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Targeting FZD7 in human cancers

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Scientific Abstract:

A major challenge in the current advancement of anti-cancer immunotherapy is the identification of tumor specific antigens that can be exploited to specifically target cancer cells with minimal adverse side effects. The WNT signaling pathway is critically important for embryonic development and the maintenance of adult tissues. Mutations in components of this pathway are associated with many diseases, including cancer. Importantly, expression of certain WNT signaling components is largely absent in adult tissues but is aberrantly activated in a variety of cancers. One component exhibiting such an onco-fetal expression pattern is encoded by the FRIZZLED7 (FZD7) gene, presenting a unique opportunity to specifically target cancers overexpressing FZD7. Many types of cancers are known to overexpress FZD7, including breast cancer, ovarian cancer, hepatocellular carcinoma, Wilms' tumor, glioma, gastric cancers, colon cancer, and melanoma. Moreover, FZD7 expression is associated with poor prognosis, as patients with FZD7-high expressing tumors have shorter survival than those with FZD7-low expressing tumors. The overarching goal of the proposed work is to establish the efficacy of a highly specific antibody to FZD7 developed in our laboratories. The proposed aims will test the hypothesis that anti-FZD7-based therapies provide an effective and specific strategy to target cancer cells. Together these studies will lead to the development of novel and highly effective cancer immunotherapies. Successful completion of these studies will be instrumental to overcome current obstacles to the effective treatment of otherwise incurable cancers and lead to clinical trials for FZD7-specific immunotherapy.

Lay Abstract:

A major shortcoming of current cancer therapies is lack of specificity. Chemotherapeutic drugs act on fast dividing cells, such as cancer cells. However, cells in normal tissues, such as skin, blood and the gastrointestinal tract, also divide and hence are highly sensitive to chemotherapeutic drugs, resulting in many undesired toxic side-effects and the all-too-common misconception that cancer treatments do more harm than good. Recent advances in immunotherapies overcome many of the issues associated with chemotherapy. With the rapid advances in molecular profiling of human cancers and precision medicine, it is now possible to identify patient-specific mutations in cancers and design specific immunotherapies to block the aggressive growth of these cancers. We have identified the gene FRIZZLED7 (FZD7) as a molecular marker of many cancer types. With its highly restricted expression pattern—absent in children and adults and present in the embryo and various cancers— FZD7 is an ideal target for immunotherapies. We have developed an antibody that only reacts with FZD7, thus providing us with a molecular handle to identify, target and potentially kill cancer cells. In this application, we propose to leverage our uniquely specific FZD7 antibody to develop highly selective strategies to combat cancers in which FZD7 is highly expressed. The short-term goals of the proposed research are foundational and basic in nature. Successful completion of this 1-year study will immediately feed into our long-term goals, including clinical development, filing of a new investigational drug (IND) application with the FDA, and initiating a Phase 1 clinical trial.