Targeting GPCRs to enhance haematopoietic stem cell transplantation

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The merit of haematopoietic cell transplantation is undisputed, but it carries the risk of graft failure, which is pronounced, if cell numbers are limiting. Haematopoietic stem cells are attracted to their niche by signals, which are transduced by G protein-coupled receptors (GPCRs). Accordingly, stimulation of several GPCRs (the prostanoid E2/EP2-, the prostanoid I/IP-, calcium-sensing receptor/CaSR, the C-X-C motif chemokine receptor 4/CXCR4 for stromal-derived factor-1/SDF1 = CXCL12) promotes engraftment of haematopoietic stem cells. These receptors can be readily targeted with approved drugs, which thus lend themselves to repurposing. We explored conditions, which lead to optimized engraftment of haematopoietic stem cells derived from murine bone marrow and human umbilical cord in lethally irradiated BALB/c and NSG mice, respectively. The G_s-dependent stimulation of bone marrow engraftment was contingent on CXR4, because the beneficial action of the EP2 and IP-receptor agonist treprostinil was blocked by the CXR4-antagonist plerixafor/AMD3100. Surprisingly, concomitant administration of vildagliptin and treprostinil resulted in poor survival of recipients indicating mutual antagonism, which was recapitulated when homing of and colony formation by HSPCs were assessed. In contrast, when administered sequentially, vildagliptin enhanced the action of treprostinil. Analogous observations were made when the combination of treprostinil and the CaSR-agonist cinacalcet were examined. These observations of regimen-dependent synergism and antagonism of treprostinil and vildagliptin or cinacalcet have translational implications for the design of clinical trials. In addition and importantly, synergism and mutual antagonism presumably arise from congruent and incongruent signals, respectively. Their nature is worthwhile exploring.