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Recombinant Human CD19 Ligand for Biotherapy of B-lineage Lymphoid Malignancies

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CD19 is a 95-kDa B-lineage restricted receptor molecule that functions as a key regulator of transmembrane signals in both B-cells and B-cell precursors [1-6]. CD19 antigen is acquired at a very early stage of B-cell ontogeny, prior to rearrangement of immunoglobulin genes and expression of other B-precursor antigens such as CD10 and CD22 [1-3]. CD19 antigen is expressed on the malignant cells from virtually all of B-lineage leukemia and lymphoma cases, but it is absent on the parenchymal cells of life-maintaining non-hematopoietic organs, circulating blood myeloid and erythroid cells, T-cells as well as bone marrow stem cells, [1-3]. In B-lineage/B-precursor acute lymphoblastic leukemia (ALL), the most common form of childhood and adolescent cancer, CD19 antigen is expressed on candidate leukemic stem cell populations with in vivo clonogenic, leukemia initiating and propagating properties in xenograft models using immunocompromised mice. The very favorable B-lineage leukemia/lymphoma vs. normal tissue expression profile of CD19 and its association with stemness properties of leukemic B-cell precursor populations make it an attractive molecular target for biotherapy in relapsed ALL [1-6].

Recently, we reported the cloning and characterization of a novel HMG-box protein as the membrane-associated natural CD19 ligand on lymphoid cells, especially T-cells and T-cell precursors [7]. Soluble recombinant human CD19-L (rhCD19L) protein exhibited exquisite specificity for the extracellular domain of CD19, perturbed CD19-associated signaling network, had profound effects on apoptosis-related signaling and gene expression in $CD19^+$ human leukemia cells and caused rapid apoptosis in leukemic B-cell precursors from chemotherapy-resistant CD19-positive human B-lineage ALL cell lines as well as in $CD19^+$ primary leukemia cells from patients with chemotherapy-resistant relapsed B-lineage ALL at nanomolar concentrations [7].

The development of human rhCD19L and/or its derivatives may lead to therapeutic innovation for B-lineage ALL as well as other B-lineage lymphoid malignancies by providing a more effective alternative for CD19-directed monoclonal antibody-based biotherapeutic agents that have encountered several limitations in clinical efforts to achieve apoptosis of chemotherapy-resistant $CD19^+$ leukemia/lymphoma cells. We are currently examining if the anti-leukemic potency of rhCD19L can be further improved by genetically fusing it with soluble tumor necrosis factor (TNF)-related apoptosis inducing ligand (sTRAIL) for simultaneous activation of the CD19 and TRAIL-R apoptosis signaling pathways and thereby induce rapid apoptosis in chemotherapy-resistant leukemia cells from relapsed B-lineage leukemia/lymphoma patients.

Nanotechnology-enabled delivery of anti-cancer therapeutics is an area of intense translational research [8-10]. Rationally designed biotargeted anti-cancer nanomedicines have the potential to substantially improve the therapeutic index of their "payload" by increasing their potency via (a) selective delivery to target cancer cells as well as (b) improved cellular pharmacokinetic/pharmacodynamics (PK/PD) features that avoid the multi-drug resistance associated drug efflux pumps and by reducing their systemic toxicity and undesired off target effects. Several non-targeted nanomedicine candidates are being evaluated in clinical trials or have been given FDA approval, including biocompatible micellar, liposomal, and polymeric formulations of standard chemotherapy drugs [8-10]. Several biotargeting moieties are being explored in pre-clinical studies including small molecules, antibodies/antibody fragments, affibodies, cell penetrating peptides, cytokines, avimers and aptamers [8-10]. rhCD19 [7] shows potential as a biotargeting moiety that can be used to functionalize nanomedicine candidates as CD19-specific therapeutics against B-lineage leukemias and lymphomas.

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