Presidential & Awards Session

Best oral presentations

O-326 LONGEVITY OF THE DIRECT AND INDIRECT CD4 T CELL ALLOIMMUNE RESPONSE

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Introduction: Recipient CD4 T cells can recognise intact alloantigen "directly" on donor antigen presenting cells (APCs) or processed alloantigen presented "indirectly" by recipient APCs. The direct and indirect alloresponses likely dominate the early and late transplant responses respectively, although the relative longevity of the pathways has not been formally examined.
Methods: The duration of direct and indirect allorecognition was assessed by comparing division of adoptively transferred monoclonal populations of CFSE-labelled TCR-transgenic CD4 T cells in B6 recipients of mouse cardiac allografts. Direct allorecognition was examined by transfer of ABM CD4 T cells ($I\text{-}A^{bm12}$-reactive) into recipients of bm12 heart grafts. Indirect allorecognition was examined by transfer of: (1) TCR75 CD4 T cells into recipients of $B6.K^{d}$ hearts (responses against K^{d}-derived MHCI allopeptide); (2) TEa CD4 T cells into recipients of $I\text{-}E^{+ve}I\text{-}A^{-ve}$ B6 hearts (responses against I-E-derived MHCII allopeptide) and; (3) Mar CD4 T cells into female recipients of male B6 hearts (responses against minor H-Y alloantigen). All 4 allorecognition pathways were additionally examined concurrently in female B6 recipients of male bm12.kd.$I\text{-}E^{+ve}I\text{-}A^{-ve}$ allografts.
Results: ABM CD4 T cells divided extensively after early adoptive transfer but only minimally when transferred 5 weeks after transplant, in keeping with a self-limiting direct alloresponse. Similarly, indirect pathway anti-MHCII alloresponses were readily apparent early after transplant but were surprisingly undetectable by five weeks, presumably due to diminished late MHCII antigen availability. In contrast, indirect anti-MHCI alloresponses were equally strong at both time points, while the indirect alloresponse against minor H-Y antigen was present but less marked at late time points.
Conclusion: Our results confirm the transience of the direct alloimmune response, but unexpectedly highlight that the indirect alloresponse against MHCII is transient while that against MHCI and minor alloantigens persist late after transplantation.

O-327 MALIGNANCY IN ORGAN DONORS IN GERMANY 2006-2009

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Background: In times of organ shortage there is an increasing acceptance of organs from donors with malignant tumors. Risk of tumor transmission has to be estimated and weighed against recipient benefit. Current literature does not yet provide sufficient data about tumor-transmission-risk. This study shows a 4-year survey of all utilized organ donors with malignancy in Germany. Recipient Follow-Up and reported tumor transmissions are documented.
Methods: Retrospective ISYS-database-analysis of all donors with malignancy in Germany from January 2006 to December 2009. Follow-Up of recipients (questionnaire filled out by transplant centre) in September 2010.
Results: 15,907 organs from 4,969 donors in Germany have been procured and transplanted. 138 donors (2.8%) showed 141 malignancies. Renal cell carcinoma (RCC, n=28), Glioblastoma multiforme (n=10) and breast cancer (n=9) were the most frequent tumors. 383 organs of these donors (2.4% of all organs) have been transplanted (182 kidneys, 112 livers, 40 lungs, 46 hearts, 3 pancreata). Organ acceptance occurred with knowledge of the malignancy in 90.8% (n=128) of the donors, in 9.2% (n=13) the donor malignancy has been diagnosed after transplantation of the organs. First recipient Follow-Up (return 85%) after median 777 days (0-1716) showed 3 tumor transmissions in 4 recipients (RCC n=2/2, neuroendocrine tumor n=1/2). None of these tumors had been diagnosed in the donor, they first appeared in the recipients. 2 recipients died of transmitted neuroendocrine tumors, the others are free of tumor after transplantnephrectomy of the diseased kidneys.
Conclusion: This first German donor-malignancy survey with recipient Follow-Up is an important component for future risk estimations of tumor-transmission-risk from donor to recipient. Rational and evidence-based risk-benefit-assessment requires detailed data collection for a maximum recipient safety. Combining European and worldwide experiences will increase evidence and help transplant physicians in their decisions about acceptance of these organs.

