

Inducing immunological chimerism in DNC organ recipients.

Arshna Qureshi^{1,2}, Zhu L^{1,2}, Reynolds J^{1,2}, Stamler J^{1,2,3}.

¹Institute for Transformative Molecular Medicine, Case Western Reserve University.

²Department of Anesthesiology, Case Western Reserve University.

³Harrington Discovery Institute, University Hospitals.

Organ recipients are treated with aggressive drug regimens to eliminate the recipient's functional immunity while adding a significant physical stress to the patients. Few researchers have proposed that the administration of donor bone marrow at the time of organ engraftment to induce immunologic chimerism can improve the outcome of the transplant. This technique was viewed as safe but showed varying efficacy. A variance perhaps due to impact of brain death (BD) on marrow function. We believe an important and under-appreciated component in this regard is the impact of BD on NO bioactivity, specifically how it impacts the main regulators of nitric oxide(NO) signaling, S-nitrosothiols (SNOs). We have determined in a pre-clinical model that induction of BD results in rapid depletion of RBC SNO-Hb levels. Current donor management practices do not account for changes in S-nitrosylation. By targeting NO bioactivity, we have a new mechanism for correcting this system-wide dysfunction, including improved bone blood flow to preserve marrow function. We have developed a first in class S-nitrosylating agent, ENO, that improves physiologic status in a pre-clinical BD preparation and we have successfully completed Phase 1 safety testing. As an initial step, we wanted to characterize the impact of brain death on the functionality of bone marrow obtained from human donors and also from a large animal model. Our data following flow cytometry determined that the percentage of CD34+ cells increases after brain death. However, their in-vitro proliferative capacity declines demonstrated by a decline in BFU-E colonies. Of additional importance, we found a positive correlation between SNO levels and BFU-E colonies. Next, in our swine brain dead models we found a similar decline in the in-vitro proliferative capacity of the bone marrow. However, this dysfunction was corrected by administration of ENO for the 24 h period following induction of BD, which resulted in 801% increase in BFU colonies compared to the control group. Thus, the addition of an S-nitrosylation agent during donor support could improve the engraftment potential of bone marrow from deceased donors and impart functional benefit to the graft recipients.