1203 TARGETED *IN VIVO* GENERATION OF CAR T AND NK CELLS UTILIZING AN ENGINEERED LENTIVIRAL VECTOR PLATFORM

James I Andorko*, Ronnie M Russell, Bruce C Schnepp, Ramesh Singh, Debasish Boral, Philip R Johnson. *Interius BioTherapeutics, Inc., Philadelphia, PA, USA*

Background CAR T cell therapies have revolutionized the treatment of B cell malignancies. *Ex vivo* CAR manufacturing is complex, costly, and cumbersome, leading to limited product access and prompting efforts that support shorter manufacturing and allogeneic or 'universal donor' strategies. Recent data also show that CAR T product efficacy is correlated with reduced *ex vivo* manipulation of cells. Here, we have designed a system to transduce effector cells *inside* the body to generate autologous CAR cells, circumventing *ex vivo* cell manipulation, avoiding patient 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 (figure 1, left). INT2104 was rationally designed with an engineered fusogen and a novel binder to provide targeted transduction of $CD7^+$ T and NK cells following intravenous delivery.

Methods To determine cell specific transduction, INT2104 was incubated with activated primary human PBMCs, B cell tumor lines, and primary PBMCs isolated from patients with B cell malignancies. INT2104-treated PBMCs were also cocultured with B cell tumor targets to determine targeted cell lysis. *In vivo* evaluation of INT2104 was conducted using humanized mouse models. Both CD34-engrafted mice and NSG mice with established B cell tumors were administered INT2104 via the tail vein injection (figure 1, middle). In the CD34-engrafted mouse model, flow cytometry was used to determine B cell depletion and CAR^+ cell persistence. In luciferase-expressing tumor bearing mice, IVIS imaging was used to determine tumor burdens while monitoring CAR^+ cells via flow cytometry.

Results *In vitro* data confirmed that T cells, including $CD4^+$ and $CD8^+$ subsets, and NK cells were specifically transduced with INT2104. No B cell transduction was seen across a wide range of MOIs. INT2104-treated PBMCs cocultured with B cell tumor targets resulted in dose-dependent killing, confirming CAR functionality. Delivery of INT2104 to CD34-engrafted NSG mice via tail vein injection resulted in B cell depletion within 7 days, with CAR^+ cells detectable in blood coincident with B cell ablation (figure 1, right). INT2104 administration to mice bearing an established B cell tumor also resulted in B cell aplasia, with complete tumor ablation seen in all treated mice across a 15-fold range in dosing, including a dose matching the proposed first-in-human dose in TU/kg.

Conclusions These preclinical data suggest that intravenous delivery of INT2104 will be both safe and effective, supporting plans to continue development and transition into the clinic.

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Ethics Approval All institutional and national guidelines for the care and use of laboratory animals were followed and approved by the IACUC and IRB committees at Saint Joseph's University (formerly University of the Sciences) under Protocol #21–002.

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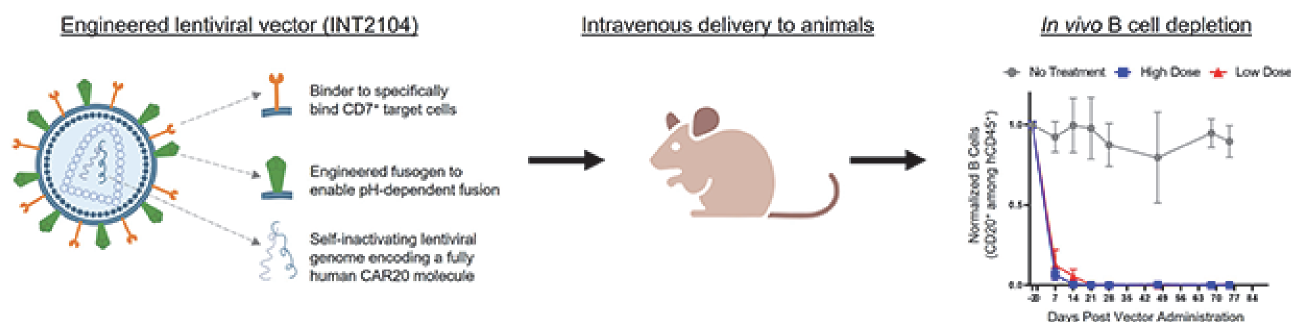

Abstract 1203 Figure 1 In vivo delivery of INT2104 results in CAR^+ cell generation and B cell depletion with no toxicity.

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