Enzyme Prodrug Therapy Using Fusion Protein

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Technology description

A new approach of enzyme prodrug therapy for cancer.

Technology

This technology is based on a new approach of enzyme prodrug therapy for cancer. Annexin V protein is utilized to selectively target an enzyme to phosphatidylserine expressed on the outer surface of tumor cells, their metastases, and endothelial cells of tumor vasculature. Treatment with an enzyme fused to annexin V and an administered prodrug is lethal to cancer cells, while the prodrug has little or no effect without the fusion protein. Cells in the tumor are killed by the generation of reactive oxygen species (ROS) as a result of the conversion of the prodrug by the targeted enzyme. Immunogenicity of the enzyme has been addressed by utilizing a mutated human protein that will generate the ROS. The effectiveness of this approach is increased by combining it with simultaneous stimulation of the immune system and with an mTOR inhibitor. This technology presents a novel, non-invasive therapeutic that can be systemically administered for eradicating tumors and metastases.
In vivotesting has demonstrated a more than doubling of survival using an immune-competent murine orthotopic breast tumor model when enzyme prodrug therapy is combined with the immunomodulator cyclophosphamide and mTOR inhibitor rapamycin. A full pathologic analysis for enzyme prodrug treatment related toxicities revealed no abnormalities among the experimental groups. In an immune-competent murine orthotopic ovarian cancer model, survival doubled when the enzyme prodrug therapy was combined with anti-CD73 and anti-OX40 immunostimulants. There was a strong antibody-mediated immune response, and an increased infiltration of cytotoxic T-cells along with a decrease in tumor promoting immune cells. Again, no treatment toxicity was observed.

Mechanism/Modality

Generation of Radical Oxygen Species, Immune Stimulation, and mTOR Inhibition/Cytotoxic Targeting and Treatment with Antibodies and mTOR Inhibitor

Application area

Oncology

Advantages

Selective targeting of the enzyme prodrug therapy to tumors and tumor vasculature.

Treatment effectiveness increased when the enzyme prodrug therapy is combined with immune stimulation and an mTOR inhibitor.
No side effects of weight change, pathology, or elicitation of neutralizing antibodies.

Institution

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