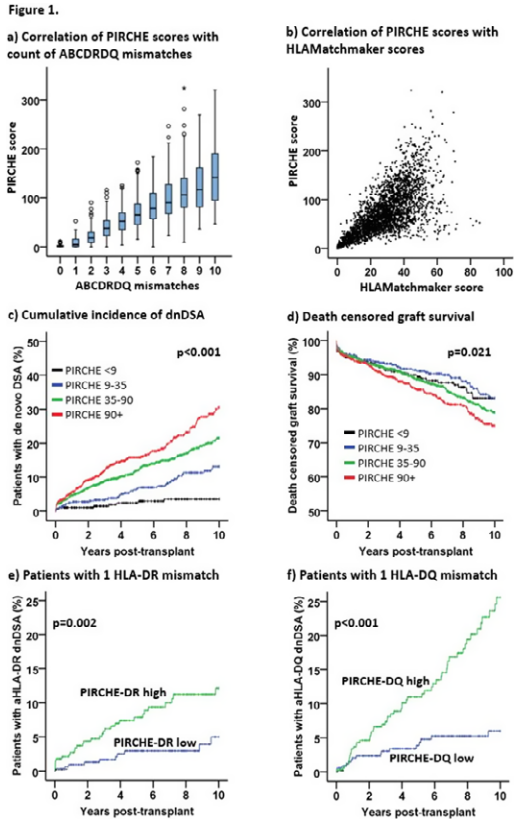
BEST ABSTRACT CHALLENGE

Clinical Kidney Histocompatibility

BAC001 OUTCOME AFTER KIDNEY TRANSPLANTATION IS INDEPENDENTLY PREDICTED BY DONOR RECIPIENT MATCHING BASED ON INDIRECTLY RECOGNIZABLE HLA EPITOPES

Staeck Oliver[1], Niemann Matthias[2], Spierings Eric[3], Reinke Petra[1], Halleck Fabian[1], Khadzhynov Dmytro[1], Budde Klemens[1], Lachmann Nils[4]
[1]Nephrology/ University Medicine Charité, Germany; [2]Pirche, Germany; [3]UMC, Utrecht ,Germany; [4]Center For Tumor Medicine, H&I Laboratory, Charité University Medicine, Berlin, Germany

Background: De novo donor-specific HLA antibodies (dnDSA) are recognized as a risk factor for graft loss. Determinants of DSA specificity are generated via the indirect allorecognition pathway. Here, we present supportive data for the relevance of predicted indirectly recognizable HLA epitopes (PIRCHE) to predict dnDSA following kidney transplantation.
Methods: A total of 2787 consecutive kidney transplantations performed 1995–2015 without preformed DSA have been analyzed. De novo DSA were detected by Luminex® single antigen assay. HLA epitope mismatches were determined by the PIRCHE and HLAMatchmaker approach and correlated in uni- and multivariate analyses with 10-year allograft survival and incidence of dnDSA.
Results: The correlation of the PIRCHE scores with the count of ABCDRDQ mismatches and with the HLAMatchmaker scores is shown in Fig. 1a,b. The PIRCHE score was a strong predictor of dnDSA ($p < 0.001$, Fig. 1c) and moderately predicted allograft survival (Fig. 1d). When analyzing the predicted impact of high versus low PIRCHE scores on dnDSA development stratified according to the degree of antigen mismatch at each HLA locus, a clear differentiation could be revealed for HLA-DR and DQ (illustrated according to low versus high PIRCHE scores (1st vs. 4th quartile) in patients with 1 HLA mismatch at the specific locus in Fig. 1e,f) and to a lesser extent also for HLA-A ($p = 0.013$) and B ($p = 0.010$). In a multivariate Cox regression analysis adjusted for antigen mismatches and HLAMatchmaker epitopes the PRCHE-II score could be identified as an independent risk factor for dnDSA ($p < 0.001$).
Conclusion: The PIRCHE score independently from the antigen mismatch and HLAMatchmaker epitopes could be revealed as having a strong predictive value for dnDSA. PIRCHE may help to identify acceptable mismatches with decreased risk of dnDSA and thus improve long-term renal allograft survival.



