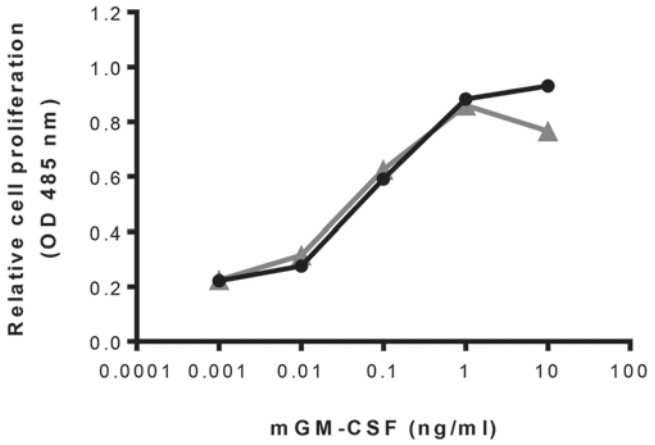

Abstract S120 Figure 1 Comparison of biological function of murine (m) GM-CSF produced after lentiviral-gene transfer and purchased purified protein (red: mGM-CSF produced through gene transfer, black: purchased mGM-CSF protein).

S121 CELL TRACKING IN LUNG CANCER

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Introduction Lung cancer is the leading cause of cancer death worldwide with over 70% of patients presenting with incurable disease and few effective treatments. We previously demonstrated that mesenchymal stem cells transduced to express TNF-related apoptosis inducing ligand (TRAIL), will home to and induce apoptosis of tumour cells *in vitro* and reduce tumour growth in multiple *in vivo* models. A key unknown of cellular therapy is the location and duration of cells following intravenous delivery. ^{111}Indium-oxine is established for lymphocyte tracking but it has low sensitivity and is toxic to cells. ^{89}Zirconium-oxine is a novel PET tracer which has better sensitivity and lower toxicity. Our study aimed to label MSCTRAIL with ^{89}Zr with the aim of tracking cells in patients enrolled in the TACTICAL trial – an early phase trial delivering MSCTRAIL to patients with metastatic lung adenocarcinoma.

Methods MSC-TRAIL cells were incubated with multiple doses of ^{89}Zr-oxine and label retention measured using a gamma counter. Cells were assessed for cell viability using cell proliferation assays, TRAIL expression was determined using flow cytometry and ELISA and apoptosis was determined using co-culture experiments with luciferase expressing cancer cell lines and bioluminescent readout. DNA damage and cellular stress was assessed using western blotting. To determine whether radiolabelled cells could be detected *in vivo*, 2×10^5 ^{89}Zr-Oxine MSC-TRAIL cells were delivered intravenously and imaging was performed at multiple time points (Mediso PET-CT, AMI-X).

Results ^{89}Zr-oxine labelling at clinically relevant doses did not affect cell proliferation and therapeutic efficacy was maintained in co-culture experiments. There was no evidence of DNA damage and cell stress response and cellular phenotype was maintained. CT/PET imaging after labelling and delivery of the cells into mice showed good correlation with bioluminescent signal confirming its use a high sensitivity tracking tool.

Conclusion ^{89}Zr-oxine can be used to successfully radiolabel genetically modified stem cells without effecting cell viability or therapeutic efficacy. We are currently performing *in vivo* studies to enable further translation into a clinical trial and will ultimately track MSC-TRAIL after patient administration via radiolabelling with ^{89}Zr-oxine.

S122 A ROLE FOR THE BONE MORPHOGENETIC PROTEIN TYPE 2 RECEPTOR (BMPR2) IN DIFFERENTIATION OF THE COMMON MYELOID PROGENITOR LINEAGE IN MICE AND HUMANS

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Rationale There is increasing evidence of a link between abnormalities in the myeloid cell lineage and pulmonary arterial hypertension (PAH). Heterozygous mutations in the gene encoding the bone morphogenetic protein type 2 receptor (*BMPR2*) are the most common genetic cause of PAH. We sought to characterise the impact of the genetic loss/reduction of *BMPR2* function in the myeloid lineage in mice and humans, and whether this altered susceptibility to PAH.

Methods Mx1-cre mice were crossed with *bmpr2*$^{flox/flox}$ mice. At approximately 8 weeks of age cre-recombinase was induced with polyinosinic-polycytidylic acid (Poly I:C). Control mice (*bmpr2*$^{flox/flox}$ mice with no cre) were also induced with Poly I:C. At approximately 16 weeks post-induction mice underwent right-heart catheterisation, exsanguination and tissue was removed for analysis. The spleens were weighed and histology was performed on the femurs. Mouse data are presented as mean ±SEM. In a large cohort of PAH patients with (n=160) and without (n=831) *BMPR2* mutations blood count indices were analysed. Data presented as median [IQR].

Results 16 weeks after induction of cre-recombinase in Mx1-cre/*bmpr2*$^{flox/flox}$mice we observed significant increases ($p<0.05$) in red blood cells ($x10^6/mm^3$) (12.7±0.9 compared with 12.1±0.2), haematocrit (%) (64.8±0.7 compared with 62.6±1) and haemoglobin (g/dl) (16±0.9 compared with 15.4 ±0.2) compared with *bmpr2*$^{flox/flox}$mice alone. A significant increase in circulating monocytes ($x10^3/mm^3$) was also observed ($p<0.05$) (0.4±0.05 compared with 0.3±0.05). In addition, we identified a significant increase ($p<0.05$) in megakaryocytes in the femurs (80±10 compared with 17±5) and a significant increase ($p<0.01$) in the ratio of spleen weight/body weight (0.003±0.0001 compared with 0.002±0.0001) in Mx1-cre/*bmpr2*$^{flox/flox}$ mice. During right heart catheterisation right ventricular systolic pressures were similar in both groups. In PAH patients significant differences ($p<0.05$) were seen in haemoglobin (*BMPR2* mutation: 162 g/L [151.75–173]) vs. no mutation: 150 g/L [135 – 163]), haematocrit (0.48 [0.45–0.52] vs. 0.44 [0.41–0.48]) and white blood cells (8.8 [7.3–10.4] vs. 8.11 [6.77–9.61]).

Conclusions we have identified a role for *bmpr2* in the differentiation of the mouse myeloid lineage, which was also confirmed in PAH patients with *BMPR2* mutations. *BMPR2* appears particularly important in the differentiation of megakaryocyte-erythrocyte lineage.