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DELIVERY OF CHECKPOINT INHIBITORS WITH NANO IMMUNOCONJUGATES FOR ACTIVATION OF LOCAL BRAIN TUMOR IMMUNE SYSTEM FOR GLIOMA TREATMENT

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Check point antibody CTLA-4 and PD-1 act on regulatory T cells (Treg) to remove their suppression of cytotoxic T lymphocytes (CTL) that start attacking the tumor. However, treatment of gliomas with combination of these antibodies was not successful because as other antibodies they do not cross the blood brain barrier (BBB). Upon this treatment, only systemic immune response was activated. The technology we had developed is focused on engineering and preclinical testing of such nanoimmunotherapeutics to treat brain cancers which activated both systemic and local brain tumor immune systems. Synthesis of immuno-nanoconjugates: immuno-nanoconjugates (INC) crossing BBB, P/PEG/msTfR/anti-CTLA-4 and P/PEG/msTfR/anti-PD-1 were synthesized. They are based on natural polymer, poly β (L-malic acid) (P), and contain anti-transferrin receptor antibody (MsTfR). Physico-chemical, pharmaceutical, and toxicological parameters of INCs were determined. Brain tumor treatment: syngeneic GL261 glioma cells (20,000) were intracranially inoculated into C57/BL mice. Six treatment groups were injected with either PBS, anti-PD-1 and anti-CTLA-4 as a control, or polymer-conjugated anti-PD-1(P/PD-1), anti-CTLA-4 (P/CTLA-4) or a combination of polymers with antibodies, (P/CTLA-4 + P/PD-1) at 10 mg/kg, 5 times I V. Immuno-nanoconjugates P/CTLA-4 and P/PD-1 significantly improved survival of brain tumor-bearing mice compared to free anti-CTLA-4 and anti-PD-1 ($p<0.04$ and $p<0.004$, respectively). The combination P/CTLA-4 + P/PD-1 showed the highest survival efficacy compared with CTLA-4, PD-1, and PBS groups ($p<0.001$, $p<0.04$, and $p<0.0001$, respectively). Flow cytometry analysis of T cell population in the brain tumor revealed reduction of the total number of CD4+ T-cells in animals treated with P/PD-1 and combination P/CTLA-4 + P/PD-1. The fraction of Tregs (CD4+FOXP3+) was also reduced by all polymer conjugates compared to free antibodies. Activation of CD8+ T-cells (CD8+IFNγ+ and CD8+CD69+) was increased by polymer-conjugated anti-CTLA-4/PD-1 and combination therapy. Animals treated with polymer-conjugated anti-PD-1 and combination treatment showed significant decrease in PD-1 expression by CD8+ cells compared to controls. Multiplex assay to measure cytokine response to treatment demonstrated significant increase in the expression of IL-1β, IL-2, IL-10, TNFα, IL-6, IL-12, and IFNγ in the brain and serum after combination therapy.

Conclusion: **Brain tumor treatment with immuno-nanoconjugates that can cross BBB significantly increased animal survival.**

Biography

Julia Y Ljubimova is Professor of Neurosurgery and Biomedical Sciences, and Director of Nanomedicine Research Center, Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, USA. She has been working in clinical and basic cancer research during her entire career. Her major scientific discoveries are: 1) The cancer biomarkers as tools for developing new nanomedicine imaging agents and drugs against primary and metastatic tumors and 2) The development of nano imaging and therapeutic agents that are crossing multiple biological barriers including blood brain barrier (BBB). Nano immunology and nano toxicology are novel important subjects of the fight against tumors and inflammation, which are currently studied in the Nanomedicine Research Center. Her research is supported by National Institutes of Health/National Cancer Institute, private and industry grants. She is the author of over 100 publications, reviews and book chapters as well as an inventor on twelve issued patents, and patent applications.

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