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## Rapid Thymic Reconstitution Following Bone Marrow Transplantation in Neonatal Mice is VEGF-Dependent.

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### Public Summary:

A healthy immune system produces T cells that can recognize and react against foreign molecules (antigens) to protect against infection, while leaving normal host cells with "self antigens" undamaged. All T cells are produced in the thymus from blood stem cells that originate in the bone marrow and migrate through the blood circulation to the thymus. During aging, the thymus shrinks in size (involuting) and T cell production is limited, causing a poorly functioning immune system. T cell production and immune recovery is also slow and incomplete after bone marrow transplantation in older patients. In previous studies we showed that the thymus grows rapidly and T production is very robust in new-born mice. We also showed that during the new-born period, a growth factor called Vascular Endothelial Growth Factor (VEGF) is made at high levels in the thymus. When VEGF is inhibited in new-borns, T cell production falls, suggesting that this molecule plays an important role in thymic growth during this period. In the current work, our goal was to find whether VEGF production was also important to immune recovery after bone marrow transplantation. We have now shown that performing bone marrow transplantation during the new-born period produces a markedly faster and stronger recovery of T cell production than when transplantation is performed in adults. Inhibition of VEGF significantly delays T cell reconstitution in the new-born (but not the adult) animal. By 6 weeks post transplantation, thymus function returns to normal. Our data suggests that VEGF is required for the rapid phase of T cell reconstitution in new-borns but is not required for the later "maintenance" phase during adulthood when T cell production is derived from a renewable source of bone marrow stem cells. Our new studies are testing whether VEGF provided locally to an adult thymus will enhance immune reconstitution.

### Scientific Abstract:

Age-related differences in thymic function influence the rapidity of T cell reconstitution following hematopoietic stem cell transplantation (HSCT). In adults, thymic reconstitution is delayed until after marrow engraftment is established, and is significantly improved by approaches that increase marrow chimerism, such as pre-transplant irradiation. In contrast, we show that neonatal mice undergo more rapid and efficient thymic reconstitution than adults, even when bone marrow engraftment is minimal and in the absence of pre-transplant radiation. We have previously shown that the neonatal thymus produces high levels of vascular endothelial growth factor (VEGF) that drives angiogenesis locally. In this report we show that inhibition of VEGF prior to HSCT prevents rapid thymic reconstitution in neonates, but has no effect on thymic reconstitution in adults. These data suggest that the early, radiation independent, thymic reconstitution unique to the neonatal host is mediated through VEGF, and reveals a novel pathway that might be targeted to improve immune reconstitution post-HSCT.

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