Title: Advances in Targeting Co-inhibitory and Co-stimulatory Pathways in Transplantation Settings: The Yin to the Yang of Cancer Immunotherapy

Running Title: Targeting T Cell Co-Signaling in Transplant

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Summary:

In the past decade, the power of harnessing T cell co-signaling pathways has become increasingly understood to have significant clinical importance. In cancer immunotherapy, the field has concentrated on two related modalities: First, targeting cancer antigens through highly activated chimeric antigen T cells (CAR-Ts) and second, re-animating endogenous quiescent T cells through checkpoint blockade. In each of these strategies, the therapeutic goal is to re-ignite T cell immunity, in order to eradicate tumors. In transplantation, there is also great interest in targeting T cell co-signaling, but with the opposite goal: in this field, we seek the Yin to cancer immunotherapy's Yang, and focus on manipulating T cell co-signaling to induce tolerance rather than activation. In this review, we discuss the major T cell signaling pathways that are being investigated for tolerance-induction, detailing pre-clinical studies and the path to the clinic for many of these molecules. These include blockade of co-stimulation pathways and agonism of co-inhibitory pathways, in order to achieve the delicate state of balance that is transplant tolerance: a state which guarantees lifelong transplant acceptance without ongoing immunosuppression, and with preservation of protective immune responses. In the context of the clinical translation of immune tolerance strategies, we discuss the significant challenge that is embodied by the fact that targeted pathway modulators may have opposing effects on tolerance based on their impact on effector versus regulatory T cell biology. Achieving this delicate balance holds the key to the major challenge of transplantation: lifelong control of alloreactivity while maintaining an otherwise intact immune system.

Introduction: The last five years have witnessed tremendous progress in cancer immunotherapy. This has included advances in both antibody- and cell-based therapies, with the success of each of these modalities significantly reliant on their ability to regulate co-stimulatory and co-inhibitory signaling to optimize T cell anti-tumor responses. The prevailing strategies for controlling and enhancing T cell signaling for cancer eradication have focused on modulating both sides of the signaling equation, to enhance T cell activation. Thus, they have harnessed co-stimulatory signaling to enable antigen-driven activation of chimeric antigen receptor (CAR)-T cells, and blocked co-inhibitory signaling to re-engage hypofunctional T cells in the tumor microenvironment. In stark contrast to the typically suppressive tumor microenvironment, transplanted allogeneic or xenogeneic tissues or cells can create a pro-inflammatory environment resulting in graft injury or loss for tissue transplants, and graft-versus-host disease (GVHD) or donor cell rejection for donor hematopoietic lineage cell infusions. If the strategy surrounding cancer immunotherapy is focused on harnessing the Yang—the optimized activation and 'heat' in T cells, then in transplantation, we seek the 'cooling' Yin, in focusing on controlling these same co-stimulatory and co-inhibitory pathways, towards the goal of inducing antigen-specific tolerance in T cells rather than T cell assault.

In what follows we will review the work in the field of transplant tolerance, highlighting the many successes that have been achieved by targeting T cell co-stimulatory and co-inhibitory pathways, and discuss the challenges that we still face on the road to the ultimate goal of tolerance-on-demand for all transplant patients. In discussing successes and challenges, we will examine the complexity of manipulating T cell co-signaling, given that both conventional, effector T cells (Teffs) are targeted by these approaches, along with regulatory T cell (Treg) populations, for which these manipulations may have opposing biologic effects and, hence, transplantation tolerance

outcomes. The search for the ideal pathway, which, when manipulated, could simultaneously tilt the balance towards tolerance in both Teffs and Tregs, remains one of the holy grails of our field of inquiry.

Transplantation tolerance is defined as the lifelong acceptance of transplanted organs or cells, in the absence of any immunosuppressive medications, and with preservation of protective immunity. Immune tolerance thus has three major components, all which must co-exist in transplant patients. Each is critical, and all are inter-related, thus raising the bar needed for achieving transplantation tolerance, especially in large animal models and patients. Efforts to blunt co-stimulation pathways in order to accomplish this goal began in earnest over two decades ago, when CTLA4Ig was first synthesized for the purpose of precluding a productive immune response in antigen-activated T cells. (1-4) These seminal studies demonstrated that this new way of interfering with T cell co-signaling could potently down-regulate T cell and antibody responses to xenogeneic (xeno) and allogeneic (allo) tissues and were heralded in the lay press as having reliably achieved the holy grail of tissue transplantation tolerance. Individual costimulatory pathway blockade reports were closely followed by a series of important publications with combination therapy. These included a 1996 study by Dr. Christopher Larsen and colleagues that demonstrated that the coordinated blockade of B7 signaling (through CTLA4Ig) and CD40/CD154 signaling (through an anti-CD154 monoclonal antibody) could produce long-term tolerance to concurrently transplanted skin and cardiac allografts, while preserving the recipient's ability to reject non-donor allografts transplanted after co-stimulatory pathway blockade had been discontinued.(5) Such reports resulted in the birth of combinatorial co-stimulation blockade for generating antigen-specific graft tolerance, a paradigm that continues to be vigorously pursued in the present day. In what follows we provide an overview of this field, as it relates to immune tolerance induction, and discuss the relevant pathways, cells and clinical

applications, highlighting where we've been, and where we need to go to make immune tolerance a reality for the patients we treat.

Simultaneous blockade of B7/CD28 and B7/CTLA-4: Confronting the double edge sword of co-stimulation and co-inhibition: The field of co-stimulation blockade began with the search for molecules that paired with antigen-specific TCR stimulation to optimize T cell activation after cognate antigen recognition. To accomplish this, researchers used agonistic monoclonal antibodies directed at newly identified T cell surface molecules, and identified the immunoglobulin (Ig)-superfamily member CD28 as a critical T cell co-signaling molecule which was required to optimally initiate, amplify and sustain T cell responses.(6) Subsequent studies demonstrated that there were two distinct CD28 ligands, CD80 (B7-1) and CD86 (B7-2) that were expressed as dual co-receptors on antigen presenting cells (APC).(7-11) While this was a central discovery, the complexities of signaling through this pathway and its surrogates is still incompletely understood, yet key to ongoing efforts to target the CD28 pathway to control T cell activation.

The first reagent used to inhibit CD28 signaling was developed by Linsley and colleagues, who developed a soluble CD28Ig, reasoning that it could block CD28 signaling by providing an alternative binding site for CD28 ligands.(12) While the data supported this molecule as the first 'costmulatory blockade' reagent, it's affinity for the ligand(s) of CD28 was relatively low such that *in vivo* experiments (and clinical applications) with this reagent were not sufficiently encouraging for further testing. At this time, a molecule with molecular similarity to CD28, named cytotoxic T lymphocyte antigen-4 (CTLA-4), now also known as CD152, was discovered Dr. Pierre Goldstein at the Pasteur Institute.(13, 14) CTLA-4 was first presumed to act as stimulator of T cell activation. However, further studies by several laboratories subsequently showed that,

while CTLA-4 was upregulated during T cell activation, the signal delivered by CTLA-4 engagement functioned as a negative, rather than positive regulator of T cell function.(15, 16)

Given the shared structure between CTLA-4 and CD28 as well as B7 ligand binding (and prior to its unequivocal identification as a negative regulator of T cell function),(14) a CTLA4Ig fusion protein, consisting of the extracellular domain of CTLA-4 fused to an IgG tail (to prolong its half-life), was developed, with the hopes that CTLA4Ig mediated blockade of positive T cell co-signaling would dominate over blocking the CTLA-4 inhibitory pathway. Dr. Peter Linsley and colleagues indeed showed that CTLA4-Ig was capable of binding B7 at clinically-relevant concentrations and in so doing, inhibited T cell allo-proliferation and T-dependent B cell antibody production.(4) This breakthrough discovery ushered in the era of T cell modulation for clinical control of undesired, aggressive donor and host T- and B- cell immune responses that precluded transplantation tolerance. As briefly mentioned above, in vitro characterization studies with CTLA4Ig were quickly followed with demonstrations of the ability of CTLA4Ig to modulate allo- and xeno- immunity in vivo, including producing striking prolongation of xeno-islet graft survival in mice.(2, 3, 17) While further studies in mice, non-human primate (NHP) and patients have indicated that this agent is not capable of producing tolerance, these first *in vivo* studies were striking in their demonstration of the impact of this first targeted co-stimulation blockade approach in small animal model systems.

