Livin-Derived Peptides As Novel Targeted Cancer Treatment (Hadasit)

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Need:

DLBCL, an aggressive tumor that can arise throughout the body, is the most common type of non-Hodgkin's lymphoma (NHL) among adults; annual incidence is ~10/100,000 in US. Underlying immunodeficiency or EBV infection are significant risk factors. Chemotherapy, often in combination with Rituxan or a related MAb, can cure ~50% of patients, and the five-year survival rate is only ~60%. Thus, there is a significant pool of patients that are resistant to treatment, many because of resistance to chemotherapy-induced apoptosis. This pool may be up to ~15,000 / year in US, hence projected to be up to 40,000 / year in developed countries. Assuming 20% penetration and a $50K treatment cost for a one-year course, the achievable annual DLBCL market would be ~$0.5B.

Innovation:

A truncated pro-apoptotic form of Livin protein (mtLivin) is conjugated with CD40L onto PLGA surface-activated nanoparticles (NP) for targeting diffuse large B-cell lymphoma (DLBCL) cells, a product design that shows enhancements in stability, bioavailability, and cellular uptake. This product candidate may be given to subjects with chemotherapy.

Findings:

Targeted bifunctional mtLivin-CD40L-NPs elicited significant cell death of DLBCL cells, much higher than achieved by treatment with mtLivin-NPs.

To best mimic human lymphoma, a disseminated lymphoma model was used to evaluate the anti-tumor effect of targeted mtLivin treatment. With time, lymphoma infiltrations were detected in brain, bone marrow, lungs, spleen and liver. All control mice exhibited paralysis and died within 28 days. In contrast, 71% of mice receiving mtLivin-CD40L-NPs achieved a complete pathological tumor response and survived significantly longer than 28 days.

Treatment was well-tolerated.

Tumors from treated mice showed high caspase-3 activity, thereby demonstrating the ability of the bifunctional NPs to target tumors and induce apoptotic tumor cell death.

Indications/Applications:

The resistance of tumor cells to drug-induced apoptosis is a major cause for the failure of various cancer treatments. The mtLitvin-targeted bifunctional nanoparticles are a personalized approach for treating resistant cancer, especially liquid tumors. Additional CD40+ types of NHL and other leukemias/ lymphomas also may be treatable with mtLivin-CD40L-NPs coupled with chemotherapy.

Competitive Advantage:

This targeted therapy should be selective for tumor cells. The Livin moiety of the therapy, once internalized to the tumor cell, will induce apoptosis. By overcoming regular drug-induced apoptosis, which is a major mechanism of resistance to chemotherapy, this candidate given with chemotherapy can offer a unique therapeutic option over conventional antibody therapy such as Rituxan that targets the tumor without overcoming drug-induced apoptosis.

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