Translational Kidney Histocompatibility

BAC002 A NOVEL COMPUTATIONAL MATCHING ALGORITHM FOR IMPROVING DONOR-RECIPIENT HISTOCOMPATIBILITY AND GRAFT OUTCOMES AFTER KIDNEY TRANSPLANTATION

Kosmoliaptsis Vasilis[1], Mallon H. Dermot[1], Bradley J. Andrew[1], Fuggle Susan[2], Watson Christopher[1], Taylor J. Craig[1]
[1]Department Of Surgery, University Of Cambridge, United Kingdom; [2]NHS Blood And Transplant, United Kingdom

Introduction: HLA matching is a central objective of kidney allocation policies, but current assessment of histocompatibility is inadequate. Building on our previous research, we have now developed a novel computational scoring system to quantify structural and surface electrostatic potential differences between donor and recipient HLA (Electrostatic Mismatch Score; EMS-3D) and applied it to examine long-term graft survival after kidney transplantation in a national patient cohort.
Methods: Data were obtained from the UK Transplant Registry on 11 018 adult, deceased-donor, first, kidney only transplants performed between 2003 and 2012. A multivariate Cox regression model was fitted to investigate the influence of HLA on death-censored graft survival. The model was risk-adjusted for donor, recipient and transplant factors. HLA comparisons were performed using our bioinformatics platform to determine the EMS-3D for each donor-recipient HLA combination.
Results: Patients were followed up for a median (IQR) of 6.5 (4.5–9.5) years. Increasing number of HLA mismatches at the HLA-A, -B, -DR and -DQ loci significantly increased the risk of graft failure (HR: 1.06 per HLA mismatch, 95% CI: 1.02–1.09, $p = 0.001$). Increasing EMS-3D (median: 1.07, range: 0–2.91) was independently associated with an incremental increase in the risk of graft failure and, when included in the same multivariate Cox model, EMS-3D was a stronger predictor of graft survival than conventional HLA mismatch grade (HR: 1.62 per EMS-3D unit increase, 95% CI: 1.06–2.88, $p = 0.03$; versus HR: 1.04 per HLA mismatch, 95% CI: 0.97–1.12, $p = 0.32$). Notably, EMS-3D enabled identification of a large number of grafts with excellent outcomes despite high HLA mismatch grade.
Discussion: This study shows that our novel HLA matching algorithm enables improved histocompatibility assessment and may help inform future deceased-donor kidney transplant allocation policies to maximise the benefits of transplantation.

Translational Others cell therapy Immunosuppressive agents

BAC003 MHC-II DONOR PEPTIDES ACTIVATE HUMAN CD8 + CD45RC^{LOW} TREGS SECRETING IFNγ, IL-10, IL-34 AND TGFβ TO INHIBIT HUMAN TRANSPLANT REJECTION

Bézie Séverine[1], Boucault Laetitia[1], Meistermann Dimitri[1], Daguin Véronique[1], Autrusseau Elodie[1], Bellier Waast Frédérique[2], Duteille Franck[2], Anegon Ignacio[1], Guillonneau Carole[1]
[1]Inserm Umr1064 – CRTI, France; [2]CHU, Nantes, France

Background: We previously reported the suppressive properties of rat CD8$^+$CD45RC^{low}Treg cells. To date, human counterparts have never been studied for their relevance as a cell-based therapy.
Materials and Methods: Cytokine secretion assay kits were used to sort IFNg/IL10 secreting Tregs from healthy volunteers PBMCs by FACSAria. Tregs were expanded for 14 days with anti-CD3/CD28 mAbs, allogeneic APCs or syngeneic APCs and peptide and analyzed for TCR repertoire. Suppressive function was assessed *in vitro* on syngeneic CD4$^+$CD25$^-$T cells stimulated by alloAPCs, and *in vivo* into NSG mice infused with PBMCs and grafted or not with allogeneic human skin for allograft survival and xenogeneic GVHD studies.
Results: We demonstrated that human CD8$^+$CD45RC^{low}T cells contain natural regulatory cells expressing Foxp3 and GITR and secreting IFNg, IL-10, TGFbeta and IL-34. CD45RC^{low}CD8$^+$ Tregs inhibited allogeneic T cell proliferation, more efficiently than classical CD4$^+$Tregs. Cytokines and a preferential contact with pDCs were required for CD8$^+$CD45RC^{low} Tregs suppressive activity, but no cytotoxicity. We developed a protocol to expand CD8$^+$Tregs using IL-2, IL-15 and donor antigens and obtained up to 2000 fold expansion. Expanded Tregs displayed a biased TCR with restricted and private alpha and beta chain repertoire. We showed that CD8$^+$ Tregs recognized a dominant 16aa peptide derived from donor MHC class II molecules, expanding

