over 3 days as 10%, 30% and 60% fractions following a Fludarabine-Cyclophosphamide preparative regimen (PR). Interim translational outcomes are presented here.

Methods, Results & Conclusion: IMN-003A was manufactured using a cGMP compliant closed system. The apheresis and final infusion product (FP) were analysed for percent CAR transduction and T cell subsets by flow cytometry (FC). Persistence of IMN-003A after infusion was evaluated in Peripheral Blood (PB) by ddPCR. Safety and efficacy data were collected for analysis. Bone marrow (BM) samples for minimal residual disease (MRD) were obtained at screening, D+28 and D+90 for efficacy. MRD was performed by FC with 10^{-4} sensitivity. Fifteen patient apheresis were obtained and transduced to achieve the final product with 100% success. The median percent transduction of IMN-003A on autologous T cells was 34.77% (range 15.49 - 58.35). The mean proportion of naïve cells ($CCR7^+$ $CD45RA^+$) was higher in both Apheresis and FP from B-ALL subjects compared to B-NHL, while the terminally differentiated T_{EMRA} and T_{EM} subsets were higher for B-NHL subjects compared to B-ALL. IMN-003A cells in PB showed maximum expansion at median 10 days following infusion (range: 7 - 21 days). B-cell aplasia was observed in all subjects consistent with IMN-003A *in-vivo* persistence. Overall Response rate was 85.7% (n=12/14) at D+28 and 70% (n=7/10) at D+90. Updated results shall be presented at the meeting. In this industry-led first-in-India phase-2 study, IMN-003A showed peak CAR-T expansion at a median of 10 days post-infusion, with durable and deep ongoing responses in both the B-ALL and NHL cohorts, despite differences in T-cell phenotype in apheresis and final product.

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Immunotherapy

RAPID ACCESS TO VIRUS-SPECIFIC T CELLS FOR ADOPTIVE IMMUNOTHERAPY FOR COMPASSIONATE USE IN AUSTRALIA

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Keywords: T cells, Cell therapy, Clinical manufacturing.

Background & Aim: Adoptive T cell immunotherapy holds great promise for the treatment of viral complications. Our group has been developing and trialling virus-specific T cell therapies for more than 20 years. Recently, we have generated a repository of multi-virus-specific T cells for our clinical trials. Unfortunately, for many patients with viral complications, there is no suitable trial through which to access these therapies. In Australia, the Therapeutic Goods Administration has a Special Access Scheme (SAS) to enable provision of unapproved therapies for compassionate use. Our research group is now a leading Australian provider of "off-the-shelf" and custom-grown allogeneic virus-specific T cells to hospitals for patients with no other treatment options.

Methods, Results & Conclusion: We have generated a repository of multi-virus-specific T cells from 20 healthy donors, with up to 150 doses of T cells per donor generated from a single blood sample. Each product batch is thoroughly characterised in terms of viral antigen specificity, HLA restriction and alloreactivity. These T cells target a combination of Epstein–Barr virus, cytomegalovirus, BK polyomavirus, John Cunningham virus and adenovirus epitopes. We have also generated a repository of SARS-CoV-2-specific T cells and occasionally grow custom patient-specific batches of T cells from nominated donors, on request. Since 2008, we have provided virus-specific T cells to 15 hospitals across Australia, and the volume of supply requests has significantly increased in recent years, as clinicians have gained interest in adoptive immunotherapy. In 2022, we provided T cells for 26 patients via the SAS. The majority were experiencing post-transplant complications, including cytomegalovirus disease, BK virus-associated haemorrhagic cystitis and post-transplant lymphoproliferative disorder. Through our clinical trials, we have developed rigorous processes for T cell therapy manufacture and characterisation, in addition to a computer-based selection algorithm, which we apply to SAS cases. As these cases are not part of a clinical trial, concomitant therapy varies, and monitoring is not uniform. However, we have received reports of clinical benefit from adoptive T cell therapy. These include cases of reduction in viral load, improvement in symptoms, and complete resolution of infection. We believe that these promising T cell therapies should be available to hospitals through a nationally funded centre for cellular therapies for critically ill patients.

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ANTI-GD2 CAR T CELLS AGAINST SMALL CELL LUNG CANCER

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Keywords: CAR T, SCLC, GD2.

