JAK Inhibitors Facilitate Hematopoietic Cell Engraftment Following Allogeneic BMT
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BACKGROUND
- Residual recipient immunity (T & NK cells) presents a barrier to donor cell engraftment following reduced intensity conditioning (RIC) allogeneic (allo) BMT
- JAK inhibitors, including the JAK1/2 inhibitor, Ruxolitinib (Rux), are immunosuppressive, short-acting, have a broad biodistribution & minimal toxicity

HYPOTHESIS
Addition of Rux to a RIC regimen will enable donor cell engraftment following allo BMT

METHODS
Fully MHC-mismatched BMTs
- B6 (H2Kb)→Balb (H2Kd)
- Balb (H2Kd)→B6 (H2Kb)
Conditioning:
- Myeloablative (MA) TBI
- RIC (50% MA) TBI
- RIC (≤50% MA) TBI + Rux

- Rux Day -5 through Day +2 (oral gavage BID) or Day +28 (chow)
- TBI on Day -1
- Whole bone marrow injected on Day 0
- Peripheral blood sampling starting Week +4 for FACS analysis

RESULTS

Fig. 1. B6→Balb Outcomes at Wk. +4

Controls:
- 8 Gy (MA) TBI = 100% engraftment
- 4 Gy (RIC) TBI = 100% rejection (≤ 5% donor)

Experimental:
- 4 Gy (RIC) TBI + 90 mg/kg Rux D-5 thru D+2 = 100% engraftment

Fig. 2. Balb→B6 Outcomes at Wk. +4

Controls:
- 13 Gy (MA) TBI = 100% engraftment
- 6.5 Gy (RIC) TBI = 100% rejection (≤ 5% donor)

Experimental:
- 6.5 Gy (RIC) TBI + 180 or 270 mg/kg Rux D-5 thru D+2 = 100% engraftment

Fig. 3. Balb→B6 (Rux D-5 thru D+2)
Donor Engraftment Over Time

Fig. 4. B6→Balb (Rux D-5 thru D+28)
Outcomes

CONCLUSIONS
- JAK1/2 inhibition (Ruxolitinib) reduces the barrier to engraftment presented by recipient NK and T cells
- Appropriately timed JAK1/2 inhibition in the peri-transplant period may represent an effective strategy to facilitate donor cell engraftment following RIC allo BMT

FUTURE DIRECTIONS
- Extended duration Rux (D-5 thru D+28) with TBI de-escalation appears promising strategy (Fig. 4)
- Testing efficacy of Rux-based RIC BMT in diseased (HgbSS, Berkley) mice with higher engraftment barrier
- Ongoing development of pediatric clinical trial incorporating Rux into RIC regimen to facilitate donor cell engraftment without added conditioning-related toxicities

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