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Humanized anti-CD47 antibody is a potential effective and safe treatment for pediatric malignant brain tumors

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Background: Pediatric brain tumors are the leading cause of morbidity and mortality among pediatric malignancies. Limited current therapeutic approaches as well as their long-lasting side effects are emerging concerns in pediatric neuro-oncology, calling for urgent need to develop new treatments. Blocking CD47- SIRPα interaction using CD47 antibodies has proven to be effective in treatment of various types of cancers though multiple translational studies. Here, we show the efficacy and safety of Humanized anti-CD47 against various types of pediatric brain tumors.

Methods: CD47 expression levels were assessed in freshly isolated surgical tissue and post-mortemsamples from different pediatric brain tumor types: Diffuse Intrinsic Pontine Glioma, Medulloblastoma, Glioblastoma, Oligodendroglioma, Atypical TeratoidRhabdoid Tumor, and Primitive Neuroectodermal Tumor. We assessed blockade of CD47-SIRPα interactions via humanized anti-CD47 monoclonal antibody (huanti-CD47Ab) treatment both in vitro with tumor phagocytosis assays and *in vivo* with orthotopicxenograft tumor models derived from human primary tumor cells. We next tested the therapeutic dose and antibody penetration through blood brain barrier. Finally, we performed toxicity studies, invitro and invivo, to assess the off-target effect of humanized anti-CD47 antibodyon normal neural stem cells.

Results: *In vitro* studies showed that tumor cells were phagocytized significantly higher by macrophages in the presence of huanti-CD47Ab. Further invivo studies using patient derived xenograft models revealed significant regression and subsequent durable therapeutic response in treated mice compared to control group. Our safety studies revealed that huanti-CD47Ab selectively target tumor cells with negligible effect on normal neural cells.

Conclusion: Huanti-CD47Ab results in effective therapeutic response infive deadly malignant pediatric brain tumors. Huanti-CD47Ab induced phagocytosis of brain tumor cells by macrophages, and induced tumor regression and prolonged survival in tumor-bearing mice. These results provide important preclinical data in support of Phase I clinical trial of huanti-CD47Ab in the treatment of pediatric patients withsuch malignancies.

Biography:

Sharareh Gholamin is a postdoctoral fellow at Institute of Stem Cell Biology and Regenerative Medicine and Department of Neurosurgery at Stanford University, USA. Over the last four years, she was leading the project, developing humanized anti-CD47 antibody treatment as a potentially safe and effective treatment for patients with pediatric brain tumors. She can confidently say that this study came to be the first and the most comprehensive pre-clinical analysis of a monoclonal antibody, both in safety and efficacy, against various malignant pediatric brain tumors. The study is currently under review in Nature Medicine journal. In continuation of a presented study, her current focus is optimizing combinational immunotherapy approach to treat various pediatric brain tumors in preclinical setting. She do believe that immunotherapy will be a promising move towardfighting various type of cancer and brain tumors, indeed, are not exceptions.