O-328 INTERNATIONAL REGISTRY ON HAND AND COMPOSITE TISSUE ALLOTRANSPLANTATION

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Background: The International Registry on Hand and Composite Tissue Transplantation includes hand and face allotransplantations.
Methods: Since September 1998 49 hands (17 unilateral and 16 bilateral hand transplantations, including one case of bilateral arm transplantation) have been reported, for a total of 33 patients. They were 31 males and 2 females, median age 32 years. In 46% of cases the level of amputation was at wrist.
Since November 2005 eleven cases of face transplantations have been reported, 9 males and 2 females, median age 34 years. In the majority of cases the deficit included cheek, nose, chin, lips and perioral area. The patients presented impairment of swallowing, eating and speaking.
In hand and face transplantation the imunosuppressive therapy included tacrolimus, mycophenolate mofetil, sirolimus and steroids; polyclonal or monoclonal antibodies were used for induction. Follow-up ranges from 6 months to 11 years for hand transplantation and from 11 months to 5 years for face transplantation.
Results: One simultaneous face and bilateral hand transplantation died on day 65. Three patients transplanted in the Western countries have lost their grafted hands, and until September 2009 seven hand grafts were removed in China.
Eighty-five percent of hand and face recipients experienced at least one episode of acute rejection within the first post-transplant year that was reversible when promptly treated. Side-effects included opportunistic infections, metabolic complications and malignancies.
Hand-grafted patients developed protective sensibility, 90% of them tactile sensibility and 82.3% also a discriminative sensibility Motor recovery enabled patients to perform most daily activities. Face-grafted patients improved their aesthetic aspect and particularly some activities such as eating, drinking and speaking, living a normal social life.
Conclusions: Hand and face transplantations are successful procedures, however careful evaluation of patients before and after transplantation and their compliance are indispensable.

O-329 12-MONTH RESULTS OF TOFACITINIB (CP-690,550)-BASED CNI-FREE IMMUNOSUPPRESSION IN A PHASE 2B STUDY IN DE NOVO KIDNEY TRANSPLANT PATIENTS

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Background: Tofacitinib (CP-690,550; formerly known as tasocitinib) is an orally active JAK inhibitor that suppresses signaling of multiple cytokines. Tofacitinib is being investigated for the prevention of allograft rejection in kidney transplant patients and for the treatment of select autoimmune diseases.
Methods: In this randomized, partially blinded, 12-month Phase 2b study, 322 de novo kidney transplant patients received either cyclosporine (CsA), or 1 of 2 tofacitinib-based regimens: a more intense regimen (MI) that started at 15 mg twice daily (BID) and then decreased to 10 mg BID after Month 6; or a less intense regimen (LI) that started at 15 mg BID and then decreased to 10 mg BID after Month 3. All patients received basiliximab induction, mycophenolic acid products (starting at 2 gm/day MMF or 1.44 gm/day MPA in all 3 groups) and corticosteroids. The co-primary endpoints were the incidence of biopsy-proven acute rejection (BPAR) at Month 6 and iohexol-measured glomerular filtration rate (GFR) at Month 12.
Results: see Table 1.

Table 1

Results at Month 12, unless otherwise stated	CsA (n=109)	MI (n=106)	LI (n=107)
BPAR rate at Month 6, %	17.7	16.1†	12.4†
BPAR rate at Month 12, %	18.8	17.4†	15.4†
Graft survival (all-cause, last follow-up risk set), %	96.0	94.5	90.9
Mean iohexol-measured GFR, mL/min	53.9	64.6*	64.7*
% patients with chronic allograft nephropathy (CAN) in protocol biopsy	48.3	25.0*	23.9*
% patients with progression of CAN from implantation	45.1	26.5	22.7*
NODAT, %	20.8	9.9	9.3
Serious infection, %	25.3	44.5*	37.0*
CMV disease including CMV syndrome, %	4.5	19.5*	13.3*
BKV nephritis, %	1.1	2.6	3.9
Number of patients with PTLD	0	2#	1

†Statistically non-inferior to CsA; *$p<0.05$ vs. CsA; #Two additional cases of PTLD occurred after Month 12.

The incidence of anemia and neutropenia in the tofacitinib groups was higher than that of CsA in the first 6 months but decreased substantially after Month 6. The tofacitinib groups had approximately 40% higher MPA exposure compared with CsA. Exposure-response analysis showed that patients with 2-hour post-dose tofacitinib level below the median had similar BPAR and infection rates to CsA.
Conclusions: At 12 months posttransplant, both tofacitinib groups had better renal function and lower proportions of patients with CAN in biopsy than CsA, while demonstrating comparable incidence of BPAR to CsA. However, there were more adverse events associated with over-immunosuppression and myelosuppression in the tofacitinib groups.

