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"**Development of a novel, anti-CD70 based platform for the treatment of peripheral T-cell lymphomas – epigenetically mediated synthetic cytotoxicity**"

Abstract:

Mature T cell lymphomas, also known as peripheral T cell lymphomas (PTCL) are rare subtypes of Non-Hodgkin lymphoma (NHL) family distinguished by unique clinicopathologic features. In general, PTCL are characterized by poor outcomes, significantly worse than their B cell counterparts. This is in part due to the fact that these malignancies have historically been treated with therapeutic regimens borrowed from B cell lymphomas ignoring specific biologic features of T cell NHL. Novel, T cell directed treatment approaches are therefore urgently needed. There is a growing evidence that epigenetic changes play an important role in T cell lymphoma etiology. Most notably, histone deacetylase inhibitors (HDACIs) romidepsin, vorinostat and belinostat are now FDA approved for the treatment of patients with PTCL.
CD70, a TNF superfamily member, serves as a ligand for CD27 and is expressed on majority of PTCL. CD70CD27 interaction leads to NFκB and cJun oncogenic pathways activation. It also leads to induction of immune tolerance by an increase in the amount of Tregs within the lymphoma changing the composition of tumor infiltrating lymphocytes. This in turn creates an immunosuppressive microenvironment which malignant cells use to escape the immune system and ultimately results in worse prognosis for CD70 positive lymphomas.
CD70 gene promoter hypermethylation was shown to be an important mechanism in silencing its surface expression on lymphoma cells. Furthermore, treatment of normal T cells with hypomethylating agents and HDACIs leads to increased surface CD70 expression. Our preliminary data shows that treatment of PTCL cell lines with either decitabine or romidepsin increases surface CD70 expression. Preliminary data also shows that CD70 negative cells can become CD70 positive once they are treated with epigenetic drugs. We hypothesize that if epigenetic treatment leads to increased CD70 expression on PTCL cells, then this effect will augment the activity of the anti CD70 antibody named ARGX110. We will explore the interaction of epigenetic drugs and ARGX110 by following Aims:

Aim 1. Analyze the changes in CD70 expression in peripheral T cell lymphomas as a function of epigenetic drug exposure and correlate these changes to ARGX-110 efficacy.
Aim 2. Study the mechanism by which epigenetic drugs and ARGX-110 synergistically increase PTCL cell death.
Aim 3. Analyze the changes on T cell repertoire in peripheral blood and primary tumor samples of the PTCL patients as a function of treatment with decitabine, romidepsin and ARGX-110.