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618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

αGal9Ab Treatment As a Novel Therapy for Blood Cancer

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Blood cancers are the most common cancer in children accounting for roughly 28% of all childhood cancers. Of these, acute lymphoblastic leukemia (**ALL**) and acute myeloid leukemia (**AML**) are the most prevalent. Advancements in treatment regiments for these diseases have led to a 5-year overall survival rate of 90% for pediatric ALL and 65˜70% for pediatric AML; however, in patients with relapsed or refractory disease, the overall survival rates decline to 30˜50% post-treatment.

We have recently demonstrated that antibody-mediated targeting of Galectin-9 (**GAL-9**), is highly cytotoxic to human B-ALL cells *in vitro* and confers a significant degree of protection for disease progression in pre-clinical models of B-ALL (M. Lee *et al.*, *Nature Communications*, 2022). In unpublished studies, we have subsequently found that anti-GAL-9 antibody (α**GAL-9Ab**) treatment is highly cytotoxic to human T-ALL and AML cells. Notably, we have found that human pediatric cell lines are more sensitive to this treatment than those derived from adult patients. Mechanistically, we have uncovered a previously unreported link between GAL-9-mediated regulation of checkpoint kinase 1 (**CHEK1**) and anti-apoptotic protein myeloid leukemia 1 (**MCL-1**), with αGAL-9Ab treatment leading to a deregulation of both proteins in T-ALL cells. Notably, αGAL-9Ab treatment synergized with multiple CHEK1 inhibitorscurrently being tested in phase I or II clinical trials (GDC-0575, Prexasertib and PF477736) to enhance the *in vitro* killing of human T-ALL, B-ALL, and AML cells. Furthermore, using xenograft models, we found that single-agent αGAL-9Ab treatment was superior to single-agent chemotherapy and vehicle treatment at conferring protection against T-ALL progression.

In conclusion, single-agent αGAL-9Ab treatment appears to be cytotoxic against multiple acute leukemia subtypes (**ALs**) and its efficacy is enhanced with CHEK1 inhibition. To validate this novel combinatorial approach for treating ALs, additional studies need to be performed to define the mechanisms of action and further pre-clinical experiments will be invaluable in determining the efficacy and safety of these therapies.

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