and activating their suppressive function. Expanded $CD8^+CD45RC^{low}$Tregs were highly suppressive *in vitro* and *in vivo* significantly delayed GVHD development and allogeneic skin graft rejection in humanized mice.
Conclusions: We identified and characterized a new natural regulatory T cell population as a promising candidate for cell therapy.

Clinical Liver Ischemia-reperfusion and preservation

BAC004 NORMOTHERMIC MACHINE PERFUSION VS STATIC COLD STORAGE IN LIVER TRANSPLANTATION: OUTCOMES FROM A RANDOMISED CONTROLLED TRIAL

Nasralla David[1], Liver Research Group Cope[1], Ploeg Rutger[1], Coussios Constantin[2], Friend Peter[1]
[1]Oxford Transplant Centre, Nuffield Department Of Surgical Sciences, University Of Oxford, United Kingdom; [2]Institute Of Biomedical Engineering, University Of Oxford, United Kingdom

Introduction: Normothermic machine perfusion (NMP) involves perfusing a liver with oxygenated blood, medications and nutrients at 37C, and may improve outcomes after liver transplantation when compared with conventional static cold storage (SCS). We present the first randomised controlled trial (RCT) comparing continuous NMP with SCS in human liver transplantation.
Methods: This multinational RCT was initiated by the Consortium for Organ Preservation in Europe (COPE) and involved seven European transplant centres. Adult DBD and type III DCD livers were randomly assigned (1:1) to continuous NMP or SCS. The primary end point was the difference in peak-AST, requiring 220 transplants (90% power). Secondary endpoints included: organ utilisation, preservation time, early allograft dysfunction (EAD), 1 year graft and patient survival and ischaemic cholangiopathy on MRCP.
Results: 270 livers (133 SCS, 137 NMP) were enrolled, consisting of 192 DBD and 78 DCD organs. 48 livers were discarded (32 SCS [15 DBD, 17 DCD] vs. 16 NMP [10 DBD, 6 DCD]; $p < 0.01$). NMP livers experienced significantly longer preservation times than SCS (7 hr 45 min vs. 11 hr 54 min; $p < 0.01$). Despite this, better early graft function was observed in the NMP group with regards to peak AST (964 IU/L SCS vs. 488 IU/L NMP; $p < 0.001$) and EAD (29.9% SCS vs. 10.1% NMP; $p < 0.001$) with the magnitude of these effects being greater for DCD organs ($p = 0.01$). There was no difference in 6 month graft (96% SCS vs. 95% NMP; $p = 0.71$) and patient (97% SCS vs. 96% NMP; $p = 0.67$) survival.
Discussion: NMP livers show better early graft function than SCS in terms of peak-AST and EAD, both of which are surrogates for long-term graft outcomes. This is despite better organ utilisation and longer preservation times in the NMP group. One year graft and patient survival and MRCP data are currently being analysed and will be available at the time of the congress.

Clinical Pancreas/Islet Other

BAC005 VALIDATION OF THE HOMEOSTATIC MODEL ASSESSMENT (HOMA) OF BETA CELL FUNCTION IN PANCREAS TRANSPLANTATION

Barnes James[1], Franklin Rachel[2], Sharples Edward[3], Friend Peter[1], Gough Stephen[2], Levy Jonathan[2], Mittal Shruti[1]
[1]Oxford Transplant Centre, Nuffield Department Of Surgical Sciences, University Of Oxford, United Kingdom; [2]Oxford Centre For Diabetes, Endocrinology And Metabolism, United Kingdom; [3]Oxford Transplant Centre, Oxford University Hospitals Nhs Foundation Trust, United Kingdom

