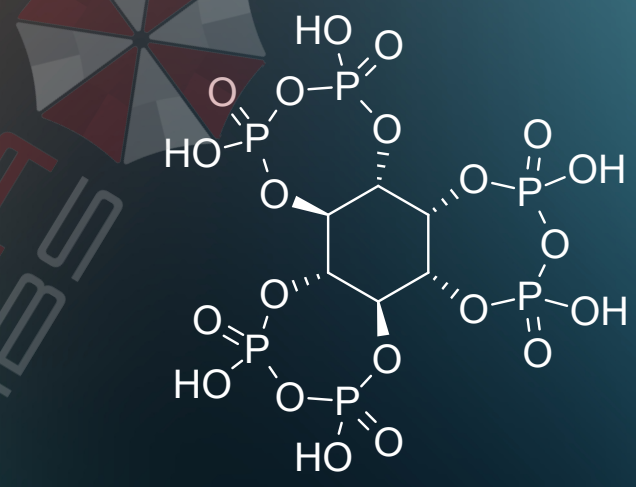


# Myo-Inositoltrispyrophosphate (ITPP): A Hemoglobin Allosteric Modifier for Overcoming Hypoxia in Cancer and Cardiovascular Disease

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## History

The first detailed description of ITPP (also known as OXY111A) as a hemoglobin allosteric effector appeared in 2005.[1] Initial publications highlighted its ability to increase tissue oxygenation without toxic effects, distinguishing it from earlier hemoglobin modifiers.[2] Soon after, studies in animal models demonstrated that ITPP could combat tumor hypoxia by re-oxygenating solid tumors, thereby inhibiting hypoxia-inducible factor (HIF-1α) activity and improving responses to chemotherapy and radiotherapy. Parallel work explored its role in cardiovascular diseases, showing benefits in heart failure and pulmonary hypertension models. ITPP is a synthetic derivative of myo-inositol hexakisphosphate (IP6, also known as phytic acid), a natural compound found in plants. Phytic acid also serves as synthetic precursor for ITPP.

## Mechanism of Action

ITPP is an allosteric modifier of hemoglobin that facilitates oxygen release in the body's tissues. By shifting the hemoglobin–oxygen dissociation curve to the right, ITPP enhances tissue oxygenation, especially under low-oxygen (hypoxic) conditions.

## Pharmacokinetics

Intraperitoneal injection of ITPP (0.5 – 3g/kg) in mice caused a dose-related increase in the oxygen level at which hemoglobin is 50% saturated (p50) , with a maximal increase of 31%. In transgenic mice with severe heart failure, i.p. ITPP increased exercise capacity, with a maximal increase of 63% . Oral administration of ITPP in drinking water increased Hb p50 and maximal exercise capacity (+34 %) in normal and transgenic mice. From this preclinical study, the authors concluded that ITPP is thus an attractive candidate for the therapy of patients with reduced exercise capacity caused by heart failure.[3]

The impact of ITPP is also additive to the bohr effect, meaning that is can influence the O2 binding affinity in addition to the known binding affinity shift from lowering pH (Bohr effect).[4]

## Analysis

A method to screen for ITPP in human urine by HPLC-MS has been reported, likely due to the doping potential of the compound.[5] Since ITPP is also frequently used in horse racing, method to detect the compound in horses have also been reported as well. After 200 mg i.v., the peak concentration was detected at 1.5

h post administration, while it was detectable up to 24 hours post administration in horses.[6],[7]

## *Preclinical Trials*

In a rat model of monocrotaline-induced pulmonary hypertension (a very serious form of hypertension in humans), ITPP helped restore right ventricular oxygen tension ($pO_2$), reduced mortality, and markedly improved survival by alleviating hypoxia and preventing right ventricular failure.[8]

Heart failure was also reduced in mice and rats that has a induced myocardial infarction. The increased oxygen levels resulting from ITPP prevents unnecessary cell death, hence resulting on more vital heart tissue after such an event.[9] Mice which already experienced severe heart failure did however also benefit from ITPP treatment, which did improve their ability for physical exersise.[3]

