Conference: Cellicon Valley '23: The Future of Cell and Gene Therapies

Title: *Targeted in vivo generation of CAR T and NK cells utilizing an engineered lentiviral vector platform*

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CAR T cell therapies have revolutionized treatment of B cell malignancies. Ex vivo CAR manufacturing is complex, costly, and cumbersome, prompting efforts that support shorter manufacturing and allogeneic or "universal donor" strategies. Recent data show that CAR T product efficacy is correlated with reduced ex vivo manipulation of cells. We have designed a system to transduce effector cells inside the body to generate autologous CAR cells, circumventing ex vivo manipulation, avoiding the need for conditioning chemotherapy, and providing an "off-the-shelf" therapy for B cell malignancies.

Our product (INT2104) is an intravenously administered lentiviral vector encoding an anti-CD20 CAR transgene. INT2104 was rationally designed with a novel binder and an engineered fusogen to provide specific tropism to CD7+ T and NK cells. Incubating INT2104 with activated primary human PBMCs confirmed that T cells, including CD4+ and CD8+ subsets, and NK cells were specifically transduced. No evidence of B cell transduction was seen when INT2104 was exposed to B cell tumor lines and primary PBMCs isolated from patients with B cell malignancies across a wide range of MOIs. INT2104-treated PBMCs cocultured with B cell tumor targets resulted in dose-dependent killing.

INT2104 was administered to CD34-engrafted NSG mice via tail vein injection. B cell depletion occurred within 7 days, with CAR+ cells peaking in blood at day 21 coincident with B cell ablation. In a separate established B cell tumor model, NSG MHCI/II KO mice were engrafted with Raji-fLuc tumor cells. Five days later, activated human PBMCs were infused followed the next day by i.v. dosing of INT2104. Complete tumor ablation occurred in all treated mice at over a 15-fold range in dosing, including a dose matching the proposed human dose in TU/kg. Preclinical data suggest that intravenous delivery of INT2104 will be both safe and effective, supporting plans to continue development and transition into the clinic.