TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

LETTER TO THE EDITORS

Reply to Vanhove *et al.*

doi:10.1111/tri.12076

In response to the discussion on 'Biologics in organ transplantation', [1] we would like to thank Drs Vanhove and Azimzadeh for raising some excellent points [2]. First, they highlight the rapid nature of drug development, as many agents we reviewed were currently or previously in preclinical stages of development and others in active recruitment phases of clinical trials for transplantation (i.e. rituximab, eculizumab, etc.). At the time of our review article's publication, the report on anti-CD40 antibody ASKP1240 in nonhuman primate liver transplantation had yet to be published until July 2012. We agree, however, that it now merits a more thorough review. Like its predecessor 4D11 mentioned in our manuscript (reference 129), the newly developed ASKP1240 is described as a fully human IgG4 to CD40 that inhibits ligation with CD154 through masking, as opposed to antibody- or complement-dependent cytoxicity [3]. When given as either induction (10 mg/kg) or maintenance (5 mg/kg) monotherapy, it significantly prolongs hepatic allograft survival in cynomolgus macaques, inhibiting alloreactive T cells, antigen-specific CD4+ CD154+ T cells, donor-specific antibodies (DSA), and anti-drug antibodies while on therapy. DSA and chronic rejection (C4d−) developed in animals upon drug cessation; prior trials in renal transplantation, however, had C4d+ deposition along with the development of chronic allograft nephropathy. A phase 1b clinical trial of ASKP1240 in renal transplantation has been completed as of January 2012 (clinicaltrials.gov, #NCT01279538).

The findings from the above study are consistent with other preclinical studies reporting effective prevention of acute rejection and alloantibody production using anti-CD40 mAbs [4–6]. These studies emphasize not only the therapeutic potential in blocking CD40 but also the avoidance of thromboembolic complications seen with CD40L blockade [7,8]. As Knosalla *et al.* commented, inhibition of the CD40:40L pathway was at the time the only agent to successfully prevent the antibody response in xenotransplantation. As many others have noted its efficacy in preventing antibody responses, perhaps its niche in transplantation will align with treating patients at higher risk for humoral rejection.

The second point made by Drs Vanhove and Azimzadeh was of their preclinical work performed on selective CD28 blockade. Our invitation from the editors was to review biologics excluding belatacept, so we indicated in our costimulation blockade section that we would be limiting the review to blockade of the CD40:40L pathway. We agree that selective CD28 blockade deserves review and appreciate this opportunity to discuss it. While CD80/86 blockade through CTLA-4Ig has gained much attention with the recent FDA approval of belatacept for kidney transplantation, this approach prohibits the natural regulatory function of CTLA-4 upon ligation with CD80/86.

In 2011, Dr. Vanhove and colleagues reviewed nicely the CTLA-4-specific functions (anti-proliferative signals to T cells, indoleamine 2,3-dioxygenase production to APCs, critical signaling for Treg function) as well as CD80/86-mediated functions (PD-1 mediated inhibitory signals) [9]. Their preclinical studies in Poirier *et al.* (2010) supported the notion of CD28 blockade (sc28AT) sparing CTLA-4-mediated regulatory functions [10]. In sc28AT-treated baboons, transplanted animals demonstrated an increase in Treg percentages and absolute counts by a factor of 2–3. One week after transplantation, kidney biopsies showed decreased mRNA concentrations of inflammatory cytokines and increased TGFβ, CD25, CTLA-4, Foxp3, heme oxygenase-1 in animals treated with sc28AT. Comparisons between sc28AT and CTLA-4Ig on regulatory T-cell numbers and cytokines would have been interesting to see, in vivo. It is also noteworthy that while regulatory populations and cytokines may have increased, graft survival was only dramatically improved when sc28AT was combined with calcineurin inhibitors for both kidney and heart transplant models. Nevertheless, their study addresses important points on the value of CD28 blockade as opposed to CD80/86 blockade, and demonstrates its safety in not inducing superagonist activity that proved devastating in the case of TGN1412.

Eugenia K. Page,[1] Wasim A. Dar[2] and Stuart J. Knechtle[1]
1 Department of Surgery, Emory University Hospital, Atlanta, GA, USA
2 UTHealth Department of Surgery, Houston, TX, USA
e-mail: Stuart.Knechtle@emoryhealthcare.org

Conflict of interest

None.

Funding

No funding.

References

1. Page EK, Dar WA, Knechtle SJ. Biologics in organ transplantation. *Transpl Int* 2012; **25**: 707.
2. Vanhove B, Azimzadeh A. Reply to "Biologics in organ transplantation". *Transpl Int* 2012; doi: 10.1111/tri.12009.
3. Oura T, Yamashita K, Suzuki T, *et al.* Long-term hepatic allograft acceptance based on CD40 blockade by ASKP1240 in nonhuman primates. *Am J Transplant* 2012; **12**: 1740.
4. Aoyagi T, Yamashita K, Suzuki T, *et al.* A human anti-CD40 monoclonal antibody, 4D11, for kidney transplantation in cynomolgus monkeys: induction and maintenance therapy. *Am J Transplant* 2009; **9**: 1732.
5. Pearson TC, Trambley J, Odom K, *et al.* Anti-CD40 therapy extends renal allograft survival in rhesus macaques. *Transplantation* 2002; **74**: 933.
6. Lowe M, Badell IR, Thompson P, *et al.* A novel monoclonal antibody to CD40 prolongs islet allograft survival. *Am J Transplant* 2012; **12**: 2079.
7. Kawai T, Andrews D, Colvin RB, *et al.* Thromboembolic complications after treatment with monoclonal antibody against CD40 ligand. *Nat Med* 2000; **6**: 114.
8. Knosalla C, Gollackner B, Cooper DK. Anti-CD154 monoclonal antibody and thromboembolism revisited. *Transplantation* 2002; **74**: 416.
9. Poirier N, Blancho G, Vanhove B. A more selective costimulatory blockade of the CD28-B7 pathway. *Transpl Int* 2011; **24**: 2.
10. Poirier N, Azimzadeh AM, Zhang T, *et al.* Inducing CTLA-4-dependent immune regulation by selective CD28 blockade promotes regulatory T cells in organ transplantation. *Sci Transl Med* 2010; **17**: 17ra10.