Background & Aim: Small cell lung cancer (SCLC) is a neuroendocrine-origin tumor accounting for 15% of all lung cancers. Despite it represents a minority of lung malignancies, it is characterized by a dismal prognosis due to a late-stage disease at the diagnosis. The lack of effective treatments, mainly represented by chemotherapy and immune checkpoint inhibitors (ICIs), does not contribute to ameliorate the prognosis. Thus, novel therapeutic approaches shall consider new targets to improve SCLC outcome. The disialoganglioside GD2 is a ganglioside known to be expressed by neuroectoderm-derived tumors, with a highly restricted expression on healthy tissues. We previously challenged anti-GD2 chimeric antigen receptor (CAR) T cells against neuroblastoma and glioblastoma, starting from these data we sought to additionally target SCLC.

Methods, Results & Conclusion: We started to assess GD2 expression on two commercial SCLC lines (H69 and H209) which resulted in 90.8% and 6% $GD2^+$, respectively. H69 were transduced by either DsRED or luciferase expressing vectors and were also grown as spheroids. We then isolated the T cell populations from healthy donors PBMC and engineered them to express our second-generation anti-GD2 CAR together with GFP, or GFP only as control T cells. CAR T cells were thoroughly characterized by FACS to assess their cytotoxic CD8+, NK, and $\gamma\delta$ lymphocytes phenotypes. We also evaluated the presence of Naïve/stem cell memory, central memory, effector memory, and terminal effector memory and the presence of exhaustion markers as PD1, LAG3, and TIM3. We observed an increase in $CD8^+$ after retroviral transduction. Moreover, GFP T only and CAR T cells had a Naïve/stem Cell memory enriched population. Interestingly, exhaustion markers did not change after the transduction process. *In vitro* 2D and 3D spheroid co-cultures were set up to assess the anti-GD2 CAR T cytotoxic effect compared

with GFP T lymphocytes at different effector target (E:T) ratios assessed at 24, 48, and 72h (Fig.1). CAR T showed a robust anti-H69 ($GD2^{high}$) activity in 2D, also efficiently penetrating SCLC spheroids with a robust anti-cancer effect (Fig. 2). These encouraging results pave the way to a CAR T approach against SCLC, demonstrating that GD2 is a valuable target for a yet poorly explored strategy.

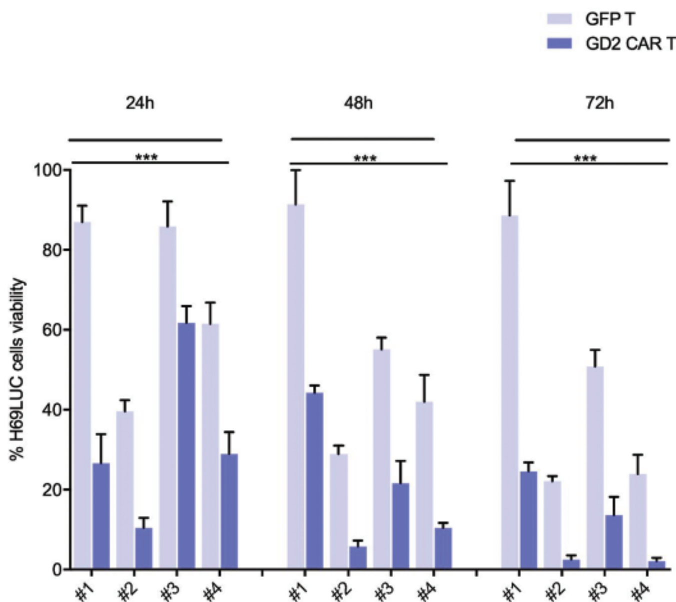

Fig. 1 (abstract 1067). In vitro 2D co-culture cytotoxicity assay comparing GFP T and anti-GD2 CAR T cells (E:T 4:1 ratio) of 4 different donors at 3 different time points. *P<0.001; p values are calculated by an unpaired two-tailed t-test.

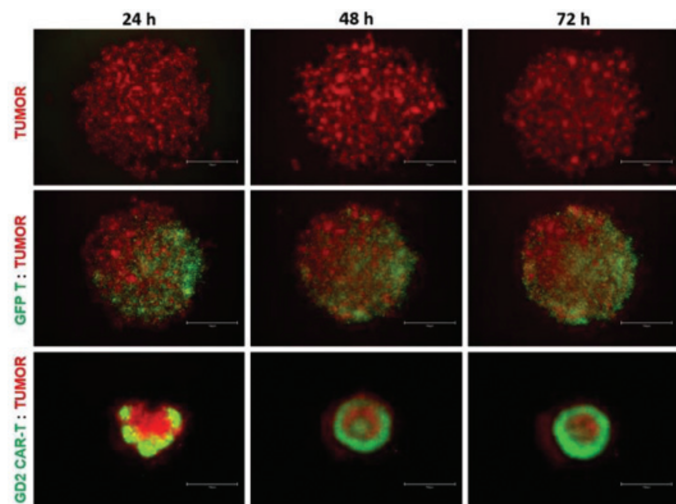

Fig. 2 (abstract 1067). 3D spheroids co-cultures of anti-GD2 CAR T cells and GFP only controls against H69dsRED cell lines E:T 4:1 at three different time points.