Given the ability of CTLA4Ig to impact both T and B cell function, it was seen as a potentially important new therapeutic for auto- as well as allo- immune indications. Murine studies demonstrated striking activity in models of lupus-like disease(18) and collagen-induced arthritis,(19) and more variable results against murine experimental allergic encephalitis (EAE), a preclinical model of a multiple sclerosis (MS)-like disease.(20) The result in EAE is noteworthy in that it foreshadowed future clinical

observations with CTLA4Ig in renal transplant (and may be related to the impact that this molecule has on Tregs, discussed in detail below) in that it found that higher doses of CTLA4Ig worsened, rather than improved results with this agent against EAE.(20)

The results in murine models of lupus, and especially arthritis, spurred the initial clinical trials of CTLA4Ig, which focused on patients with psoriasis(21) and rheumatoid arthritis (RA). In a series of Phase II and Phase IIII trials and now with over a decade of follow-up, CTLA4Ig (known as abatacept and marketed as Orencia™) has shown significant clinical activity for patients with RA,(22-26) and was the first FDA-approved co-stimulation blockade agent, approved for use in RA in 2005. Given its significant activity in RA, it is somewhat surprising that CTLA4Ig has not developed a larger sphere of clinical indications, with trials in MS, asthma, Type I diabetes, ulcerative colitis, and lupus not yielding significant enough clinical improvement to lead to efforts to obtain FDA approval for those diseases(27-31) especially in the context of other therapeutic options available for treatment of these diseases. Whether the suboptimal clinical results are due to an unwanted impact of abatacept on CTLA4-mediated co-inhibitory signaling, untoward effects on Tregs in these diseases, or other causes has not been determined. Despite the lack of widespread clinical applications in autoimmunity, the success of abatacept in RA patients supported continuing clinical investigation of B7 blockade with CTLA4Ig for other indications, especially solid organ and hematopoietic stem cell transplantation (HCT). In HCT, our work and that of others in murine and NHP models suggested that abatacept has biologic activity in preventing GVHD.(32-37) This led to a promising first-in-disease feasibility trial(38) which demonstrated the pharmacodynamic impact of abatacept in controlling T cell proliferation early post-transplant, providing the foundational data for our ongoing Phase II study designed to evaluate the efficacy of abatacept in preventing severe GVHD after either mismatched or matched unrelated donor HCT (Clinicaltrials.gov # NCT01743131).

In solid organ transplant, although the abatacept formulation of CTLA4Ig showed significant promise in murine models,(39-51) including evidence for a critical role in immune tolerance when combined with CD154-based co-stimulation blockade (discussed in detail below), initial studies in NHP renal transplant models were underwhelming.(52, 53) These results may have been mechanistically linked to the fact that CD28 and CTLA-4 compete for B7 ligands (CD80 and CD86) that are required for CD28 activation, and that the interaction of CD80 with both CD28 and CTLA-4 appears substantially better than that of CD86. Because abatacept has decreased affinity for CD86 compared to CD80, CD80/CD86 interactions with CD28 and CTLA-4 may be incompletely blocked with the abatacept formulation of CTLA4Ig.(12) Therefore, the group at Bristol-Myers Squibb, in collaboration with Larsen's group at the Emory Transplant Center decided to create directed mutations in the CTLA4Ig molecule designed to increase its affinity for CD86.(52) The resulting formulation, differing in 2 amino acids from abatacept (known first as LEA29Y and subsequently as belatacept, and now marketed as Nulojix™), increased both affinity and avidity of CTLA4Ig towards both B7 molecules. In so doing, belatacept resulted in increased blockade of both CD28- and CTLA-4 mediated T cell activation *in vitro* and prolonged allograft survival in NHP models when compared to abatacept.(48, 52) A subsequent series of Phase II and Phase III trials in renal transplant patients demonstrated that belatacept led to improved long-term renal functional outcomes after transplant and fewer off-target toxicities.(54) These results have been verified in long-term follow-up studies.(55-57)

Two important observations from the belatacept trials point to important biological complexities of targeting T cell co-stimulation using CTLA4Ig: First was the observation that patients treated with a lower-intensity regimen of belatacept actually had superior graft outcomes than those treated with a higher-intensity regimen.(54) Second was the observation that while overall results were improved with belatacept, patients treated

with this drug experienced higher rates of early (reversible) rejection events. (54-57) There are two potential explanations for these observations: First, is the fact that belatacept, like abatacept, not only targets CD28 positive co-signaling but also targets CTLA-4-based co-inhibition. CD28 is a highly expressed but low-affinity receptor, in contrast to CTLA-4, which is in low abundance but is a higher-affinity receptor. At high *in vivo* concentrations, both CD28 and CTLA-4 would be blocked, whereas at lower *in vivo* concentrations, CTLA4Ig would preferentially block the high abundant CD28 receptor and restricting available ligand for the low abundance CTLA-4 receptor. CTLA-4 has a clear regulatory function as evidenced by CTLA-4 knockout mice.(58) These mice develop fatal lymphoproliferative disease at 3–4 weeks of age, suggesting a key role for CTLA-4 in maintaining self-tolerance. By restricting available ligand for the low abundance CTLA-4 receptor at low CTLA4Ig concentrations, tolerance induction induced by CTLA-4 signalling remains more intact than the co-stimulatory CD28 pathway.(59) This points to the knifes-edge that many of these studies may be on, in terms of the balance of CTLA4Ig being a co-stimulation *blocker* or *enhancer*, dependent upon the relative effects on co-stimulatory CD28 and co-inhibitory CTLA-4 pathways, which could lead to disease-specific impacts on efficacy given differential reliance on CD28 versus CTLA-4 signaling in different auto- and allo-immune entities.

A second important consideration also exists, as mentioned at the beginning of this review: this is the impact of CTLA4Ig on $CD4^{+}CD25^{+}FOXP3^{+}$ Tregs. As one of the key regulatory mechanisms to combat Teffs, Tregs represent a major force for tolerance-induction in normal immune homeostasis. These cells have been well documented to express both CD28 and CTLA-4. Their activation augments Treg CTLA-4 expression,(60, 61) critical for the ability of Tregs to prevent autoimmunity, in part by competing for B7 ligands that would otherwise be engaged by CD28 on conventional T cells (Tconv).(58, 62) In addition to the role that Treg-expression of CTLA-4 may have

on restraining immune activation, Tregs also rely on CD28 expression in order to maintain their peripheral homeostasis.(63, 64) Thus, an agent like belatacept might well produce an unexpected negative impact on tolerance induction through the impact of CTLA4Ig on CD28 signaling in Tregs. In fact, these data are consistent with results from our group and others that show that CTLA4Ig can lead to decreased levels of Tregs after both solid organ(65, 66) and HCT,(67) which raise the possibility (although this hasn't been directly proven yet) that one of the potential relative contraindications of the use CTLA4Ig may be an undesired negative effect on Treg homeostasis and function.

Direct targeting of CD28: Superior to CTLA4-Ig? Given the fact that CTLA4Ig can target both co-stimulation through CD28 and co-inhibition through CTLA-4, there has been deep interest for many years in directly targeting CD28 alone rather than targeting B7 ligands (that would affect CD28 along with CTLA-4). However, progress in this field was negatively affected by the tragic Phase 1 trial of TGN1412 in healthy controls, in which super-agonist activation by the cross-linked anti-CD28-specific intact mAb produced life-threatening cytokine storm in all 6 participants.(68, 69) Recently, at least two independent efforts have led to second-generation CD28-targeting molecules that are incapable of cross-linking and have demonstrated broad safety in a number of pre-clinical settings and in clinical trials. Bristol-Myers Squibb is developing anti-CD28 'domain-specific' antibodies that are pegylated to prolong their half-life.(70) Preclinical work has demonstrated significant in vitro and in vivo activity of these molecules.(71, 72) The clinical formulation, lilizumab, has now completed Phase 1 studies,(73, 74) and is being studied in a Phase 2 trial in lupus as well as in a proof-of-concept study in Sjögren's syndrome.

Led by Dr. Bernard Vanhove, Effimune independently developed a pegylated anti-CD28 Fab', 'FR104', which has now been licensed to Janssen Biotech. FR104 has

been shown to have biologic activity in a number of auto-immune and allo-immune settings, including in prolonging renal allograft survival in NHP and in preventing xeno-GVHD in a NHP-→mouse model recently developed by our group.(75-81) Importantly, FR104 performed superiorly to belatacept in NHP models of renal transplant(80) and human xeno-GVHD.(76) The mechanisms that were critical for this improved activity have not been determined, although experiments in both systems suggest that both CTLA-4- and Treg-mediated mechanisms may be operative.(76, 77, 80) FR104 is also now in clinical trials, being studied in patients with RA.

CD40:CD154-directed costimulation blockade: The story of on-target potency being sidelined by an unexpected toxicity. In preclinical studies, there has been no class of molecules that has seen more success in transplant tolerance-induction than those that target CD40: CD154 signaling. CD40 (a member of the tumor necrosis factor receptor (TNFR) superfamily, expressed on most APCs), and its ligand, CD154 (expressed primarily on activated T cells, but also found on other hematopoietic cells, discussed below) are critical for T cell function, as well as for the B and T cell interactions that result in the generation of high affinity antibodies that can be pathological in solid organ transplantation and HCT.(82) Consistent with its TNFR structure, CD40 signaling depends on its interactions with TNFR-associated factors (TRAFs),(83) which when engaged, lead to T cell activation through a variety of secondary signals, including NF-kB, Jnk and AKT pathways.(82)

The importance of CD40:CD154 engagement likely is due to its critical impact both on T cell activation and on the initiation and perpetuation of the germinal center response in lymph nodes, thus being a critical hub for both T and B cell immunity.(84, 85) The potential translational importance of targeting this pathway has been demonstrated numerous times, in murine, canine and NHP models. The early studies

concentrated on blocking CD154, and led to the striking result that a single dose of the MR1 anti-CD154 mAb permitted long-term cardiac transplant acceptance when combined with donor splenocyte infusion, and that anti-CD154 mAb infusion led to skin acceptance in mice.(86, 87) In addition, striking synergy was observed when blockade of CD154 was combined with B7 blockade (using CTLA4Ig), which was demonstrated in numerous publications, including the seminal observation of its ability to lead to tolerance to both heart and skin allografts in the allogeneic Balb/c→C3H model.(86) Additionally, a series of studies by the Sykes, Larsen and Blazar laboratories demonstrated the potent effects of anti-CD154 mAb on facilitating donor chimerism in sub-optimally conditioned recipients, attributed to either peripheral host anti-donor Teff deletion followed by central tolerance or alternatively, by peripheral immune regulatory mechanisms.(42, 44, 49, 87-94) Moreover, when anti-CD154 mAb was combined with donor bone marrow, immune tolerance to skin allografts was achieved even in the stringent B6→Balb/c model system.(46, 49, 50)

