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Alloreactive T-cell trafficking after hematopoietic stem cell transplantation

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Acute graft-versus-host disease (aGVHD) is the major limitation for a broader application of allogeneic hematopoietic stem cell transplantation (allo-HSCT). In aGVHD alloreactive donor T-cells attack the recipient's gastrointestinal tract, liver and skin. To address this unusual tissue tropism we developed luciferase transgenic (*luc+*) mice and utilized bioluminescence imaging to track adoptively transferred *luc+* T-cells non-invasively in living recipients. Either myeloablative conditioned BALB/c (H-2d, 8Gy) or C57Bl/6 (H-2b, 9Gy) recipient mice were transplanted with allogeneic *luc+* T-cells (FVB/N, H-2q) and FVB/N wild type bone marrow. We observed that T-cell proliferation was confined to secondary lymphoid organs until day+3 after allo-HSCT. At this time alloreactive T-cells up-regulated specific homing receptors and subsequently migrated via the blood to aGVHD target tissues. When we blocked T-cell entry to specific lymphoid organs we found a high redundancy of these priming sites. However, by preventing T-cell entry to all secondary lymphoid organs aGVHD was completely averted. In subsequent experiments we isolated *in vivo*

primed alloreactive *luc+* T-cells from mesenteric lymph nodes, peripheral lymph nodes or the spleen and transferred these cells into conditioned secondary transplantation recipients. *Luc+* T-cells attacked aGVHD target tissues irrespective of the original priming site. In contrast, after secondary transfer into non-conditioned recipients *luc+* T-cells preferentially homed to lymphoid organs. These data suggests that not the lymphoid priming sites but instead signals from the aGVHD-target tissues dictate the distinct tissue tropism in aGVHD.

A.B. and St. S. contributed equally to this study.