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INITIAL CO-CULTURE WITH CLINICAL-GRADE UMBILICAL CORD-DERIVED MESENCHYMAL STROMAL CELL ENHANCES EX VIVO HUMAN REGULATORY T CELL EXPANSION

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Keywords: regulatory T cells expansion, mesenchymal stem cells (mscs), monocyte/macrophages.

Background & Aim: $CD4^+$/$FOXP3^+$ regulatory T-cell (T-reg)-based therapy for immune-mediated and inflammatory diseases faces challenges related to scale-up, phenotypic stability, longevity, bio-distribution and functional complexity. Mesenchymal stromal cells (MSC) promote T-reg expansion in vitro and in vivo as part of their immune modulatory/anti-inflammatory properties. We investigated whether clinical-grade human umbilical cord MSCs (hUC-MSCs) enhance ex vivo culture expansion of highly purified human blood Treg from low initial cell numbers.

Methods, Results & Conclusion: Highly purified human T-reg were obtained from healthy volunteer 50 mL blood samples by Ficoll separation of peripheral blood mononuclear cells (PBMCs) followed by magnetic column enrichment of $CD4^+$ cells and, finally, fluorescence-activated cell sorting of viable $CD4^+CD25^+CD127^{lo}$ cells. The purified cells were cultured for an initial 7 days in 96-well plates at 12,500-25,000 cells/well with 1000IU/ml IL-2 and 100ng/mL rapamycin, CD3/CD28 MACSiBeads (beads:cell=4:1) with or without clinical-grade hUC-MSC (2.5:1 MSC/T-reg ratio) with medium exchange every 2 days. On day 7, proliferating T-reg were transferred to new wells under the same stimulation conditions without hUC-MSC. On day 21, yields for T-reg generated from initial cultures with and without hUC-MSC were compared. MSC-facilitated Treg were analysed for phenotype/function by flow cytometry, $CD4^+$ and $CD8^+$ T-effector cell suppression assays and monocyte/macrophage suppression assays. From n=7 donors, $4.3\pm1.9\times10^5$ highly purified T-reg were obtained, representing 0.97±0.20% of PBMC. T-reg yields (expressed as fold expansion Day 0 to 21) were significantly higher for MSC-facilitated vs. non-MSC-facilitated cultures (100.4±84.0 vs 15.4±10.8, $p<0.05$; mean fold difference in yield 4.3±2.0, $p<0.01$). MSC-facilitated, culture-expanded T-reg potently suppressed polyclonally-stimulated $CD4^+$ and $CD8^+$ T effector (Teff) proliferation at 1:1 ratio (75.2±35.6%supp and 86.4±19.3%supp, respectively) and 1:2 ratio (60.8±40.1%supp and 79.2±29.1%) with no difference in potency to non-MSC-facilitated Treg. In co-culture, MSC-facilitated T-reg suppressed LPS-stimulated TNF in primary monocytes using $CD4^+$ T cells as cell control for coculturing (61±29%supp vs 18±15%supp, $p<0.05$). Thus, initial co-culture with hUC-MSC substantially enhanced the yield of multi-potent human Treg from low numbers of highly purified $CD4^+/CD25^+/CD127^{lo}$ cells.

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THERAPEUTIC IMPROVEMENT OF PARKINSON'S DISEASE TRANSPLANTATION THERAPY THROUGH MODULATING THE IMMUNE SYSTEM

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Keywords: Parkinson's disease, IPSC-derived mDAPs, Immune system.

Background & Aim: The specific loss of midbrain dopamine (mDA) neurons in the substantia nigra results in major motor dysfunction in Parkinson's disease (PD), and cell replacement has been considered a promising therapeutic approach. We report clinically the implantation of patient-derived midbrain dopaminergic progenitor cells (mDAPs), differentiated *in vitro* from autologous induced pluripotent stem cells (iPSCs), in a patient with idiopathic Parkinson's disease (PD). The patient-specific mDAPs were produced under Good Manufacturing Practice conditions and characterized as having the phenotypic properties of substantia nigra pars compacta neurons; testing in a humanized mouse model indicated an absence of immunogenicity to these cells. The cells were implanted into the putamen (left hemisphere followed by right hemisphere, 6 months apart) of a patient with PD, without the need for immunosuppression. Clinical measures