Background: Five-year graft survival after pancreas transplantation remains low and is limited by the lack of validated biomarkers for identification of graft dysfunction. The Homeostatic Model Assessment (HOMA) quantifies β-cell function (B) and insulin sensitivity (S) in healthy and diabetic patients, but is not applicable to pancreas transplantation recipients with markedly higher insulin concentrations due to systemic venous drainage.
Methods: We developed a modified HOMA (HOMATx) to allow for post-hepatic insulin delivery. A 2-step hyperglycaemic clamp was performed in 12 pancreas recipients and 12 matched healthy controls. Glucose infusions were titrated every 2.5 min in 90 min steps to achieve steady-state at 8 M and 12 M. Insulin concentrations and glucose infusion rates were calculated at the end of each clamp stage. Fasting B and S were calculated using HOMATx in recipients and HOMA in controls and correlated with clamp data.
Results: The two groups were matched for demographic factors. Fasting insulin was higher in the transplant recipients, 76.9 pmol/l (8.69) vs. 40.2 pmol/l (4.56), $p = 0.001$, but there was no significant difference in HOMA-Tx derived B or S between groups: B 71.5 (5.1) vs. 64.43 (4.3), $p = 0.29$; S 114.2 (10.0) vs. 138.2 (18.6), $p = 0.27$ in recipients and controls, respectively. In the recipients, Pearson correlation was confirmed between HOMATx B and insulin secretion rate at both 8 mmol ($r = 0.84$, $p = 0.001$) and 12 mmol ($r = 0.75$, $p = 0.008$) clamp glucose levels.
Conclusion: HOMATx is the first model to be derived for assessment of graft function in whole pancreas transplantation. It provides a validated measure of graft function that is simple and practical to calculate, and correlates well with directly measured β-cell function. Although fasting insulin values differ markedly in transplant recipients, HOMATx enables meaningful assessment of B and S. Further work is required to evaluate its utility in identifying and monitoring graft dysfunction.

Clinical Kidney Rejection

BAC006 BORTEZOMIB IN LATE ANTIBODY-MEDIATED KIDNEY TRANSPLANT REJECTION - A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED TRIAL (BORTEJECT STUDY)

Eskandary Farsad[1], Regele Heinz[2], Bond Gregor[1], Kozakowski Nicolas[2], Wahrmann Markus[1], Hidalgo Luis[3], Haslacher Helmuth[4], Kaltenecker C. Christopher[1], Aretin Marie-Bernadette[5], Oberbauer Rainer[1], Reeve Jeff[6], Halloran F. Philip[6], Böhmig A. Georg[1]
[1]Department Of Nephrology And Dialysis, Medical University, Vienna, Austria; [2]Institute Of Clinical Pathology, Medical University, Vienna, Austria; [3]Department Of Laboratory Medicine And Pathology, University Of Alberta, Canada; [4]Department Of Laboratory Medicine, Medical University, Vienna, Austria; [5]Pharmacy, General Hospital, Vienna (Akh Wien), Austria; [6]Alberta Transplant Applied Genomics Centre, Atagc, University Of Alberta, Canada

Background: Antibody-mediated rejection (ABMR) is a leading cause of long-term kidney transplant loss. Optimal treatment of late ABMR is unclear, and our current knowledge is mostly based on uncontrolled studies.
Methods: In this randomized, double-blind, placebo-controlled, single-center phase 2 trial (NCT01873157), we investigated whether two cycles of the proteasome inhibitor bortezomib (each cycle: 1.3 mg/m^2 on days 1, 4, 8 and 11) are able to halt the progression of late ABMR, using eGFR slope (Over 0, 3, 6, 12, 18 and 24 months) as primary endpoint (44 patients; 1:1 randomization). Secondary outcomes were mGFR at 24 months, donor-specific antibody (DSA) course and morphological/molecular results of 24-month follow-up biopsies.
Results: Upon systematic cross-sectional HLA antibody screening of 741 recipients [inclusion criteria: age >18a, eGFR >20 ml/min/1.73 m^2 at ≥180 days post-transplantation] we identified 111 recipients with DSA. Forty-four DSA+ recipients with morphological evidence of ABMR were included in the trial. Twenty-one patients were allocated to receive bortezomib, and 23 placebo. Despite a trend in reduction of DSA levels, bortezomib neither affected eGFR decline (bortezomib vs. placebo: -4.6 ± 2.7 vs. -4.8 ± 2.5 ml/min/1.73 m^2/year), nor median mGFR at 24 months (33 ml [IQR: 28–40] vs. 43 ml [26–51], $p = 0.2$). There were also no differences regarding two-year overall graft survival (81% vs. 96%, $p = 0.1$) and morphological (ABMR category, g+ptc score, IFTA score, C4d) and molecular results (Molecular-ABMR score, MMDx) of 24-month follow-up biopsies. Bortezomib treatment was associated with a higher rate of GI adverse events (diarrhea: 67% vs. 22%, $p = 0.005$) and thrombo- and leukocytopenia.
Conclusion: The BORTEJECT trial demonstrates that proteasome inhibition does not ameliorate the two-year course of late ABMR. Our results underscore the need for randomized trials to dissect the efficiency and safety of new treatment strategies in this context.

