TOPS-ester: Targeted Caged Nitric Oxide as a Topical UV and Radiation Protectant[1]

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Ultraviolet and nuclear radiation of the skin generates reactive oxygen species (ROS), which are involved in all three aspects of carcinogenesis (initiation, promotion and progression). ROS induce free radical cascades which attack enzymes, other proteins, lipids, and DNA, producing widespread disruption of normal cell activities that can result in pathologies such as sunburn, skin cancer and skin aging.

We have developed a "targeted" caged nitric oxide (CNO) technology that is able to catalytically neutralize ROS and thereby block their cytotoxic attributes. This technology creates new biopharmaceuticals based on synthetic, highly stable nitroxyl radicals (nitroxides). Nitroxides, which are essentially a class of "caged" nitric oxide analogs, react with biological free radicals in vivo to protect cells from diverse oxidative insults. To achieve specific intracellular targeting, we have developed a prodrug construct in which a diester of nitroxide succinate (*TOPS-ester*), for example t-butyl, ethyl-2,2,6,6-tetramethylpiperidylidene succinate (BE-TOPS), is formulated to be selectively cell membrane permeable. After entering the cell, the ester bonds on the prodrug are cleaved by intracellular esterases, making the nitroxide succinate much less membrane permeable, and effectively compartmentalizing the drug within the cell.

The power of the CNO technology is its ability to neutralize ROS that form during many pathological states. This antioxidant action blocks cellular damage that is usually mediated by these molecules. While CNO technology uses specific catalytic mechanisms to accomplish the destruction of the reactive oxygen species, this technology can be broadly applied to a variety of pathologies characterized by excess production of ROS. Compartmentalizing the anti-oxidant drug within cells produces localized, long-lasting, and effective concentrations of the drug with minimal systemic effects.

Because BE-TOPS penetrates the dead stratum corneum and is preferentially taken up by living skin cells when applied as a topical gel, it should protect skin cell DNA against the carcinogenic effects of ROS that are generated by ultraviolet or radiological radiation. Skin cancer is the most common and most rapidly increasing type of cancer in the country. Furthermore, it is likely that BE-TOPS' antioxidant actions will protect skin cells against other ROS mediated lesions including psoriasis, sunburn, and skin aging.

We also hypothesize that TOPS-ester treatment will reduce the incidence of skin cancer of military personnel or civilians exposed to cutaneous nuclear dust after a nuclear accident or terrorism event.

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[1] The author would like to dedicate the development of targeted CNO as a new treatment modality in dermatology to the memory of the pioneering work of the late Professor Lawrence H. Piette.