Several mechanistic studies have provided important insights into the mechanisms of CD154 blockade and tolerance induction. For example, anti-CD154 mAb added to an *in vitro* mixed lymphocyte reaction induced antigen-specific tolerance, measured both *in vitro* and *in vivo* in a GVHD reaction, with evidence that this effect was dependent upon Tregs. (46, 88, 95-98) Notably, activated Tregs express high levels of CD154, although a direct signaling mechanism for CD154 in T cells has not been described. In other studies, investigators demonstrated that anti-CD154-induced tolerance resulted in the abortive expansion of the alloreactive, Teff pool with a loss of cytokine production, activation marker expression, and absence of memory T cell markers. Additionally, the tolerant alloreactive T cell phenotype induced by CD154 was long-lived but could be reversed by in vivo Treg depletion. (46, 88, 95-98) Dr. Mandy Ford and colleagues further showed that blockade of this pathway not only controlled

donor-reactive CD8+ T cell responses, but also was associated with the expansion of peripherally-generated antigen-specific CD4+FoxP3+ Tregs. (99-101) These observations suggest that blockade of CD154 may create the balance that was missing with CTLA4Ig, with pro-tolerogenic effects on both Tconv and Treg populations.

The impressive results in mice led to a large number of studies in NHP. In those studies, anti-CD154 antibodies were a critical component for the prolonged acceptance of both bone marrow and renal allografts.(67, 102-105) While the induction of true immune tolerance in mice was not able to be directly extrapolated to NHP, CD154 blockade results were sufficiently impressive that they led to widespread interest in the clinical translation of CD154-directed therapies, as potential adjuncts to both conventional immunosuppression and CTLA4Ig-based therapeutics.

Unfortunately, the clinical translation of the first anti-CD154 antibodies was halted quickly, when thromboembolic complications were noted. This was found to be due to the expression of CD154 on activated platelets, leading to anti-CD154-mediated platelet activation and clotting in treated patients.(106-109) This unfortunate turn of events led the field to explore CD40 blockade as a potential alternative to CD154. While numerous studies have shown that CD40 blockade can also serve to prolong allograft survival in both mouse models and NHP,(110-120) the combined impact on both Tconv and Tregs noted for anti-CD154 antibodies has not yet been demonstrated for those blocking CD40.

Nonetheless, the large body of preclinical evidence supporting a central role of CD40:CD154 pathway blockade in prolonging allograft survival has sustained significant interest in CD40 for clinical translation, with a Phase 2 trial of the anti-CD40 antibody ASKP1240 currently underway in renal transplantation (Clinicaltrials.gov # NCT01780844). As with CD28, the advent of single-chain domain-specific antibodies has also presented an important solution to the clinical toxicity observed with anti-CD154

antibodies that were dependent on cross-linking. A domain-specific antibody for CD154 has now been developed, and has shown significant activity in murine models of allo-immunity.(100, 121) These reagents are now being tested in NHP models of solid organ transplant and early-phase clinical trials are being planned.

ICOS/L, a supporting player in germinal center targeting and co-stimulation blockade. Structurally similar to CD28, Inducible T-cell Costimulator (ICOS, also known as CD278) is also an Ig superfamily member, expressed as a homodimer in activated (but not resting) T cells, as well as NK and NKT cells.(122-124) As with CD28, binding of ICOS to its ligand, CD275, results in T cell activation, including expanded T cell proliferation, survival, cytokine production and effector differentiation.(125-127) Consistent with these properties, ICOS blockade inhibited murine acute GVHD induced by CD4+ and/or CD8+ T cells and also was shown to promote alloengraftment of donor bone marrow in suboptimally conditioned recipients. Murine experiments also have documented that ICOS is required for T-mediated B cell function, including a critical role in T-follicular helper (Tfh) generation and CD40-mediated Ig isotype switching.(127-129) While the impact of ICOS signaling on T cell function is striking(130) and positive effects have been seen in acute GVHD models, monotherapy mAb-mediated ICOS blockade in a solid organ cardiac allograft model only demonstrated a modest impact, although synergistic activity was seen when ICOS blockade was combined with cyclosporine to produce >100 day survival in a cardiac transplant model.(131) ICOS/L blockade has also been shown to effectively partner with anti-CD40L in prolonging islet allograft survival(132, 133) and blockade of ICOS;ICOSL reduced alloreactivity in an acute GVHD.(134) Moreover, ICOS has been demonstrated to be upregulated on activated T cells in a canine model of chronic GVHD,(135) and in a murine model of chronic GVHD model induced by injecting parental splenocytes into unirradiated F1 recipients, anti-

ICOS mAb inhibited B cell activation, autoantibody production and glomerulonephritis, the primary manifestation of chronic GVHD in that model system.(136) In addition, using a murine multi-organ system model of chronic GVHD with a hallmark of lung and bronchiolitis obliterans that is due to antibody production and depostion, blockade of ICOS in mice with active chronic GVHD restored pulmonary function to the level seen in no-GVHD controls.(137) In that setting, ICOS/L blockade resulted in a significant reduction in germinal center formation, essential for chronic GVHD generation in that model system.

Whether these encouraging results in mice will be translatable to the clinic is unclear. Indeed, a recent study showed that in a NHP renal transplant model, ICOS blockade did not prolong allograft survival, either as a monotherapy or when combined with belatacept.(138) However, combination blockade of this pathway with other potential partners was not tested in this study, nor was a comprehensive examination of its impact on diseases that are more reliant on GC formation. The mixed results notwithstanding, an anti-ICOSL antibody (AMG-557) is currently in clinical trials for lupus (Clinicaltrials.gov # NCT01683695 and NCT00774943), and as such, a direct test of the impact of ICOS pathway blockade in patients is being undertaken.

Targeting OX40:OX40L: An additional avenue for the 'right' targeting of Tconv and Tregs? Given the complexities of the impact that co-signaling pathway blockade makes on both conventional and regulatory T cell populations, the search for the ideal therapeutic continues in the fields of both autoimmunity and transplantation. New studies are identifying a role for OX40 (CD134):OX40L (CD252) blockade in transplant immunomodulation, given that, like CD154 pathway blockade, it may be able to simultaneously control Tconv effector function while potentially permitting Treg homeostasis and function. It has been well-documented that OX40 is upregulated on

CD4>>CD8 cells during T cell activation.(139-142) In several murine acute GVHD models, OX40:OX40L blockade augmented survival associated with anti-host hyporesponsiveness with the major effects being seen on CD4+ T cell mediated acute GVHD.(143-147) OX40 is also upregulated on human alloreactive T cells, and depletion of CD134+ T cells during an allogeneic mixed lymphocyte culture reaction with HLA-mismatched stimulator cells dramatically reduced anti-host but not anti-third party alloresponses.(148)

In the context of solid organ transplantation, blockade of OX40:OX40L signals was shown to prevent allograft rejection in murine models, in a manner that is non-redundant with blockade of CD28 or CD154.(149) Of note, several of the murine solid organ allograft studies showed that OX40:OX40L blockade did not impact T cell proliferation, but rather, inhibited T cell survival, and thus resulted in fewer cells available to infiltrate and reject allografts.(141, 142) Of significant interest is the fact that in contrast to the positive impact that OX40 ligation makes on Tconvs, Vu et al have shown that its ligation on Tregs results in the opposite effect, inhibiting Treg survival(142) and resulting in inhibition of their ability to suppress Tconv activation.(150) These results have led to significant interest in the field, and experiments in NHP investigating the impact of OX40:OX40L are underway in models of both solid organ and HCT, which are documenting that targeting this pathway may be an important avenue for tolerance induction (Kean et al., unpublished results). If these effects in NHP are robust, OX40:OX40L blockade agents are poised to be one of the next agents in the clinical pipeline for controlling auto- and allo-immune activation.