Clinical Kidney Infection

BAC007 LOW INCIDENCE OF ACUTE REJECTION WITHIN THE SIX MONTHS AFTER TRANSPLANTATION IN HIV RECIPIENTS TREATED WITH RALTEGRAVIR, THE ANRS 153 TREVE TRIAL

Matignon Marie[1], Lahiani Amani[2], Lelievre Jean-Daniel[3], Abbassi Khadidja[2], Desvaux Dominique[4], Diallo Alpha[5], Peraldi Marie-Noelle[6], Taburet Anne-Marie[7], Saillard Juliette[5], Delaugerre Constance[8], Costagliola Dominique[2], Assoumou Lambert[2], Grimbert Philippe[1]
[1]Aphp, Nephrology And Transplant Unit, Henri Mondor Hospital,France; [2]Sorbonne Universités, Inserm, Upmc Univ Paris 06, Iplesp Umrs 1136, France; [3]Aphp, Clinical Immunology Unit, Henri Mondor Hospital, France; [4]Aphp, Anatomopathology Unit, Henri Mondor Hospital, France; [5]Anrs, Recherhce Nord Et Sud Sida-Hiv Hépatites, France; [6]Aphp, Nephrology And Transplant Unit, Saint Louis Hospital, France; [7]Aphp, Pharmacology Unit, Hôpitaux Universitaires Paris-Sud Bicêtre, France; [8]Aphp, Virology Department, Saint Louis Hospital, France

Renal transplantation is safe and effective in HIV patients with end stage renal disease (ESRD). High rates of acute rejection (AR) have been reported because of antiretroviral (ARV) and immunosuppressive treatments interactions through CYP450 metabolization. Raltegravir (RAL) is not a substrate of CYP450 enzymes. We conducted a trial to determine incidence of clinical AR in HIV recipients treated with RAL.

The ANRS 153 TREVE (NCT01453192) was a national multicenter prospective open label single arm trial in adult HIV ESRD patients awaiting transplant, with controlled viral load, CD4 count >200/μl and stable ARV regimen for at least 3 months, and viruses sensitive to RAL. After transplant,

the ARV regimen included RAL. The trial aimed to demonstrate that the clinical AR rate was below 30%. A blind pathologist reviewed all biopsies. We assessed patient survival on the waiting-list, after transplant and, allograft survival compared to a control group of HIV-negative recipients matched on age, sex and date of registration on the waiting list.

Between 12/2011 and 12/2014, 26 HIV ESRD patients enrolled in the trial underwent renal transplantation. Median age was 48 years, 69% were male and 62% were from Sub-Saharan Africa. Median CD4 count was 387/μl. AR occurred in two patients, leading to 8% rejection at 6 and 12 months (95% CI: 2–24). One subclinical rejection occurred 10 days after transplant. The 3-year survival on the waiting-list was 100% in HIV patients compared to 87% in controls ($p = 0.031$). After transplant, the 3-year survival was similar in both groups; 89% and 96% ($p = 0.197$). Three-years allograft survival was similar in both groups; 92% and 87% ($p = 0.415$). HIV infection remained controlled in all patients except one who discontinued ARV. Another patient, with a prior AIDS event, developed a Kaposi Sarcoma.

