."*

Lactation and Breastfeeding

- **Low Excretion:** Ivermectin is excreted in human milk in low concentrations **(<2% of maternal dose).**
- **Compatibility:** Generally considered compatible with breastfeeding; risk to infant is deemed minimal.

WHO Recommendations (2026)

- **First Trimester:** Standard practice is to **avoid ivermectin** during the first trimester of pregnancy.
- **Risk-Benefit Analysis:** In endemic areas (Onchocerciasis/Scabies), use in 2nd/3rd trimesters may be considered if benefits to maternal health outweigh risks.
- **Scabies Policy:** Topical ivermectin is often preferred over oral for localized dermatological needs in pregnancy.

Meta-Analysis of Human Outcomes

- **Nicolas et al. (2020):** Systematic review of 147 inadvertent exposures found no evidence of increased risk for major malformations or spontaneous abortions.
- **Safety Signal:** Despite historical caution, current real-world data supports a reassuring safety profile for late-pregnancy exposure.

> *"Future guidelines may shift toward broader acceptance in pregnancy based on extensive MDA pharmacovigilance."*

Nicolas P et al. Lancet Infect Dis. 2020;20(12):e307–e317.
Halma M, Vottero P. J Indep Med. 2025;1(1):37–65.
WHO Guideline on Scabies Management. 20

DRUG INTERACTIONS & FORMULATION RISKS

SECTION VII: PHARMACOVIGILANCE & CLINICAL SAFETY

INDEPENDENT MEDICAL ALLIANCE

FORMULATION & VETERINARY PRODUCT RISKS

Veterinary Concentration Risks

- Livestock preparations are highly concentrated and designed for large animals.
- Dosing errors—not ivermectin itself—account for most reported toxicity events.
- Human-grade ivermectin manufactured under USP/GMP standards has decades of established clinical use.

Human Grade Ivermectin

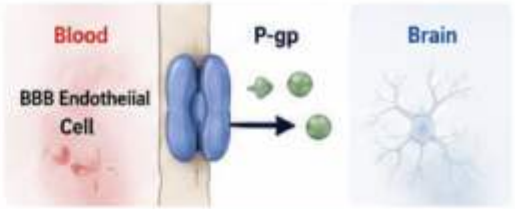
Veterinary Injectable (1%–10%)

Formulation Concerns

- Veterinary excipients and solvents may not be purified for human administration.
- Concentration variability can lead to accidental overdose.

Blood–Brain Barrier (BBB) Considerations

- Ivermectin is a substrate of P-glycoprotein (P-gp) which limits CNS penetration under normal conditions.

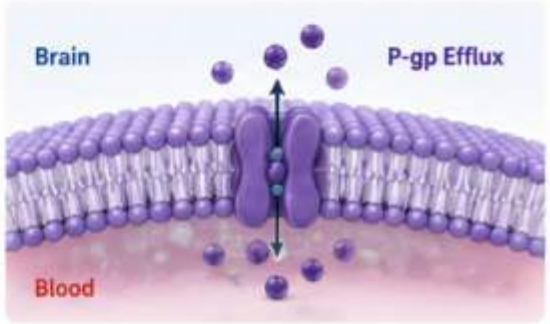


The issue is inappropriate formulation and dosing— not the intrinsic safety of ivermectin when prescribed appropriately.

PHARMACOKINETIC & DRUG INTERACTIONS

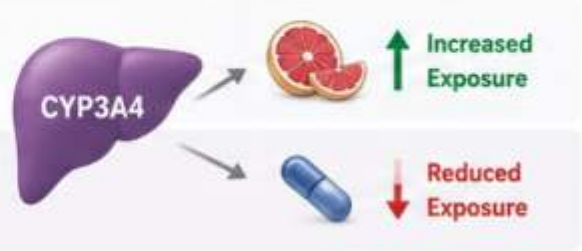
P-Glycoprotein (ABCB1) Interactions

- Verapamil, ketoconazole, quinidine, and some statins may inhibit BBB efflux mechanisms.
- Excess CNS penetration may increase neurologic toxicity risk in susceptible individuals.



CYP3A4 Metabolism

- Clarithromycin, grapefruit juice, and azole antifungals may increase systemic ivermectin exposure.
- Rifampin and enzyme inducers may reduce therapeutic levels.



Anticoagulant Considerations

- Monitor INR when co-administered with warfarin or in complex polypharmacy regimens.

Over four decades of clinical experience support ivermectin's excellent safety profile when human-grade formulations are used responsibly.

1. Nicolas P et al. Lancet Infect Dis. 2020;20(12):e307–e317.
2. Guzzo CA, et al. J Clin Pharmacol. 2002;42(11):1122–33.
3. Halma M, Vottero P. J Indep Med. 2025;1(1):37–65.

REGULATORY POSITIONS 2026: FDA, WHO, AND NIH

SECTION III: GLOBAL GOVERNANCE, CONTROVERSIES, AND FUTURE OUTLOOK

Science evolves. Policies lag. Evidence will prevail.

Evidence over ideology.
The world needs open science, transparent data, and patient-first policies.