4-1BB/4-1BBL blockade: More central to tumor immunology than transplant immunology? 4-1BB has emerged as a major component of CAR-T cell engineering, (151, 152) as a key intracellular signaling domain that can lead to long-term T cell

persistence in vivo after CAR T cell adoptive transfer. However, the impact of blockade of this pathway on solid organ transplant outcomes are, in general, less striking. A member of the TNF family of receptors, 4-1BB (also known as CD137 and tnfrsf9) is expressed on activated Tconv (but not their naïve counterparts), Tregs,(153) as well as being expressed on B cells and dendritic cells.(154-157) An agonistic anti-4-1BB mAb amplified donor anti-host alloreactive T cell responses, accelerating GVHD as well as cardiac and skin allograft rejection, associated with heightened CD8+ T cell proliferation and IFNg response.(158) In other studies, both CD4+ and CD8+ T cell-mediated alloresponses were regulated by 4-1BB:4-1BBL interactions to approximately the same extent as assessed in acute GVHD and host bone marrow allograft rejection models, (159) and 4-1BB receptor-facilitated CD4+ T cell-mediated alloresponses were partly CD28 independent. Additionally, agonistic 4-1BB antibodies increased the graft-vs-leukemia effect of a suboptimal number of donor splenocytes given in a delayed fashion after bone marrow transplantation by bolstering allogeneic responses resulting in leukemia elimination. In other studies, host 4-1BBL deficiency reduced the capacity of the host to resist the GVHD lethality effect of delayed donor splenocyte infusion, which was used to simulate the clinical settings in which donor lymphocytes are given later post-transplant to treat or prevent leukemia relapse.(160) Consistent with these murine data, selective depletion of human alloreactive T cells after a mixed lymphocyte reaction was highly effective in reducing alloresponses. (161) In parent-into-F1 unirradiated GVHD models, blocking anti-CD137 mAb ameliorated acute GVHD, while unfortunately enhancing chronic GVHD associated with reduced CD8+ T cells expansion and IFNg expression along with enhanced antibody production.(162)

In solid organ allograft models, using 4-1BBL deficient recipients, skin allograft survival was not prolonged, and the combination of 4-1BB and CD28 deficiency only slightly delayed rejection kinetics.(163)These data suggest that 4-1BB was not the main

pathway of escape in the absence of CD28 signaling. Despite the lack of striking effect of the genetic absence of 4-1BBL, blockade of the pathway has had positive impact on allograft survival in mice, prolonging corneal, intestinal and cardiac allo-transplants.(164-167) Signaling through 4-1BB and its ligand therefore clearly play a role in allo-immunity; however, its supporting role in this process has thus far hindered its pathway towards the clinic for control of T cell activation, quite distinct from the central role its played in CAR-mediated T cell activation and subsequent tumor clearance.

Blockade of T cell trafficking to secondary lymph nodes and target organs and tissues: impact on transplant outcomes and interactions with co-signaling blockade: One of the most critical steps in both organ transplant rejection and GVHD pathogenesis is the recruitment of activated T cells to target organs. As such, there is high interest in the impact that adhesion and chemokine blockade may have on both processes. Much of the work on adhesion blockade has been pioneered in autoimmune disease, where several targeted therapies have been investigated.(168-173) These include blockade of the lymphocyte function antigen-1 (LFA-1; CD11a) pathway, the alpha4 (CD49d), beta 1 (CD29) integrin very late antigen-4 (VLA-4) pathway, and the sphingosine-1-phosphate receptor (S1P1R) pathway, that controls lymphocyte egress from lymph nodes and can be blocked by the S1P1R antagonist, FTY720.(174-196) While the predominance of the published data suggest important roles for both LFA-1 and VLA-4 pathway blockade in improving GVHD and graft acceptance (176, 177, 197-199) the latter analyzed in murine, NHP and patient trials, the significant risk of infectious disease with both these agents has limited their use in transplant settings.(184) Thus, while LFA-1 blockade has shown some promise in both murine and some, but not all NHP studies, and was also included in several islet transplant clinical protocols, the identification of the risk of progressive multi-focal leukoencephalopathy (PML) in patients

treated with the anti-LFA-1 antibody efilizumab for autoimmune disease prompted it to be withdrawn from the market. Similarly, while pre-clinical efficacy was observed with the anti-VLA-4 antibody natalizumab in both autoimmune and transplant settings, it has also been associated with a significant risk of PML. Patient advocacy has retained its approval for MS, but, given this risk, there has been limited adoption for other indications, especially in settings where there are viable alternatives.

As with anti-LFA-1 and anti-VLA4, there is also evidence to suggest that FTY720 can prevent acute GVHD, and at least temporarily prevent rejection as assessed in preclinical murine models of transplantation.(200-214) In murine acute GVHD systems, FTY720 has been shown to prevent GVHD lethality without impairing graft-versus-lymphoma or -leukemia effects. Mechanisms in these studies have been attributed to impairing lymphocyte migration, inducing donor anti-host alloreactive T cell apoptosis, and reducing splenic CD11c+ cells along with T cell responder frequencies.(205, 208, 212, 214, 215) In a chronic GVHD scleroderma model, FTY720 suppressed the immune response by promoting the expansion of Tregs and reducing vascular damage and infiltration of immune cells into the skin. In contrast to these positive results in GVHD in mice, in a large animal DLA non-identical acute GVHD model, FTY720 was ineffective in reducing acute GVHD, though the number of recipients studied was somewhat limited.(213) In the context of non-myeloablative transplants, FTY720 treatment in mice markedly but only transiently inhibited graft rejection due to the emigration of mature graft rejecting T cells from the host thymus upon drug withdrawal. However, when combined with tolerigenic anti-CD154 mAb, graft rejection did not occur upon drug withdrawal.(205) In the canine model, graft rejection rates did not differ from non-treated historical controls.(216) Although clinical studies with FTY720 have been completed and have resulted in drug approval for MS, and there was initially significant enthusiasm for it as a potential novel therapy to prevent GVHD and organ graft rejection, trials in renal

transplant patients failed to show an advantage of this drug compared to standard therapy, despite encouraging early results. Thus, FTY720 is no longer being evaluated in this setting.

It should be noted that each of these three modifiers of T cell trafficking have demonstrated more efficacy in autoimmune disorders than in transplant settings. It is still not clear what the mechanistic underpinnings of this observation are; however, one of the important observations in large animal models, similar to the murine model of sub-optimal conditioning and bone marrow graft rejection discussed above, has been the rebound effect that occurs when drug was withdrawn. Thus, in both NHP renal(185, 190) and bone marrow transplant (LSK unpublished), rejection occurred rapidly after withdrawal of anti-LFA1, ostensibly from alloreactive cells that were restrained from reaching their targets but not deleted or tolerized by the anti-integrin treatment. While patients treated long-term with these agents might benefit from the chronic inhibition of T cell trafficking, this strategy would be expected to increase the cumulative risk of infectious toxicities.

As with the adhesion and egress inhibitors, there has been significant interest in blocking chemokine–chemokine receptor interactions to improve transplant outcomes. Of the many chemokines that could be targeted, CCR5 has been investigated most thoroughly, after having been shown to be a central molecular mediator of T cell trafficking to GVHD target organs, including the GI tract.(217, 218) In preclinical studies, CCR5 blockade has shown protection against GVHD in sublethally irradiated recipients, associated with reduced homing to the intestinal Peyer's patches in some models using knockout donor T cells(217, 219), and, somewhat paradoxically, acceleration of GVHD in heavily but not lightly irradiated recipients.(219, 220) Based upon the positive data in murine non-myeloablated recipients, the CCR5 inhibitor maraviroc (NCT00948753), an FDA approved drug designed to limit CCR5-mediated HIV entry into CD4 T cells, was

given for 1 month post-transplant, along with standard of care pharmacological agents, to high-risk patients receiving matched unrelated or 1 antigen mismatched unrelated donor grafts. Although acute GVHD of the skin was not eliminated, patients given maraviroc had a low incidence of GI and liver GVHD which constituted one of the first demonstrations of a target-organ-specific effect of a biologic anti-GVHD prophylaxis regimen.(221) The durability of the impact of maroviroc on GVHD control is still undetermined, however, and there may be conditioning-regimen-specific effects in patients as seen in rodent models.(219) This agent is now being investigated as part of a large multicenter study sponsored by the BMT-CTN, (Clinicaltrials.gov # NCT02208037) where issues of conditioning and durability of the GVHD protective effect will be investigated more thoroughly.

LFA-3 (CD58): CD2 Blockade: A missed opportunity? In the last several years, there have been multiple demonstrations of the potential importance of targeting LFA3:CD2 with an LFA-3/Fc fusion protein to control T cell (and NK cell) activation and effector function, with several important lines of evidence suggesting that it might preferentially target memory rather than naïve T cells. These have included *in vivo* studies of anti-CD2 mAb in rodent xenogenic islet and allogeneic cardiac transplant models,(222) as well as *in vitro* studies of the human allo-response(223), and translational studies in NHP demonstrating a role for CD2 blockade in renal transplant.(224) The clinical benefits of anti-CD2 mAb could be seen in studies in both bone marrow transplant(225) and Type I diabetes(226, 227) indicating the potential importance of this pathway in controlling T cell mediated disease. However, although alefacept is currently FDA approved for the treatment of psoriasis, the parent company for the marketed version of the drug decided to discontinue marketing this drug in 2011 for financial reasons, making future clinical applications uncertain. Given the wide array of indications in which this agent may have

significant activity, and its potentially unique pre-disposition for memory, rather than naïve T cells, this likely represents a missed opportunity, and one that the transplant and autoimmune communities would welcome revisiting.

