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A novel genetic-based therapeutic platform for eradicating metastatic cancer

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Abstract

We developed a therapeutic platform for eliminating a wide range of metastatic cancer types including melanoma, which was utilized as a test model for the studies below. The first generation of our therapeutic modality has demonstrated a 70-100% killing efficiency in chemo- and radioresistant human melanoma cells through apoptosis, with no apparent effect on non-transfected cells. Recently, through the optimization of transfection efficiency, our therapeutic modality eliminated five different primary/metastatic human melanoma types with a 96-100% killing efficiency. Only half of the initial therapeutic dose was utilized in the above preliminary in vitro survival assays, indicating that the in vitro potency of our therapy is greater than initially observed.

Our therapeutic modality has been devised to overcome cancer resistance to apoptosis, which accounts for the inability of conventional and recently developed therapies to eradicate metastatic cancer. Our therapy is based on the novel approach of triggering apoptosis without activating the apoptosis signaling cascade or using the native apoptosis executioner nuclease. This is achieved by triggering apoptosis from the bottom end of the cascade, at the level of the DNA-degrading nuclease, resulting in the bypass of all upstream anti-apoptosis defense mechanisms.

We engineered a human recombinant deoxyribonuclease1 (hrDNase1) that avoids being secreted from the cell, resists inactivation by its major intracellular inhibitor, actin and can access nuclear DNA. Next, we constructed and tested the killing efficiency of a second hrDNase1 generation, which was designed to have greater resistance to intracellular inhibition. The hrDNase1 approach provides several substantial advantages over other therapies in that it: (1) overcomes cancer resistance to chemotherapy-, radiotherapy- and immunotherapy-induced apoptosis; (2) eliminates cancer cells without needing to recruit the patient's immune system, indicating that hrDNase1 should maintain its high therapeutic efficacy in severely immunocompromised patients; (3) has demonstrated selective killing of transfected cells through apoptosis. Clinically, these features will enable the hrDNase1 therapeutic modality to achieve high, selective tumor targeting and minimal adverse effects.

hrDNase1 structure, killing efficiency in various settings and future clinical capacity as a personalized therapy that can be customized to each patient will be discussed.

Biography

Dr. Rosner obtained his M.D. from Ben-Gurion University (Israel), followed by obtaining his specialty in Dermatology and Venereology from the Ha'emek Medical Center (Israel) in 1996. In 2001, he graduated with a Ph.D. in Immunology and Molecular Biology from the University of Copenhagen (Denmark). Dr. Rosner conducted postdoctoral research in the laboratory of Dr. Vilhelm Bohr at the National Institute of Aging (United States). Since 2006, Dr. Rosner has been Principal Investigator and Director of Dermatology Research at Wayne State University (United States). Over the last decade, Dr. Rosner's research has focused on the development of genetic-based melanoma therapy, as well as the identification of novel melanoma biomarkers. In 2011, Dr. Rosner published a new anti-cancer therapeutic platform, which he pioneered and developed to treat melanoma and other cancer types by utilizing a novel form of suicide gene therapy. His therapeutic platform is comprised of a series of genetic constructs that have initially demonstrated 70-100% killing efficiency in melanoma cells. Recently, Dr. Rosner has extended the repertoire of his genetic constructs and has further elucidated their anti-cancer properties.