After kidney transplantation, ARV including RAL is effective to prevent AR. Patients and kidney allograft survivals are similar

Translational Kidney Rejection

BAC008 MISSING-SELF TRIGGERS NK MEDIATED MICROVASCULAR INJURIES AND CHRONIC REJECTION OF ALLOGENEIC KIDNEY TRANSPLANTS

Koenig Alice[1], Chen Chien-Chia[2], Marçais Antoine[2], Mathias Virginie[3], Sicard Antoine[4], Rabeyrin Maud[6], Racapé Maud[6], Duong-Van-Huyen Jean Paul[7], Bruneval Patrick[7], Dussurgey Sebastien[8], Ducreux Stéphanie[3], Morelon Emmanuel[4], Charreau Béatrice[9], Defrance Thierry[2], Dubois Valérie[3], Walzer Thierry[2], Thaunat Olivier[1]

[1]Inserm U 1111, Hospital Edouard, Herriot, France; [2]Inserm U 1111, France; [3]Efs, Rhône-Alpes, France; [4]Hospital Edouard, Herriot, France; [5]Hospices Civils De Lyon, France; [6]Paris Cardiovascular Research Center, France; [7]APHP, France; [8]Sfr Biosciences, France; [9]Inserm Umr-S 1064, France

Background: Natural Killer cells (NK) are effectors of the innate immune system carrying inhibitory KIR (iKIR), which regulate the killing function of these cells by interacting with MHC class I molecules (MHC-I). The "missing self" hypothesis proposes that NK can sense the absence of self MHC-I on the surface of allogeneic cells. This unique characteristic suggests that NK could promote innate-driven rejection, a concept that has not been validated in clinical transplantation.

Methods and results: 938 kidney transplant recipients had a graft biopsy between 2004 and 2012 in our center. Among them, 130 had microvascular inflammation (mvi), which is usually attributed to humoral rejection. Only 69 had donor specific anti-HLA antibodies (DSA) and 6 had anti-endothelial cell antibodies susceptible to explain this mvi. We hypothesize that "missing self" could be responsible for the lesions of the 55 remaining patients (mvi+DSA-). A matched control group of 55 patients with no mvi and no DSA was constructed (mvi-DSA-). Recipients' KIR genes and donors' and recipients' HLA ligands were genotyped and the licensing of the 5 iKIR with known MHC-I ligands (KIR2DL1/C2, 2DL2-3/C1, 3DL1/Bw4, 3DL2/A3, A11) was assessed for both groups. The proportion of patients with at least 1 iKIR-ligand mismatch was higher in mvi+DSA- group (64% vs. 36%, $p = 0.009$).

In a human *in vitro* model, we demonstrated that the lack of self MHC-I on endothelial cells can activate NK. This activation triggers NFAT and mTOR pathways in NK which can respectively be blocked by cyclosporin and rapamycin. Using a murine *in vivo* cellular model of missing-self mediated killing, we found that only rapamycin can prevent the killing of targets. Finally, we confirmed the existence of missing-self induced rejection in a murine heart transplantation model.

Conclusion: Missing-self seems sufficient to trigger NK-mediated chronic vascular rejection of allogeneic kidneys. MTOR inhibitors might be of interest to prevent this rejection.

Translational Kidney Rejection

BAC009 SPECIFIC GENE EXPRESSION SIGNATURE OF COMPLEMENT-ACTIVATING DONOR SPECIFIC ANTI-HLA ANTIBODY-MEDIATED REJECTION IN KIDNEY ALLOGRAFTS

Lefaucheur Carmen[1], Viglietti Denis[1], Aubert Olivier[1], Zeevi Adriana[2], Halloran Philip[3], Loupy Alexandre[1]

[1]Paris Translational Research Center For Organ Transplantation, France; [2]University Of Pittsburgh Medical Center, USA; [3]Alberta Transplant Applied Genomics Center, Canada

We investigated whether the complement-binding capacity of circulating donor-specific anti-HLA antibodies (DSA) is associated with specific gene expression signature in the kidney allograft.