The Central Role of Tregs in Transplant Tolerance: In solid organ transplant models, it is clear that achieving long-term allograft survival and/or tolerance through the manipulation of co-signaling pathways is associated with an expansion of Tregs.(228). What is less clear, however, is whether this is a specific result of blocking costimulatory pathways *per se*, or rather, a secondary effect of antigen presentation in an environment where inflammation has been deliberately suppressed, promoting the expansion of pre-existing Tregs (tTregs) and the induction of *de novo* induced pTregs. Obviously, these are not mutually exclusive hypotheses; however there is some evidence in favor of the latter. For example, recent studies indicate that CD28 is an important homeostatic survival signal for Tregs(229) and thus CTLA4Ig would interfere with this survival signal. We suggest that promotion of Tregs in the setting of costimulatory blockade likely is an indirect effect of inhibition of inflammation, which promotes TGF-b. In addition, inflammatory cytokines are able to activate the PI-3 kinase pathway in T cells, which, when unopposed, inhibits Treg differentiation and promotes destabilization of pre-existing Tregs.(230) Thus dampening inflammation may promote Tregs via multiple mechanisms. In BMT, it is increasingly clear that Tregs can play a major role in controlling unwanted allo-reactivity, and can function both to prevent acute GVHD and treat chronic GVHD. Thus, our group and others have shown that Treg adoptive transfer early after transplant is safe, feasible and has efficacy in reducing acute GVHD, both in murine models(231-233) and in patient trials.(234-243) Important studies have also shown that adoptive transfer of these cells can also function to promote engraftment(244) and do not impair GVL.(245-248) These data underscore the central

role that Tregs play in both establishing and maintaining successful engraftment, and in restraining alloreactivity. Thus, in an era of manipulation of T cell co-signaling with targeted therapies, choosing those that 'walk the fine line' of restraining effector T cell activation while supporting Treg reconstitution and function will likely be necessary in order to achieve immune tolerance after both solid organ and HCT.

The key role of memory T cells in escaping co-stimulatory pathway blockade and approaches to prevent Tmemory cell escape:

As noted above, CD28 is required for optimal activation, function and survival of naïve T cells, with a particularly important role in CD4 T cell function. However in a number of studies (albeit not all), memory T cells have been shown to be relatively independent of CD28 costimulation.(249) Indeed, mouse models of solid or tissue transplantation have clearly demonstrated that costimulatory blockade is relatively ineffective in animals harboring pre-existing anti-donor specific T cells.(250) This presents a particularly problematic clinical situation since it can be anticipated that a large number of patients, even without evidence of prior antigenic exposure or pre-existing anti-donor humoral immunity, will have memory T cells capable of recognizing donor antigen. This is likely due to a variety of factors, most prominently heterologous immunity(251, 252) and the frequent expression of more that one TCRab heterodimer on human T cells(253) (the latter implying that a T cell with anti-donor alloantigen specificity based on one TCR might have memory phenotype/function acquired due to prior exposure to the antigen recognized by its second TCR).

Studies to overcome pre-existing memory have focused on non-CD28 mediated pathways. Pre-clinical studies in mice suggest that OX-40 may be a useful target.(254), and data in non-human primates points to CD2 as a potential useful target for memory T cells.(224) As noted above, this has been supported by an early phase clinical study in

type I diabetes suggesting that using LFA3Ig (a soluble CD2-ligand) may deplete Teffector/memory cells and/or promote T cell exhaustion.(226)

The Co-Inhibitory Pathways: Turn them off to fight cancer, turn them on to fight rejection and GVHD. The significant success in re-awakening anti-tumor T cell responses through checkpoint blockade has opened up new treatment possibilities for patients for whom conventional chemotherapeutic approaches are inadequate. In the clinic, these approaches have focused on blockade of two prominent inhibitory pathways: CTLA-4 and PD-1 (programmed death-1). Given the success of blockade of both of these pathways in activating T cell immunity, there has been much interest in activating these pathways for tolerance induction. We've discussed the CTLA4 pathway at length above, which plays a central role in the function of both Teffs and Tregs. Unfortunately, an agonistic reagent that specifically activates CTLA-4 is not available in the clinic, therefore, agonism of this pathway for immune tolerance-induction is not currently a viable clinical goal.

The other behemoth of the checkpoint blockade pathways for cancer immunotherapy is the PD-1 pathway. PD-1 was described as a novel Ig supergene family member by Professor Tatsuku Honjo in 1992.(255) PD-1 is expressed on dendritic cells, NK, NKT cells and on activated T cells. In BALB/c mice, PD-1 deficiency can result in autoimmune cardiomyopathy, consistent with its negative regulatory function.(256) The first identification of the critical importance of this pathway in antigen-responsive T cells *in vivo* was made by Dr. Rafi Ahmed's group, which showed that PD-1 is upregulated on exhausted T cells that accumulate during chronic infection.(257) Further studies showed that working through both immunoreceptor tyrosine-based inhibitory and switch motifs, PD-1 recruits SHP phosphatases leading to the inactivation of multiple T cell signaling pathways.(258)

Experiments with knockout mice for PD-1 and one of its ligands, PD-L1, as well as with PD-1 and PD-L1 blocking antibodies, demonstrated the necessity of this pathway for costimulation-blockade-mediated allograft acceptance.(259-261) Additionally, acute GVHD studies indicate a major role for PD-1 in down-regulating lethality, as shown with PD-1 KO donor T cells and anti-PD-1 blocking mAbs, which were demonstrated to function via an IFNg-dependent mechanism.(262-264) In addition, in a sublethally irradiated minor antigen mismatched model of sclerodermatous chronic GVHD, blockade of the PD-1 pathway worsened disease.(265) These data reinforce the central role that PD-1 pathways play in T cell activation. While this has yielded several important new drugs to augment T cell responses by blocking this pathway, unfortunately, no agonists of PD-1 have yet been developed to inhibit T cell auto- or allo-activation, and thus it is not possible to manipulate this pathway clinically to improve solid organ or bone marrow transplant outcomes..

PD-L1 vs PD-L2: Predominance of PD-L1 due to more promiscuous tissue expression? In its negative-regulatory functionality, PD-1 is known to interact with both PD-L1 and PD-L2, and the relative importance of these ligands has been a matter of significant investigation. PD-L1 (B7-H1, CD274) is expressed constitutively on hematopoietic cells and nonhematopoietic cells and upregulates after activation. PD-L2 (B7-DC, CD273) expression is restricted primarily to DCs, macrophages, and cultured bone marrow -derived mast cells. The broad PD-L1 expression suggests an important role in inhibiting immune responses in lymphoid and nonlymphoid organs.

Using a TCR transgenic system, we demonstrated that only blockade of PD-L1, and neither PD-1 nor PD-L2 abrogated skin graft tolerance in a transplant model with MHC Class II disparity.(266) In the same study, we found that in an adoptive transfer model, both PD-1 and PD-L1 were critical early after transfer, with PD-L1 becoming the

predominant inhibitor of T cell allo-proliferation as time progressed. This effect was dependent on the presence of CD4+ Tregs, suggesting that a multicellular mechanism of transplant acceptance may be in play, with both Teffs and Tregs necessary for the ultimate control of alloreactivity. The prominence of PD-L1 signaling in a model of Class II-mediated alloreactivity was also demonstrated by Yang et al., who found that in Class-II-disparate cardiac allograft model, signaling through PD-L1 was critical for allograft acceptance, but blockade of neither PD-1 nor PD-L2 had a negative impact on engraftment.(267, 268) Moreover, PD-L1 was found to be critical for the induction of Tregs.(269) In acute GVHD studies, PD-L1 has been shown to be the dominant host PD-L1 ligand that controls apoptosis of donor T cells, Teff expansion, function, and metabolism.(270) This is also true when delayed lymphocyte infusions are given. The expression on non-hematopoietic cells likely substantially contributes to this dominance, resulting in a markedly diminished GVL effect after delayed lymphocyte infusion.(264, 271, 272) Recent studies also indicate that PD-L1 expression on donor T cells regulates acute GVHD lethality, further complicating interpretation of the use of anti-PD-L1 mAbs.(273) Indeed, in an autoimmune-like minor histocompatibility antigen mismatched GVHD model, host APC PD-L1 reacting with CD80, was shown to augment donor Treg survival and expansion, suppressing GVHD.(274, 275)

Another potential explanation for the predominance of PD-L1 signaling in controlling allograft acceptance came from the discovery that PDL1 (and not PD-L2) can interact with CD80 in addition to PD1.(276) In acute GVHD, PD-L1/CD80 interactions induce apoptosis of donor T cells in a PD-1 dependent manner, resulting in amelioration of GVHD. Similarly, PD-L1/CD80 interactions can control diabetogenic Teffs. Thus PD-L1 may provide a parallel track for the control of alloreactivity that renders it as a central player in allograft survival. Evidence for this role was further strengthened by the identification of a monoclonal antibody that specifically targets the PDL1:CD80 binding

motif, providing a structural basis for the previously identified biologic activity. (268)

The downside of blocking co-inhibitory receptors: unwanted T cell activation, GVHD, autoimmunity: While this review is focused on manipulation of co-stimulatory and co-inhibitory molecules to control rather than stimulate T cell function, it is important to consider the impact of these agents on both auto-and allo-immunity, since patients at risk for both these processes are now being treated with checkpoint blockade agents. There have now been several reports of immune activation syndrome in patients treated with both anti-CTLA-4 (ipilimumab) and anti-PD-1 (novolumab). These include evidence for pulmonary, skin, cardiac, hepatic, GI and bone marrow disease.(277-282) The range of clinical severity of these diseases is large, and unfortunately includes some patients who have required extensive hospitalization and treatment with broad-acting immunosuppressive drugs, with patient death occurring in some instances. However, there are also numerous reports of patients with de novo inflammation or flare of known autoimmune disease being successfully treated with conventional immunosuppression while continuing to receive check-point blockade. Indeed, early-phase data showed that administration of ipilimumab was feasible in patients with recurrent hematologic cancers after allogeneic HCT, and resulted in durable responses, especially of extramedullary acute myeloid leukemia, although immune-mediated toxic effects and GVHD occurred.(283) In other studies, PD-1 pathway blocking reagents have been used to treat relapse post-allo-HCT, although early data does point to higher acute GVHD incidence and severity in treated patients.(284) It is still not clear what the impact of combining these two opposing therapies will be on tumor biology, as a large enough study has not yet been undertaken, but, at least in melanoma and small cell lung cancer, pre-existing autoimmunity is not considered an absolute contraindication for treatment with checkpoint blockade.