O-330 LONG TERM CLINICAL RECOVERY OF PARKINSON'S DISEASE FOLLOWING TRANSPLANTATION OF CTLA4-IG$^+$ PORCINE EMBRYONIC NEURONAL CELLS IN NON HUMAN PRIMATE

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Neural allo- and xeno-transplantation has been attempted as a therapeutic approach in Parkinson disease (PD) with variable outcomes. Here we have analyzed the clinical effects of neural precursors from CTLA4-Ig$^+$ transgenic pigs transplanted into the brain of PD macaques.
Methods: PD was induced in 17 macaques by repeated exposures to MPTP. Once stable lesions were obtained, PD monkeys were unilaterally injected in the left putamen with neural cells from CTLA4-Ig$^+$ (n=14) or wild type pig embryos (n=3). All primates were immunosuppressed using a clinically applicable immunosuppressive regimen. Xenograft survival and function was determined by clinical neurological assessment, analysis of locomotor function (Ethovision software), brain imaging (PET scan with ^{18}F-L-DOPA), and histological studies at the end of each experiment.
Results: Xenografted animals have been monitored for up to 720 days post transplantation (median: 186 days) with the longest surviving recipient still ongoing. Behavioural studies showed significant recovery of spontaneous locomotion (40% to 100% PD improvement) in all animals receiving CTLA4-Ig$^+$ cells associated with a partial restoration of dopaminergic activity detected by PET at 6 months postoperatively in at least 6 primates. No improvement in spontaneous locomotion and no dopaminergic activity was observed in wild type neuronal cells transplanted primates. Histological analysis of the brain from clinically improved animals revealed the existence of large porcine grafts composed of dopaminergic, serotoninergic and GABAergic differentiated neurons and various glial components. As PTLD occurred in several long term recipients, 3 ongoing animals are being treated with sub-therapeutic levels of the drugs.
Conclusion: Transplantation of porcine neuronal precursors in the striatum of immunosuppressed PD primates may represent a useful therapeutic tool for PD. CTLA4-Ig expression is essential for longterm xenograft survival and differentiation, associated with significant improvement of locomotor activity.

O-331 CD160Ig FUSION PROTEIN TARGETS A NOVEL COSTIMULATORY PATHWAY AND PROLONGS ALLOGRAFT SURVIVAL

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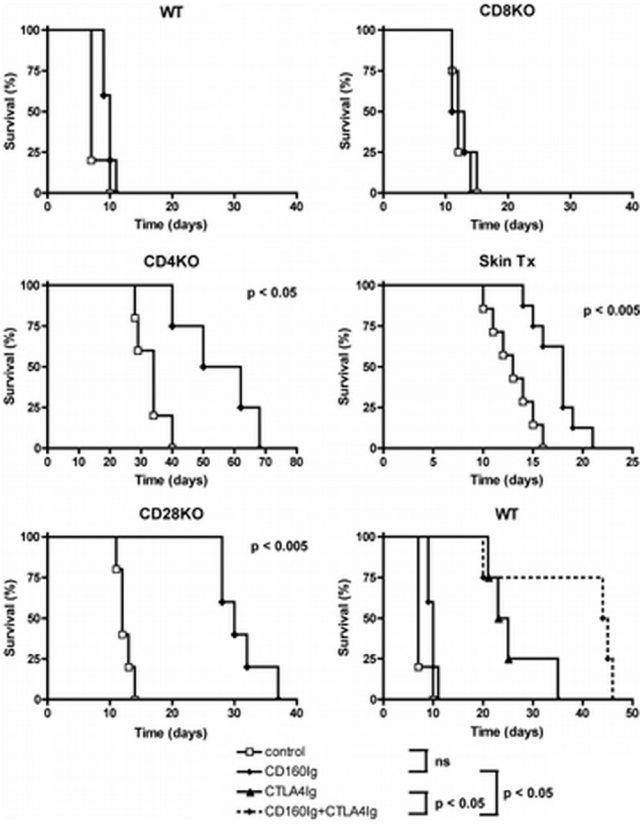
CD160 is a cell surface molecule expressed by most murine NK cells and approximately 50% of CD8$^+$ cytotoxic T lymphocytes. Engagement of CD160 by MHC class-I directly triggers cytokine production and cytotoxic function in NK cells and provides a costimulatory signal to TCR-induced proliferation, cytokine production and cytotoxic effector function in CD8$^+$ T cells. The role of CD160 in alloimmunity is unknown. Using a newly generated CD160 fusion protein (CD160Ig) we examined the role of the novel costimulatory molecule CD160 in mediating CD4$^+$ or CD8$^+$ T cell driven CD28- dependent and independent allograft rejection. CD160Ig inhibits alloreactive CD8$^+$ T cell proliferation and IFN-g production *in vitro*, in particular in the absence of CD28 costimulation. CD160Ig prolongs fully mismatched murine cardiac allograft survival in CD4$^{-/-}$ and CD28$^{-/-}$ knockout and CTLA4Ig treated WT recipients, but not in WT or CD8$^{-/-}$ knockout recipients.
The prolonged cardiac allograft survival in CD4$^{-/-}$ and CD28$^{-/-}$ knockout and



CTLA4Ig treated WT recipients is associated with reduced alloreactive $CD8^+$ T cell proliferation, allospecific Th1 cytokine production and generation of effector/memory $CD8^+$ T cells. Thus, CD160 signaling is particularly important in CD28-independent effector/memory $CD8^+$ alloreactive T cell activation *in vivo* and may therefore serve as a novel target for prevention of allograft rejection.