Addressing immune responses to therapy in EB - T cell skin immunity

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For genodermatoses such as the inherited skin blistering disease Epidermolysis bullosa (EB) a promising and successful therapeutic approach is ex vivo gene therapy, where disease-causing defective genes are replaced in tissue stem cells, skin grafts generated ex vivo and transplanted on to the recipient. This therapy introduces the wild-type version of the mutated protein (that is expressed by untreated skin of the recipient) and thus the recipient may mount an immune response against the neo-antigen (i.e. the wild-type protein) expressed in the graft. Therefore a critical aspect for the success of this therapy is the prudent selection of patients that may already have tolerance towards the therapeutic antigen.

We have followed systemic and local immune responses in a JEB patient that had received ex vivo skin gene therapy. Additionally, we have established mouse models in which we transplanted skin that expressed a defined neo-antigen. With these we determined that the immune response against an epidermal neo-antigen lead to graft rejection. Furthermore we found a $CD4^+$ T cell infiltrate in the skin graft which might be involved in acute rejection. We hypothesized that regulatory T cells (Treg) could attenuate skin graft rejection. We established a protocol to generate and expand peripheral Treg in vivo using a modified IL-2/anti-IL-2 complex therapy. Using our preclinical models of neo-antigen skin graft rejection we found that Treg can prolong skin graft survival in combination with small molecule inhibitors such as rapamycin. We will use our mouse models to investigate the function and maintenance of skin-resident Treg, which are both crucial for the long-term success of immuno-therapy to suppress skin-graft rejection. Our long-term goal is the induction and maintenance of immunological tolerance in clinical settings in humans.