The issue of intercurrent allo-activation during checkpoint blockade or CAR-T therapy is also critical to the design of relapse-prevention strategies for patients that have undergone allogeneic BMT. In these patients, there is concern about the risk of induction or exacerbation of GVHD with checkpoint blockade, and it is not currently offered clinically. Although murine studies have suggested that GVHD can occur with allogeneic CAR therapy in the setting of transplant,(285) this has not been a major problem in patients, and many post-allo-BMT patients are treated with CAR-T cells.(286) However, there is concern with giving CAR-T cells in post-transplant patients who are being treated for GVHD, and this is not currently standard practice, given the concern of exacerbating GVHD with these therapies. There is also a concern for negatively impacting the efficacy of CAR-T cells when patients are receiving treatment with steroids and other agents to control GVHD. Engineering CAR-T cells to be resistant to these agents may increase the application of this therapy post-transplant. However, given the potential hazard of having a T cell population that cannot be controlled by conventional immunosuppression(287), having a suicide trigger engineered into these T cells is considered a necessary safety criteria.(288, 289)

Co-inhibitory ligands other than CTLA-4 and PD-1. In addition to CTLA-4 and PD1-, another of the major co-inhibitory molecules, LAG-3, has also become a major target for checkpoint blockade, with trials of anti-LAG-3 antibodies in glioblastoma, other solid tumors as well as hematologic malignancies.(290-292) In immune tolerance studies, its expression on induced Tregs is upregulated by exposure to IL-27 and is critical for the optimal function of these cells in controlling autoimmune diseases.(292, 293) In acute GVHD, studies have shown that LAG-3 KO Tconv induce significantly more severe GVHD than wild-type Tconv and that the absence of LAG-3 on CD4 but not CD8 T cells is responsible for worsening GVHD.(294) Notably, Tregs from LAG-3 KO mice were

functionally intact. While there is significant interest in modulating LAG-3 to enhance control of both auto-and allo-immunity, no targeted agents to upregulate this molecule yet exist.

More limited data exist for B7-H3 (CD276), a B7 family member overexpressed in a variety of solid tumors, which can be associated with poor prognosis. In allograft rejection, different studies have demonstrated either the promotion of rejection or prolongation of allograft survival by B7-H3 suppression of Th1 responses.(295, 296) In acute GVHD, B7-H3 expression by donor and host cells negatively regulates GVHD lethality.(297) Similar to LAG3-3, clinical agonistic reagents are not available. Notably, both resting and activated murine Tregs were found to lack B7-H3 messenger RNA.(297, 298)

Similar to B7-H3, B7-H4 is another B7 family member that is a negative regulator of T cell responses. This molecule is expressed on tumors and can be associated with a poor prognosis. Although GVHD studies have not been reported to date, B7-H4 expression has been shown in multiple studies to prolong islet allografts and in CD28-deficient recipients, B7-H4 blockade resulted in accelerated cardiac allograft rejection associated with increased frequencies of IFNg, IL4 and granzyme B producing splenocytes.(299) Moreover, the efficacy of CTLA4Ig in promoting allograft survival was diminished in mice that did not have an intact B7-H4 pathway. B7-H4 agonistic reagents are not clinically available at this time.

2B4 (CD244, SLAMf4) is also a central co-inhibitory molecule. Although it was originally identified on NK cells, it is clear that 2B4 is upregulated on activated T cells.(300-303) While delineation of the major function of 2B4 has proven complex, (and has included its associated with both T cell activation and inhibition), studies from Dr. Arlene Sharpe's laboratory,(304) and from Dr. Mandy Ford and others provide strong evidence for its role as a co-inhibitor of CD8+ T cell alloresponses in vivo.(72, 305)

Although the 2B4 pathway has not yet been harnessed for the promotion of tumor immunity, these studies suggest that it may be a viable candidate, especially in combination with either PD-1 or CTLA-4 blockade.

T cell immunoglobulin mucin-3 (TIM-3) was also found to be a critical player in transplantation tolerance when the Kuchroo laboratory demonstrated that anti-TIM3 blocking antibodies prevented transplant tolerance by interfering with Treg function.(306, 307) TIM-3 is expressed on pathogenic T cells in acute GVHD and its ligand, galectin-9 is up-regulated in inflamed tissues.(308) Tim-3/galectin-9 blockade accelerates acute GVHD, while conversely, galectin-9 transgenic recipients have demonstrated reduced acute GVHD. Pardoxically, TIM-3/galectin-9 blockade in recipients of Treg-depleted grafts reduced GVHD due to activation-induced Teff cell death as a result of increased IFNg production. In skin allograft recipients, activation of the TIM-3/galectin-9 pathway negatively regulates CD8+ alloreactive T cells and prolongs allograft survival,(309, 310) a finding also observed with cardiac allografts.(311, 312) TIM3+ Tregs, which are frequently PD-1+, were found to be a short-lived Treg subset that can restrain skin allograft rejection responses.(313) Unlike CTLA-4 and PD-1, an agonistic reagent does exist for TIM3, with its ligand, Galectin-9 recently being shown to promote acceptance of solid organ allografts.(314-316) Thus, TIM3 represents a molecule of considerable interest for both the cancer immunotherapy and transplant tolerance fields, with promise as both immune modulator and immune stimulator.

The special role of large animal models in understanding co-signaling in transplantation: Most of the pathways and molecules involved in T cell co-signaling have been first identified in murine models, using both genetic knock-out technologies and antibody- and small-molecule based blockade. While these murine studies have been absolutely critical to the progress in the field, canine models(135, 213, 317-322),

and NHP models(323) have been central to the translation of co-stimulation blockade to the clinic, in both solid organ and bone marrow transplant. The best example of this is with the FDA approval of belatacept for clinical use in renal transplantation. In the path to the clinic, Bristol-Myers Squibb closely collaborated with academic investigators to first design the higher avidity version of CTLA4Ig that belatacept represents(52), and then performed the key IND-enabling studies in NHP prior to launching pivotal clinical trials. These NHP studies closely predicted both the success of belatacept in being a true calcineurin-sparing agent (with all of the attendant advantages in terms of renal and cardiovascular function that accompanies a calcineurin-free regimen) and also predicted the belatacept-resistant rejection that has been observed clinically. For belatacept, the cycle of murine→NHP→patient and back to murine and NHP studies has been realized, with the detailed investigation of belatacept-resistant rejection being vigorously pursued in both murine and NHP models. While a clear solution to this issue has not yet been identified, ongoing studies in mice and NHP focused on identifying the causative mechanisms, and using a range of agents designed to overcome these early rejection responses is underway.

The utility of NHP models in moving co-stimulation blockade to the clinic has also been demonstrated in the field of BMT. While the success of both abatacept in RA and belatacept in renal transplant should have predicted the utility of these approaches in bone marrow transplant (along with the murine data that supported a role for this pathway in the pathogenesis of acute GVHD), (32-37) until our demonstration of the activity of CTLA4-Ig in preventing GVHD in an NHP model,(33) there was hesitation in the field to use *in vivo* co-stimulation blockade as a novel approach for GVHD prevention. (There had been one trial of ex-vivo exposure of bone marrow products to either CTLA4Ig or anti-B7 antibodies,(324) but this was not followed with significant adoption by the BMT field). The demonstration in NHP that combination co-stimulation

blockade could significantly protect recipients from GVHD provided the necessary rationale for clinical translation of this strategy to patients.(38) We are now completing a large Phase II study (Clinicaltrials.gov# NCT01743131) designed to determine both the benefits and risks of the addition of abatacept to standard-of-care GVHD prophylaxis in both adult and pediatric transplant patients.

Importantly, while NHP studies proved critical in identifying both the efficacy and the breakthrough rejection of belatacept in renal transplantation, not all clinical toxicities have been correctly identified in NHP studies. A major example of this is the fact that studies in cynomolgus macaques, one of the most prevalent of the NHP models used, did not identify the risk of uncontrolled T cell activation and cytokine storm that accompanied clinical use of the cross-linking anti-CD28 agonist targeting the C''D loop of CD28, TGN1412(68), likely due to the lack of expression of CD28 on CD4+ effector cells in macaques, and its increased expression on the human counterpart.(325-327) Vanhove and colleagues have subsequently shown that baboons represent a much more predictive NHP model for testing the toxicity of reagents targeting CD28, (328) and used this model to provide compelling data for the safety of their single-chain anti-CD28 reagent, FR104. They have gone on to demonstrate the potential efficacy of this therapeutic (originally developed by Effimune, now licensed to Janssen) in a number of NHP models of transplantation(76-81, 328), and it has now completed Phase 1 trials in RA (Clinialtrials.gov # NCT02800811). BMS has also developed a similar single-chain anti-CD28 antibody, 'Lulizumab', which has also been moved into early phase clinical trials for Sjogrens syndrome and lupus (Clinicaltrials.gov # NCT02843659 and NCT02265744).