We prospectively enrolled 931 kidney recipients transplanted between 2011 and 2014, with systematic screening for circulating DSA in the first year post-transplantation. We assessed DSA specificity, MFI, C1q-binding capacity and IgG1-4 subclasses using SAB. All patients underwent allograft biopsy at the time of post-transplant DSA detection to assess gene expression using microarray. We compared gene expression according to DSA C1q-binding status.

We identified 157 (17%) patients with DSA, 44 (28%) with C1q-binding DSA, and 113 (72%) with non-C1q-binding DSA. Patients with C1q-binding DSA showed higher MFI levels ($p < 0.001$) and greater prevalence of IgG1 ($p < 0.001$) and IgG3 ($p < 0.001$) subclasses than patients with non-C1q-binding DSAs. Among the 9954 inter-quartile range filtered transcripts that were most significantly expressed in the C1q-binding DSA patients, those most associated with C1q-binding DSAs were composed primarily of NK, endothelial, interferon gamma, macrophage, and effector T cell genes. We defined a discriminative gene set for C1q-binding DSA status (CXCL11, CCL4, MS4A6A, GBP1, MS4A7) that outperformed conventional histology to predict DSA C1q-binding status (AUC of 0.85 vs. 0.76, $p = 0.006$). The 5-gene set was associated with the C1q-binding capacity of DSA independently of MFI level and IgG subclass composition. The integration of the gene set to conventional histology in unsupervised hierarchical clustering and principal component analysis allowed identifying a distinct pattern of allograft injury reflecting DSA C1q-binding capacity.

We identified a gene expression signature for kidney allograft injury related to the complement-binding capacity of circulating DSA that outperformed conventional histology.

Clinical Kidney Rejection

BAC010 MULTIPLE DOSING OF ANTI-C1S ANTIBODY TNT009 - EFFECT ON HLA ANTIBODY-TRIGGERED COMPLEMENT ACTIVATION IN HEALTHY VOLUNTEERS AND KIDNEY TRANSPLANT RECIPIENTS WITH ANTIBODY-MEDIATED REJECTION

Mühlbacher Jakob[1], Jilma Bernd[2], Wahrmann Markus[3], Eskandary Farsad[3], Gilbert C. James[4], Panicker Sandip[4], Böhmig Georg[3]

[1]Department Of Surgery, Medical University Of Vienna, Austria; [2]Department Of Clinical Pharmacology, Medical University Vienna, Vienna, Austria; [3]Department Of Medicine Iii, Medical University Vienna, Vienna, Austria; [4]True North Therapeutics, Inc., South San Francisco, CA, USA

Background: Complement inhibition may be an attractive strategy to prevent antibody-mediated allograft injury. One promising therapeutic target may be the enzymatic activity of key classical pathway (CP) component C1. In this first-in-human trial (NCT02502903) we evaluated the impact of 4 weeks treatment with TNT009, a humanized anti-C1s antibody on CP activity in healthy individuals and kidney transplant recipients with late antibody-mediated rejection (ABMR).

Methods: Sixteen healthy volunteers received 4 weekly IV doses of TNT009 or placebo (6:2 randomization, two cohorts: 30 or 60 mg/kg). Subsequently, 10 kidney transplant recipients diagnosed with late ABMR were treated with TNT009 (initial test dose of 10 mg/kg followed by 4 weekly doses of 60 mg/kg). To assess ex vivo HLA antibody-triggered complement activation, sera from dosed subjects were analysed on microbeads sensitized with HLA antibodies using the read-out of C3d fixation.

Results: Baseline C3d deposition levels were not significantly different between healthy volunteers and transplant recipients (mean C3d MFI: 4882 ± 754 versus 4367 ± 1030, $p = 0.15$). In healthy volunteers, multiple doses of TNT009 led to a persistent (≥4 weeks) and >80% inhibition of HLA antibody-triggered C3d deposition (and in parallel CH50 activity). Similarly, sustained complement inhibition was also achieved in the cohort of ABMR patients, with a comparable degree of CP blockade (Figure 1). CP inhibition tightly correlated with plasma levels of TNT009.

Conclusion: Multiple doses of TNT009 allowed for a prolonged and near complete CP inhibition both in healthy volunteers and ABMR patients. Our results provide a valuable basis for future studies evaluating the effect of prolonged C1s blockade on the course of antibody-mediated rejection.