Tumors often create hypoxic micro-environments because their rapid growth outpaces blood vessel formation. This low oxygen tension stabilizes hypoxia - inducible factor 1α (HIF-1α), a transcription factor that drives angiogenesis, glycolysis, and other pro-survival pathways, making tumors more aggressive and resistant to therapy. This shows ITPP increases hemoglobin oxygen release in tissues—including tumors—thereby increasing local oxygen availability. By improving oxygen delivery, ITPP helps re-oxygenate hypoxic tumor regions, which suppresses HIF-1α activity and reduces the expression of its downstream targets like VEGF which ultimately slows tumor progression by counteracting hypoxia - driven survival advantages. For example, it was observed that ITPP was observed to improve tumor oxygenation in 6 tumor models and improved the results in some gliomas (brain tumors) but not in rhabdomyosarkomas.[10]

In mice with colon cancer, ITPP had a significant survival benefit compared with respective controls, while a combination of FOLFOX (a standard chemotherapeutic regime in colon cancer) with ITPP conferred the maximum benefits, including dramatic improvements in survival (mean 86 vs 188 d).[11],[12] However, another study showed no improved survival of living animals with glioblastoma.[13] The reason for such different results may be that some tumor are actually non-hypoxic in their normal state and some studies suggest that mostly hypoxic tumors can be affected using ITPP.[14]

In fact, some very promising results were achieved in rats with early liver cancer. ITPP showed a strong potency for tumor growth inhibition, thus allowing long-term survival and even cure of almost all the treated animals. ITPP did not affect hematologic parameters during treatment. The observations of in vivo tumor eradication suggest a significant clinical potential for ITPP in cancer therapy.[15]

ITPP successfully increased oxygen levels inside mice with aggressive tumor lines, which was confirmed using a special imaging technique called photoacoustic imaging (PAI). When tumors had more oxygen, this study also found a better immune response of the surrounding tissue. Combining ITPP with immune checkpoint inhibitors (ICB) treatment worked better than ICB alone—improving both tumor control and survival in the mice. The researchers suggest that monitoring tumor oxygen with PAI could help design better combination therapies in the future.[16]

Early results of a study with zebrafish show that ITPP increases cancer cell death, reduces cell division, and may improve blood vessel function inside tumors in models with human pancreatic cancer cells. In rodents, ITPP was able to increase the response of pancreatic tumors to gemcitabine (a common anti-tumor compound).[17] This suggests it could become a promising new approach to treating pancreatic cancer.[18]

One study found that ITPP alone does not affect tumor growth significantly, but it was able to increase the tumor sensitivity to radiation therapy.[19]

## *Clinical Trials*

A study reported on the results of an unrandomized, open-labeled, 3 + 3 dose - escalation phase Ib study (NCT02528526) including 28 patients with advanced liver or pancreatic cancer and liver metastases of colorectal cancer receiving nine 8h - infusions of ITPP over three weeks across eight dose levels (1000-10.000 mg

/dose), followed by standard chemotherapy. Primary objectives were assessment of the safety and tolerability and establishment of the maximum tolerated dose, while secondary objectives include assessment of pharmacokinetics, antitumor activity via radiological evaluation and assessment of circulatory tumor-specific and angiogenic markers. The maximum tolerated dose was 7.500 mg, and ITPP treatment resulted in 32 treatment-related toxicities (mostly hypercalcemia) that required little or no intervention. 52% of patients had morphological disease stabilization under ITPP monotherapy. Following subsequent chemotherapy, 10% show partial responses while 60% have stable disease. Decreases in angiogenic markers are noted in ~60% of patients after ITPP.[20] The study was performed until 2015, afterwards no new clinical studies have taken place.

ITPP also has promising properties in the treatment of cancer through its disturbance of tumor hypoxia. Many animal tumor models show positive results under ITPP treatment, mostly with gastrointestinal cancers. A human clinical trial has also been performed in patients with terminal colorectal or pancreatic cancer, where patients received ITPP prior to chemotherapy, where it did seem that ITPP was able to slow down the progression of the disease, although data is hard to interpret because there was no placebo group. More clinical studies are needed to confirm effects in human cancers. The main adverse event was hypercalcemia.

## *Conclusion*

In cardiovascular disease models—including post-myocardial infarction heart failure and pulmonary hypertension in animals—ITPP has shown promising benefits: it increases myocardial partial pressure of oxygen ($pO_2$), prevents adverse cardiac remodeling, improves exercise capacity, and may serve as a promising therapeutic candidate for both left and right heart failure. The increased ability to release oxygen can also be used for performance enhancement in aerobic sports.

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