The importance (and also the limitations of NHP models) in facilitating the translation of new therapeutics to the clinic have also been demonstrated with anti-CD154 and anti-CD40 antibodies. In murine tolerance models, strategies targeting

CD154 have long been demonstrated to be amongst the most potently tolerogenic, for both solid organ and BMT applications. These striking results in mice were recapitulated in NHP models,(104, 329-331) where anti-CD154 antibodies were found to be critical components of calcineurin-sparing regimens for many solid organ transplant models as well as for bone marrow chimerism-induction. Given the many positive attributes of targeting this pathway, both in terms of its impact on effector cells as well as on Tregs, there was much enthusiasm for translation to the clinic, and two trials were opened, one in renal transplant (Clinicaltrials.gov # NCT00001857) and one for patients with lupus neprhritis.(332) However, both clinical trials were halted shortly after their initiation, given an unusually high rate of thromboembolic complications in treated patients. Subsequently, Cosmi and colleagues reported a new regimen that incorporated anti-CD154 antibodies in NHP that also demonstrated the thromboembolic events;(109) however, many previous studies had failed to identify this complication. The combined lessons with anti-CD28 and anti-CD154 have pushed the field of NHP transplantation research to evolve more stringent practices for evaluating the potential toxicity and efficacy of therapeutics prior to clinical translation, and the road to the clinic through primate investigation has continued to be robust.

Following the identification of the thrombosis risk with anti-CD154, there was a significant push to develop and evaluate anti-CD40 reagents in NHP for use in transplantation, and these studies suggested that targeting CD40 had significant efficacy, on par with what was observed for CD154-directed therapies. These NHP results are now being translated to the clinic, with the first anti-CD40 antibodies being tested for psoriasis and renal transplantation (clinicaltrials.gov # NCT01585233, NCT01780844 and NCT02217410). In addition, the thromboembolic complications with the conventional anti-CD154 antibodies have now been overcome, with domain-specific, single-chain antibodies, (rigorously determined to not induce thrombosis), having been

developed. These are being re-introduced into the fields of both autoimmunity and transplantation with high hopes for significant efficacy without toxicities.

The experience with both anti-CD28 and anti-CD154 antibodies have reinforced the contention that no animal model is a perfect surrogate for carefully conducted clinical trials. However, the strengths of NHP models have been critical for the streamlining of translation of co-stimulation blockade to the clinic for autoimmunity and transplantation. These studies permit combination therapies that are more difficult to interrogate in murine models, given significant differences in pharmacokinetics and in receptor:ligand expression patterns in mice compared to humans. They also permit the direct evaluation of reagents that are developed for human use, which usually cross-react with NHP targets but rarely do so with their murine counterparts. Finally they permit intensive monitoring of both the blood and transplant target organs (eg kidney, heart, skin, GI tract) such that both the peripheral and tissue-specific immunologic consequences of transplant and novel therapeutic strategies can be fully assessed. This is essential for both the evaluation of safety and efficacy, with the proviso that careful attention be paid to any species-specific heterogeneity of target expression, as occurred with TGN1412.

In order to maximize their utility for clinical transplantation, the field of NHP experimentation has greatly benefited from recent advances that help assure that the immune milieu of these transplants is understood in the greatest detail possible. One significant example is the establishment of a new ‘gold standard’ in transplant studies, where the degree of MHC disparity between donors and recipients is now expected to be defined, and equivalent amongst different treatments in any transplant series.(102, 333) Until 2010, this degree of information about the MHC was not included in transplant planning, which opened up these studies to the potential confounder of serendipitously close MHC matching leading to transplant outcomes that were more successful than they otherwise would have been (or vice versa with highly disparate transplant pairs).

Our group and others created a new paradigm in NHP transplant planning by applying first microsattelite-(102, 333) and now MHC-allele-level typing to multiple NHP colonies(334), with the NIAID providing critical support for this effort, by funding the detailed MHC typing of their sponsored macaque colony. In addition to the rigorous MHC matching that is now possible in NHP transplant experiments, the detailed annotation of the rhesus transcriptome(335, 336) has allowed a systems approach to understanding the impact that new therapies make on the T cell transcriptional networks controlling transplant outcomes. This has led to new insights about the breakthrough alloreactivity (336) that occurs with both standard and CTLA4Ig-based immunomodlulation for GVHD prevention, as well as the identification of new potential targeted therapies to control the T cell activation that leads to GVHD.(337) These advances have helped solidify the depth of analysis that is possible with NHP models of T cell co-signaling, thereby helping to optimize the ability of these models to most efficiently advance novel targeted therapeutics to the clinic.

Conclusions and Perspectives: In this review, we have discussed the co-signaling pathways that lead to T cell activation. However, our focus has not been on controlling these pathways in order to activate T cells, or awaken them from senescence (what one might call harnessing the 'Yang' in T cells) but rather, we have concentrated on the field of immune tolerance, a field that is focused on the Yin, or the specific 'cooling' of T cells, to control T cell activation and to lead to lifelong acceptance of allografts, without the need for ongoing immunosuppression. This work has its philosophical underpinnings in the landmark work of Billingham, Brent and Medawar, over 60 years ago, which introduced the concept that under some conditions, life-long acceptance of foreign cells and tissues could occur.(338) As we have learned more about the complex molecular networks that control T cell activation, and T cell tolerance, two things have happened:

First, we are more and more able to manipulate T cell programming to achieve our goals (whether they be T cell activation or T cell tolerance) and second, we are increasingly aware of the extremely delicate balance that exists, that makes these manipulations extremely difficult to fully control. This has been shown in both the fields of cancer immunotherapy and in immune tolerance work. In cancer immunotherapy, we have seen toxicities directly attributable to our unleashing of T cell activation in a manner that has many fewer brakes than exist in the natural setting. In immune tolerance, we have seen the consequences of ‘over-cooling’ of T cell immunity, which can lead to defects in protective immunity against both infectious pathogens and tumor cells. Moreover, our increasing awareness of the impact of manipulating T cell co-signaling pharmacologically, affecting both effector and regulatory T cells, has led to an understanding that we must induce immune tolerance on a ‘knifes edge’: We must seek to understand in exquisite detail the complex systems that control T cell programming such that we can simultaneously induce tolerance in all T cell subpopulations, both effector and regulatory. The ongoing work in murine NHP and patient trials are geared toward just this goal: understanding the programming that naturally induces tolerance, and recapitulating this with targeted therapies such that we induce just the right amount of Yin for our patients undergoing transplantation.

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Conflicts of Interest (COI):

BRB has the following conflicts to declare: He is a founder of Tmunity Therapeutics, Inc. He receives funding from Tmunity Therapeutics Inc, Kadmon Corporation and Nektar Therapeutics.

LSK receives research funding from Bristol Myers Squibb and Kymab Ltd.

LAT has financial interests in Third Rock Ventures and Neon Therapeutics.

References:

