# New Use for FDA Approved Drug -Treatment of Microbial Infections with NTBC

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## Technology description

Dr. Graham Moran and collaborators have shown that 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) decreases pigment production in the bacterium B. cenocepacia and aids in phagolysosomal fusion in macrophages infected with this bacteria in vitro.

The researchers have shown that treatment of a pigmented strain of Pseudomonas aeruginosa with NTBC decreases the resistance of both planktonic cells and biofilms to oxidative stress. In preliminary data, NTBC administration also prevented death in mice infected with Pseudomonas aeruginosa versus untreated mice. These results further support the potential use of NTBC in the treatment of microbial infections. Originally developed for herbicide use, NTBC is approved by the FDA for the treatment of specific rare inherited metabolic defects. The mechanism of action is based on the inhibition of an enzyme known as 4-hydroxyphenylpyruvate dioxygenase (HPPD).

Many infectious bacteria and fungi alter their metabolism in response to the elevated temperature of their host. One way in which some of these pathogens act is through the HPPD pathway. They produce a pigment known as pyomelanin, which is made directly from a product of the HPPD reaction. It is thought that pathogenic bacteria and fungi use pyomelanin and other melanins to suppress the efficiency of the host' s initial immune response. Thus, inhibition of these pigments may aid in fighting infection.

Microbial infections can either be superficial (affecting skin, nails, hair, and mucous membranes) or systemic (entering the bloodstream and affecting internal organs or the nervous system). Systemic infections can be caused by an invasive organism common to a specific geographic area or an opportunistic organism that attacks those with a weakened immune system. Some people who are at a greater risk for systemic infections include cancer patients, cystic fibrosis patients, AIDS patients, diabetes patients, those taking corticosteroids, and organ transplant patients. Bacterial infections have become increasingly problematic due to multiple drug resistant strains.

Dr. Graham Moran is an Associate Professor in the Department of Chemistry and Biochemistry at the University of Wisconsin-Milwaukee. He obtained his Ph.D. in 1996 in Protein Chemistry from the University of Michigan and conducted postdoctoral work at Texas A&M University. In 2008 Dr. Moran received a UWM Research Foundation Catalyst Grant sponsored by the Lynde and Harry Bradley Foundation for his work on novel treatments for fungal infections.

The antifungals market was estimated at $7.4 billion in 2009 by Research and Markets. The market is expected to grow to $8.4 billion by 2016. There remains significant unmet need due to low spectrum activity of commercial drugs, unfavorable interactions with other medications, toxicity problems, and fungal resistance issues. The antibacterial market is predicted by Visiongain to reach $43.8 billion by 2016. Antibiotic resistance continues to complicate bacterial infections and nosocomial infections remain a major burden on the health care budgets in developed and developing countries.
NTBC has great potential for antifungal and antibacterial treatments both for systemic and superficial infections. With FDA approval already completed, NTBC will be an ideal candidate for combination therapies with other commercial antimicrobial agents. The excellent toxicity profile and long half life in humans after oral ingestion are further advantages of this drug. Other applications include formulations for topical treatments in humans and treatment of animals in veterinary or farm livestock practices.

## Advantages

Safer- Excellent toxicity profile in humans
More stable- Longer half life in humans after oral ingestion
Less time to market- FDA approved and original composition and use patents have expired
Easier to use- Can be used orally as opposed to creams and suppositories
Combination therapy- Potential to be used in combination with currently used commercial antifungals and antibacterials to create new treatment composition and extend patent life

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