THEMA: .....(Bitte einsetzen, ob Abdomen (Leber, Niere, Pankreas), Thorakale Organe, KMT, Basic Science)

PRÄSENTATION (PRÄFERENZ): ..... (Bitte einsetzen: Mündlich oder Poster)

YOUNG INVESTIGATOR AWARD: .....(Bitte ja oder nein einsetzen)

MUSTER ABSTRACT (ENGLISCH wegen Publikation im TI Journal, max. 300 Worte exkl. Titel und Autoren, Sprecher in fett angeben, Autoren: Vornamen ausschreiben, Aufbau: Background, Methods, Results, Conclusions), Arial, 10pt:

Thema:	Basic Science
Präsentation (Präferenz):	Poster
Young investigator award:	ja
Abstract:	**O** klinisch **O** experimentell (bitte zutreffendes eintragen)

Mechanisms of IL2/anti-IL2 complex induced transplantation tolerance

Nina Pilat[1, 2], Joanna Warren[1], Theresa Corpuz[1], Kylie Webster[1], Jonathan Sprent[1]
[1]Immunology Division, Garvan Institute of Medical Research, Sydney, Australia
[2]Department of Surgery, Medical University of Vienna, Vienna, Austria

BACKGROUND: Interleukin-2 (IL-2) complexed with a specific antibody against IL-2 (IL2-complexes) was shown to rapidly expand and activate Tregs *in vivo*. Moreover, treatment with IL2-complexes has shown potency in suppressing autoimmune diseases and inducing tolerance towards islet allografts. However, preliminary data show little effect in a fully mismatched model of skin allografts. Here we investigated the potency of IL2 complex based therapy to prolong skin allograft survival and the mechanisms of tolerance therein.
METHODS: Recipient mice (C57BL/6) received fully mismatched skingrafts (Balb/C) and treatment with IL2-complexes (0.5mg IL2/2.5mg JES6-1; i.p. d-3/-2/-1) and rapamycin (1mg/kg; i.p. d-1/0/1). Indicated groups received prolonged treatment with Il2-complexes and rapamycin (3x/week till d29) and additional short-term treatment with anti-IL6 (300µg i.v. d-1/1/4/6). Mechanisms of tolerance were investigated by analysis of anti-donor-reactive antibodies, flow-cytometric analysis and MLRs. Groups of mice were challenged with a second skingraft to test for infectious tolerance and for memory responses.
RESULTS: We could show that combination with rapamycin significantly prolongs survival of fully mismatched skingrafts (MST=13.5d, p=0.0079) which is even more pronounced with extended IL2-complex/rapamycin therapy (MST=22d, p=0.0046). Anti-inflammatory treatment with anti-IL6 at the time of skingrafting leads to prevention of acute rejection, even after complete stop of treatment at d29 (MST=84.5d, p=0.0010). Analysis of sera revealed complete absence of donor-specific antibodies even after short-term treatment (p=0.01) and kinetics of rejection of a second graft (post primary-graft rejection) suggested additional absence of T cell memory response. Operational tolerant mice challenged with a second graft and MLRs suggest absence of systemic immunosuppression or donor-specific tolerance. Flow cytometric analysis of the graft indicates increased frequencies of intragraft Tregs and active regulatory mechanisms.
CONCLUSIONS: We could show that Treg expansion via IL2-complexes synergizes with low-dose rapamycin and anti-inflammatory treatment with anti-IL6, leading to significantly prolonged skin allograft survival and prevention of acute rejection even in the absence of ongoing treatment. Further experiments to find an optimal dosing regimen leading to indefinite survival and a deeper understanding of the underlying mechanisms are warranted. We think that these encouraging results will have significant impact on the development of new protocols for tolerance induction in transplantation.