INDEPENDENT MEDICAL ALLIANCE

U.S. FDA

- **Maintains non-approval** for COVID-19 treatment; warns against high-dose veterinary formulations.
- **Authorized multiple IND Phase 2 trials** for solid tumors (TNBC, Colorectal) as of Q1 2026.
- **Topical 1% ivermectin (Soolantra®)** remains Gold Standard for Rosacea management.

Off-label prescribing remains legal but highly scrutinized for viral protocols.

WHO

- **Reaffirms position on the Model List of Essential Medicines** for NTDs.
- **Strong endorsement for mass drug administration** (MDA) in Onchocerciasis and Scabies elimination programs.
- **COVID-19 recommendation:** "Only in clinical trials" (low certainty of evidence for routine use).

Critical success in River Blindness elimination in 14 African nations (2026 update).

NIH (U.S.)

- **Finalized ACTIV-6 data analysis** (2025); concluded no significant mortality benefit for COVID-19 at 400 µg/kg.
- **National Cancer Institute (NCI) 2026:** Evaluating ivermectin for **Immunogenic Cell Death** induction.
- **Funding exploratory studies on** repurposed drugs for neurological post-vaccination sequelae.

Shift in focus toward synergistic oncology combinations & metabolic pathways.

Regulatory positions reflect politics, liability, and risk aversion — not the full body of evidence.

The science will not be silenced. The truth will not be buried.

REFERENCES:

1. Halma M, Vottero P. Ivermectin: A Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65.
2. World Health Organization. Therapeutics and COVID-19: living guideline. 2026 Update.
3. National Institutes of Health. COVID-19 Treatment Guidelines. Updated Jan 2026.
4. FDA Regulatory Review: Repurposed Drugs in Oncology. 2026 Clinical Update.

CONCLUSION: THE 50TH ANNIVERSARY AND CALL TO ACTION

SECTION III: THE FUTURE OF IVERMECTIN

From a single discovery to global impact — the next chapter starts now.

50 YEARS 1972–2022+

INDEPENDENT MEDICAL ALLIANCE

50 YEARS OF EXCELLENCE (1972–2022+)

A LEGACY OF GLOBAL IMPACT

DISCOVERY TO NOBEL
From a single soil sample in Kawana to the 2015 Nobel Prize in Medicine.

2015 NOBEL PRIZE IN MEDICINE

BILLION-DOSE SAFETY
Over 4 billion doses administered with a safety record rivaling aspirin.

4+ BILLION DOSES

MOLECULAR VERSATILITY
A "Swiss Army Knife" targeting parasites, viruses, and inflammation.

PUBLIC HEALTH TRIUMPH
19.1 million DALYs saved; near-elimination of River Blindness in Africa.

19.1 MILLION DALYs SAVED

ACCESS & EQUITY
Affordable, off-patent, and available worldwide — a model for neglected disease control.

THE ONCOLOGY FRONTIER (2026+)

Repurposing Ivermectin: Beyond Parasitology

TARGETING STEMNESS
Validated mechanisms against Cancer Stem Cells via Wnt/β-catenin and Notch pathways.

IMMUNE SYNERGY
Induction of Immunogenic Cell Death (ICD) to prime checkpoint inhibitors and enhance anti-tumor immunity.

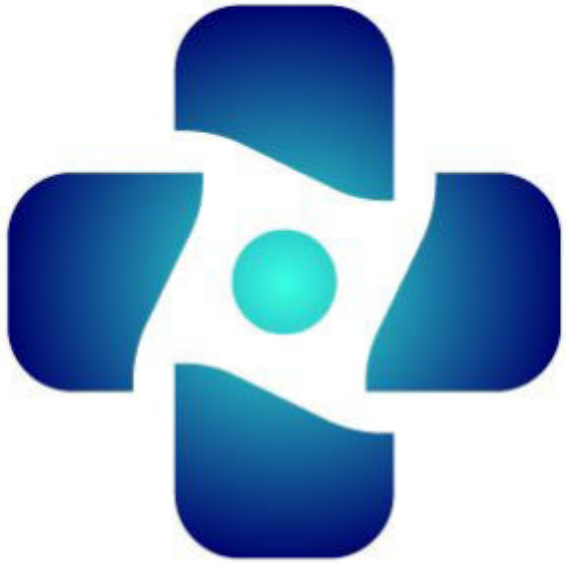
MDR REVERSAL
Potent P-glycoprotein inhibition to restore sensitivity to standard chemotherapy and targeted therapies.

URGENT CALL TO ACTION
We demand immediate, large-scale, independent clinical trials to validate Ivermectin's role as an adjunctive metabolic and immune-modulating agent in oncology.

THE NEXT 50 YEARS WILL BE WRITTEN BY COURAGE, CURIOSITY, AND COMPASSION.
LET'S PUT PATIENTS FIRST. LET'S FOLLOW THE SCIENCE. LET'S BUILD THE FUTURE.

REFERENCES

1. Halma M, Vottero P. Ivermectin: A Molecular Swiss Army Knife. J Indep Med. 2025;1(1):37-65.
2. World Health Organization. Therapeutics and COVID-19: living guideline. 2026 Update.
3. National Institutes of Health. COVID-19 Treatment Guidelines. Updated Jan 2026.
4. FDA Regulatory Review: Repurposed Drugs in Oncology. 2026 Clinical Update.


INDEPENDENT
MEDICAL ALLIANCE™