

# Hematopoietic Cell Transplants Induce Tolerance to Composite Tissue Allografts

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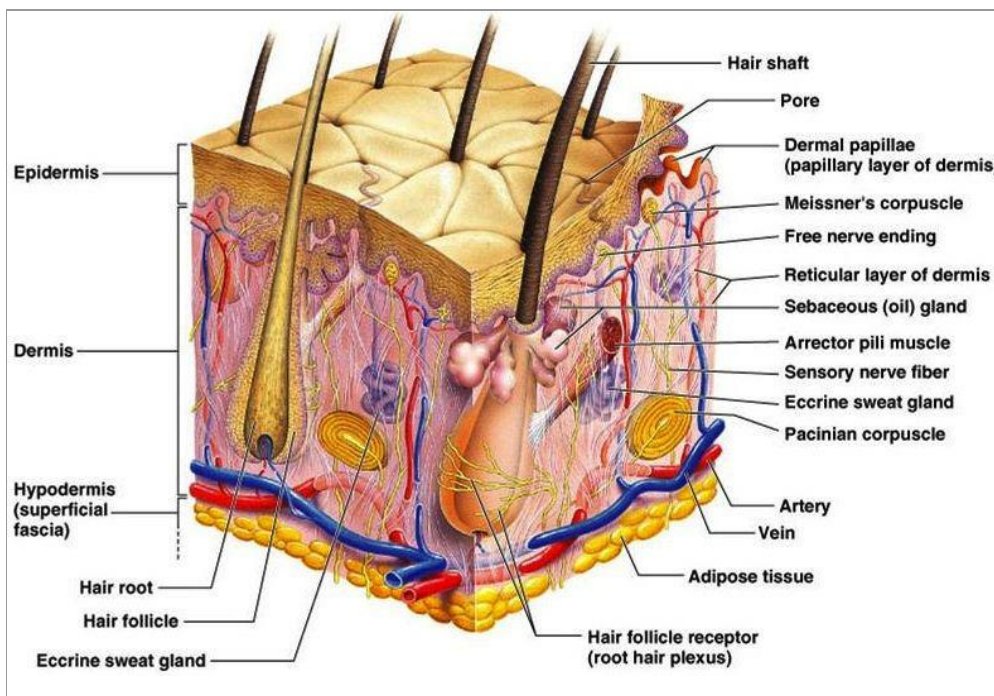
Persons with severe burns often require transplantation of large skin grafts for their survival. Previous attempts to engineer artificial skin or tissue in vitro have been ineffective, and grafting of one's own skin from one site to another is confined to small patches of skin and can have severe complications. Allogenic skin could meet the needs for large amounts of grafting material; however, because these allografts are obtained from genetically non-identical people they are acutely rejected. While immunosuppressive agents can prevent the early rejection of organ transplants such as the kidney and pancreas, they have been ineffective against skin, which is highly immunogenic. Thus, strategies to induce immune tolerance to skin allografts in the absence of chronic widespread immunosuppression are necessary. To address this need, Dr. David Mathes and colleagues in the Clinical Research Division have recently established a non-myeloablative conditioning regimen in a canine model that allows for engraftment of a multi-tissue vascularized skin graft. Furthermore, the resulting mixed chimerism of host and donor hematopoietic cells was stable and associated with locally increased numbers of FoxP3+ regulatory T-cells that mediate immune tolerance.

Mixed host-donor chimerism was established in dogs by giving a sublethal dose of total body irradiation followed by hematopoietic cell transplantation and a short-term regimen of immunosuppressive therapy. Following confirmation of stable mixed chimerism, which took anywhere from five months to more than four years, the authors transplanted composite tissue grafts from the bone marrow donors to their respective recipients, and vice versa. Composite allografts allow for the evaluation of tolerance to multiple different tissues, as they are comprised of skin, muscle, fat, nerves and lymphatic and blood vessels. Composite allografts are an excellent transplantation model for complex tissues involving skin and muscle. While non-chimeric controls rejected grafts within 29 days, chimeric recipients accepted grafts ranging from 52-90 weeks. Acceptance was indicated by normal skin color and hair growth, normal blood cell counts, and histological absence of cellular infiltrates, vascular disease, or epidermal architecture damage within the graft region. Rejected grafts from control donors were marked by tissue necrosis and infiltrating effector T-cells. In contrast, skin, muscle and draining lymph nodes of chimeric recipients had increased frequencies of FoxP3+ regulatory T-cells. Regulatory T-cells are a subpopulation of the

immune system that suppresses the function of other immune cells to prevent autoimmune disease, maintain tolerance to self-antigens, and facilitate organ transplantation.

This study demonstrates durable tolerance to all portions of a vascularized composite allograft in an out-bred dog population following a non-myeloablative conditioning regimen and short-term immunosuppressive treatment. It remains to be seen if these methods will be applicable to severe burn patients, who require rapid and extensive skin or composite tissue grafting. However, the methods developed in this study may obviate the need for long-term immunosuppressives in other less immunogenic and more commonly transplanted organs.

[Mathes DW, Hwang B, Graves SS, Edwards J, Chang J, Storer BE, Butts-Miwongtum T, Sale GE, Nash RA, Storb R.](#) 2011. Tolerance to vascularized composite allografts in canine mixed hematopoietic chimeras. *Transplantation* 92:1301-1308.



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Multiple tissues make up a composite skin graft.