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ORAL ABSTRACTS

703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

CXCR4 Enriched T Regulatory Cells Preferentially Home to Bone Marrow and Decrease Inflammation

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Background and aim

Adoptive therapy with T regulatory cells (Tregs) is emerging as an important therapeutic strategy for several autoimmune and inflammatory diseases. Optimal homing and payload delivery of these anti-inflammatory cells remain a cornerstone of optimizing their therapeutic efficacy. CXCR4 cell surface expression has been shown to be critical for homing of hematopoietic cells to the bone marrow (BM). Also, CXCR4/CXCL12 axis plays a major role in the pathogenesis of BM inflammatory disorders including myelofibrosis. We hypothesize that enrichment of CXCR4 on the Tregs cell surface will enable their trafficking to BM and ensure a homogenous delivery.

Methods/results/conclusion

Magnetic enrichment of CD25 $^{+}$ cells was performed on umbilical cord blood on day 0, followed by dual enrichment on CXCR4 using CRANE ^{TM} (cord blood Tregs, activated and enriched) process on day 3 or 4 (Fig 1A). The enrichment process led to increased number of Tregs expressing CXCR4 on their cell surface (Fig 1B; Treg ^{CXCR4}) as well as a CXCR4 ^{hi} Treg cells when compared to Treg ^{control} (Fig 1C, $p<0.0001$; $n=16$). In a Transwell ^{TM} system, a higher number of Treg ^{CXCR4} migrated to the bottom well in chemotactic response to SDF1α at 15 minutes as compared to the Treg ^{control} cells. Such migration was inhibited by CXCR4 antagonist, AMD3100 (Fig 1D). The migration superiority of Treg ^{CXCR4} was maintained at 30 and 60 min (Fig 1E). In order to understand in vivo transit kinetics, Treg cells were injected into NSG mice and organs were harvested at 12 and 24 hours (Fig 1F). Treg ^{CXCR4} showed preferential homing to BM (Fig 1G), where a higher expression of CXCR4 and CXCL12 than control, was observed (Fig 1H). Other markers including CD62L (homing and suppression), CD39 & CD73 (conversion of ATP to immunosuppressive adenosine), and CXCR5 (Follicular Treg) were also increased in Treg ^{CXCR4} recipients. A decrease in biomarkers including TGFα and TNFβ (inflammation), IL-13 (fibrosis) (Fig 1I) with an increase in GM-CSF (increase Treg potency) (Fig 1J), was observed in Treg ^{CXCR4} recipients with a corresponding decrease in TGFβ family (hematopoietic suppressor) (Fig 1K). We conclude that Treg ^{CXCR4} shows superior homing to BM and is currently being studied in a clinical setting to treat myelofibrosis with suboptimal response to ruxolitinib (NCT05423691).

Disclosures Sadeghi: *Cellenkos Inc:* Current Employment, Current equity holder in private company. **Masarova:** *MorphoSys US:* Membership on an entity's Board of Directors or advisory committees. **Flowers:** *Pharmacyclics Jansen:* Consultancy; *Foresight Diagnostics:* Consultancy, Current holder of *stock options* in a privately-held company; *Genentech Roche:* Consultancy, Research Funding; *Gilead:* Consultancy, Research Funding; *Genmab:* Consultancy; *Cellectis:* Research Funding; *Acerta:* Research Funding; *4D:* Research Funding; *Kite:* Research Funding; *Ziopharm:* Research Funding; *SeaGen:* Consultancy; *Celgene:* Consultancy, Research Funding; *Denovo Biopharma:* Consultancy; *Jannsen Pharmaceuticals:* Research Funding; *Xencor:* Research Funding; *TG Therapeutics:* Research Funding; *N-Power Medicine:* Consultancy, Current holder of *stock options* in a privately-held company; *Morphosys:* Research Funding; *V Foundation:* Research Funding; *Amgen:* Research Funding; *National Cancer Institute:* Research Funding; *Iovance:* Research Funding; *Allogene:* Research Funding; *Eastern Cooperative Oncology Group:* Research Funding; *Karyopharm:* Consultancy; *Pfizer:* Research Funding; *Guardant:* Research Funding; *Nektar:* Research Funding; *Bayer:* Consultancy, Research Funding; *Adaptimmune:* Research Funding; *Beigene:* Consultancy; *Novartis:* Research Funding; *Spectrum:* Consultancy; *Burroghs Wellcome Fund:* Research Funding; *Takeda:* Research Funding; *Sanofi:* Research Funding; *Pharmacyclics:* Research Funding; *Cancer Prevention and Research Institute of Texas:* Research Funding; *Abbvie:* Consultancy, Research Funding; *CPRIT Scholar in Cancer Research:* Research Funding. **Parmar:** *Cellenkos Inc:* Current

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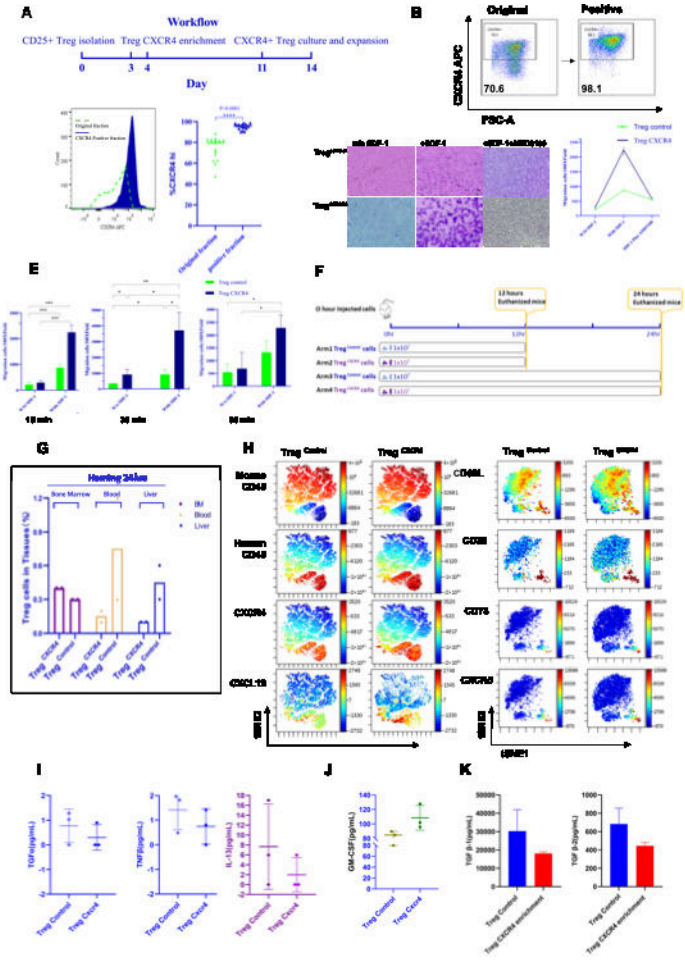

Figure 1

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