DKMS Stiftung Leben Spenden

Project Summary

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CIS checkpoint deletion in cord blood derived iC9.CAR19.IL-15 NK cells for the treatment of B-cell hematologic malignancies

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Results with CD19-chimeric antigen receptor (CAR) T-cell therapy are extremely promising. However, the limitations of generating an autologous cellular product and the challenges of toxicity and disease relapse following CAR-T cells underscore the need to develop novel cellular therapy products that are universal, safe and more potent. Natural killer (NK) cells are attractive contenders since they exert potent cytotoxicity against tumor cells and unlike T-cells, lack the potential to cause graft-versus-host disease in the allogeneic setting.

Our group has developed a novel strategy to genetically modify cord blood (CB)-derived NK cells to express a CAR, ectopically produce IL-15 to support NK cell proliferation and persistence in vivo, and express a suicide gene, inducible caspase 9 (iC9), to address any potential safety concerns. We have initiated a first-in-human, phase I/II clinical trial of iC9/CAR19/IL15-NK cell therapy in patients with relapsed/refractory B-cell lymphoid malignancies. We now propose to build on this platform to further enhance the potency of CAR engineered NK cells by blocking their intrinsic checkpoint molecules.

Cytokine inducible SH2 containing protein (CIS), encoded by the CISH gene, is as an important checkpoint molecule in NK cells and is upregulated in response to IL-15. We hypothesized that CIS may act as a potent checkpoint in iC9/CAR19/IL-15 transduced NK cells and that targeting this pathway would enhance their potency at lower doses.

The aims of this project are: 1) To determine if CISH KO can improve the anti-tumor activity of iC9/CAR.19/IL-15- NK cells in mice with B-cell lymphoma, without causing toxicity; 2) Evaluate if CISH KO enhances the activity of iC9/CAR.19/IL-15 NK cells by modulating their metabolic profile; and 3) Perform scale up experiments and develop GMP-grade CISH KO iC9/CAR.19/IL-15 NK cells in anticipation of a clinical trial.