1. Lin H, Bolling SF, Linsley PS, Wei RQ, Gordon D, Thompson CB, Turka LA. Long-term acceptance of major histocompatibility complex mismatched cardiac allografts induced by CTLA4Ig plus donor-specific transfusion. The Journal of experimental medicine. 1993;178(5):1801-6. PubMed PMID: 8228826; PMCID: PMC2191223.
2. Linsley PS, Wallace PM, Johnson J, Gibson MG, Greene JL, Ledbetter JA, Singh C, Tepper MA. Immunosuppression in vivo by a soluble form of the CTLA-4 T cell activation molecule. Science. 1992;257(5071):792-5. PubMed PMID: 1496399.
3. Lenschow DJ, Zeng Y, Thistlethwaite JR, Montag A, Brady W, Gibson MG, Linsley PS, Bluestone JA. Long-term survival of xenogeneic pancreatic islet grafts induced by CTLA4lg. Science. 1992;257(5071):789-92. PubMed PMID: 1323143.
4. Linsley PS, Brady W, Urnes M, Grosmaire LS, Damle NK, Ledbetter JA. CTLA-4 is a second receptor for the B cell activation antigen B7. The Journal of experimental medicine. 1991;174(3):561-9. PubMed PMID: 1714933; PMCID: PMC2118936.
5. Larsen CP, Elwood ET, Alexander DZ, Ritchie SC, Hendrix R, Tucker-Burden C, Cho HR, Aruffo A, Hollenbaugh D, Linsley PS, Winn KJ, Pearson TC. Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways. Nature. 1996;381(6581):434-8. doi: 10.1038/381434a0. PubMed PMID: 8632801.
6. June CH, Ledbetter JA, Linsley PS, Thompson CB. Role of the CD28 receptor in T-cell activation. Immunol Today. 1990;11(6):211-6. PubMed PMID: 2162180.
7. Linsley PS, Clark EA, Ledbetter JA. T-cell antigen CD28 mediates adhesion with B cells by interacting with activation antigen B7/BB-1. Proceedings of the National Academy of Sciences of the United States of America. 1990;87(13):5031-5. PubMed PMID: 2164219; PMCID: PMC54255.
8. Freeman GJ, Freedman AS, Segil JM, Lee G, Whitman JF, Nadler LM. B7, a new member of the Ig superfamily with unique expression on activated and neoplastic B cells. Journal of immunology. 1989;143(8):2714-22. PubMed PMID: 2794510.
9. Gimmi CD, Freeman GJ, Gribben JG, Sugita K, Freedman AS, Morimoto C, Nadler LM. B-cell surface antigen B7 provides a costimulatory signal that induces T cells to proliferate and secrete interleukin 2. Proceedings of the National Academy of Sciences of the United States of America. 1991;88(15):6575-9. PubMed PMID: 1650475; PMCID: PMC52129.
10. Freeman GJ, Gribben JG, Boussiotis VA, Ng JW, Restivo VA, Jr., Lombard LA, Gray GS, Nadler LM. Cloning of B7-2: a CTLA-4 counter-receptor that costimulates human T cell proliferation. Science. 1993;262(5135):909-11. PubMed PMID: 7694363.
11. Lenschow DJ, Su GH, Zuckerman LA, Nabavi N, Jellis CL, Gray GS, Miller J, Bluestone JA. Expression and functional significance of an additional ligand for CTLA-4. Proceedings of the National Academy of Sciences of the United States of America. 1993;90(23):11054-8. PubMed PMID: 7504292; PMCID: PMC47920.
12. Peach RJ, Bajorath J, Brady W, Leytze G, Greene J, Naemura J, Linsley PS. Complementarity determining region 1 (CDR1)- and CDR3-analogous regions in CTLA-4 and CD28 determine the binding to B7-1. The Journal of experimental medicine. 1994;180(6):2049-58. PubMed PMID: 7964482; PMCID: PMC2191786.
13. Brunet JF, Denizot F, Luciani MF, Roux-Dosseto M, Suzan M, Mattei MG, Golstein P. A new member of the immunoglobulin superfamily--CTLA-4. Nature. 1987;328(6127):267-70. doi: 10.1038/328267a0. PubMed PMID: 3496540.
14. Harper K, Balzano C, Rouvier E, Mattei MG, Luciani MF, Golstein P. CTLA-4 and CD28 activated lymphocyte molecules are closely related in both mouse and human as to sequence, message expression, gene structure, and chromosomal location. Journal of immunology. 1991;147(3):1037-44. PubMed PMID: 1713603.

15. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, Thompson CB, Bluestone JA. CTLA-4 can function as a negative regulator of T cell activation. Immunity. 1994;1(5):405-13. PubMed PMID: 7882171.
16. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. The Journal of experimental medicine. 1995;182(2):459-65. PubMed PMID: 7543139; PMCID: PMC2192127.
17. Turka LA, Linsley PS, Lin H, Brady W, Leiden JM, Wei RQ, Gibson ML, Zheng XG, Myrdal S, Gordon D, et al. T-cell activation by the CD28 ligand B7 is required for cardiac allograft rejection in vivo. Proceedings of the National Academy of Sciences of the United States of America. 1992;89(22):11102-5. PubMed PMID: 1332070; PMCID: PMC50492.
18. Finck BK, Linsley PS, Wofsy D. Treatment of murine lupus with CTLA4Ig. Science. 1994;265(5176):1225-7. PubMed PMID: 7520604.
19. Knoerzer DB, Karr RW, Schwartz BD, Mengle-Gaw LJ. Collagen-induced arthritis in the BB rat. Prevention of disease by treatment with CTLA-4-Ig. The Journal of clinical investigation. 1995;96(2):987-93. doi: 10.1172/JCI118146. PubMed PMID: 7543497; PMCID: PMC185286.
20. Racke MK, Scott DE, Quigley L, Gray GS, Abe R, June CH, Perrin PJ. Distinct roles for B7-1 (CD-80) and B7-2 (CD-86) in the initiation of experimental allergic encephalomyelitis. The Journal of clinical investigation. 1995;96(5):2195-203. doi: 10.1172/JCI118274. PubMed PMID: 7593605; PMCID: PMC185869.
21. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, Menter A, Lowe NJ, Krueger G, Brown MJ, Weiner RS, Birkhofer MJ, Warner GL, Berry KK, Linsley PS, Krueger JG, Ochs HD, Kelley SL, Kang S. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. The Journal of clinical investigation. 1999;103(9):1243-52. doi: 10.1172/JCI5857. PubMed PMID: 10225967; PMCID: PMC408469.
22. Moreland LW, Alten R, Van den Bosch F, Appelboom T, Leon M, Emery P, Cohen S, Luggen M, Shergy W, Nuamah I, Becker JC. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum. 2002;46(6):1470-9. doi: 10.1002/art.10294. PubMed PMID: 12115176.
23. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, Russell A, Dougados M, Emery P, Nuamah IF, Williams GR, Becker JC, Hagerty DT, Moreland LW. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. The New England journal of medicine. 2003;349(20):1907-15. doi: 10.1056/NEJMoa035075. PubMed PMID: 14614165.
24. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty DT, Dougados M. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. The New England journal of medicine. 2005;353(11):1114-23. doi: 10.1056/NEJMoa050524. PubMed PMID: 16162882.
25. Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, Steinfeld S, Tindall E, Becker JC, Li T, Nuamah IF, Aranda R, Moreland LW. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005;52(8):2263-71. doi: 10.1002/art.21201. PubMed PMID: 16052582.
26. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Li T, Ge Z, Becker JC, Westhovens R. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Annals of internal medicine. 2006;144(12):865-76. PubMed PMID: 16785475.

27. Viglietta V, Bourcier K, Buckle GJ, Healy B, Weiner HL, Hafler DA, Egorova S, Guttmann CR, Rusche JR, Khoury SJ. CTLA4Ig treatment in patients with multiple sclerosis: an open-label, phase 1 clinical trial. Neurology. 2008;71(12):917-24. doi: 10.1212/01.wnl.0000325915.00112.61. PubMed PMID: 18794494.
28. Parulekar AD, Boomer JS, Patterson BM, Yin-Declue H, Deppong CM, Wilson BS, Jarjour NN, Castro M, Green JM. A randomized controlled trial to evaluate inhibition of T-cell costimulation in allergen-induced airway inflammation. Am J Respir Crit Care Med. 2013;187(5):494-501. doi: 10.1164/rccm.201207-1205OC. PubMed PMID: 23292882.
29. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Marks JB, Monzavi R, Moran A, Raskin P, Rodriguez H, Russell WE, Schatz D, Wherrett D, Wilson DM, Krischer JP, Skyler JS, Type 1 Diabetes TrialNet Abatacept Study G. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;378(9789):412-9. doi: 10.1016/S0140-6736(11)60886-6. PubMed PMID: 21719096; PMCID: PMC3462593.
30. Sandborn WJ, Colombel JF, Sands BE, Rutgeerts P, Targan SR, Panaccione R, Bressler B, Geboes K, Schreiber S, Aranda R, Gujrathi S, Luo A, Peng Y, Salter-Cid L, Hanauer SB. Abatacept for Crohn's disease and ulcerative colitis. Gastroenterology. 2012;143(1):62-9 e4. doi: 10.1053/j.gastro.2012.04.010. PubMed PMID: 22504093.
31. Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace DJ, Bae SC, Sigal L, Becker JC, Kelly S, Raghupathi K, Li T, Peng Y, Kinaszczuk M, Nash P. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62(10):3077-87. doi: 10.1002/art.27601. PubMed PMID: 20533545.
32. Blazar BR, Taylor PA, Linsley PS, Vallera DA. In vivo blockade of CD28/CTLA4: B7/BB1 interaction with CTLA4-Ig reduces lethal murine graft-versus-host disease across the major histocompatibility complex barrier in mice. Blood. 1994;83(12):3815-25. PubMed PMID: 7515723.
33. Miller WP, Srinivasan S, Panoskaltsis-Mortari A, Singh K, Sen S, Hamby K, Deane T, Stempora L, Beus J, Turner A, Wheeler C, Anderson DC, Sharma P, Garcia A, Strobert E, Elder E, Crocker I, Crenshaw T, Penedo MC, Ward T, Song M, Horan J, Larsen CP, Blazar BR, Kean LS. GVHD after haploidentical transplantation: a novel, MHC-defined rhesus macaque model identifies CD28- CD8+ T cells as a reservoir of breakthrough T-cell proliferation during costimulation blockade and sirolimus-based immunosuppression. Blood. 2010;116(24):5403-18. Epub 2010/09/14. doi: 10.1182/blood-2010-06-289272. PubMed PMID: 20833977; PMCID: 3012549.
34. Saito K, Sakurai J, Ohata J, Kohsaka T, Hashimoto H, Okumura K, Abe R, Azuma M. Involvement of CD40 ligand-CD40 and CTLA4-B7 pathways in murine acute graft-versus-host disease induced by allogeneic T cells lacking CD28. Journal of immunology. 1998;160(9):4225-31. PubMed PMID: 9574523.
35. Hakim FT, Cepeda R, Gray GS, June CH, Abe R. Acute graft-versus-host reaction can be aborted by blockade of costimulatory molecules. Journal of immunology. 1995;155(4):1757-66. PubMed PMID: 7636232.
36. Wallace PM, Johnson JS, MacMaster JF, Kennedy KA, Gladstone P, Linsley PS. CTLA4Ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers. Transplantation. 1994;58(5):602-10. PubMed PMID: 8091487.
37. Via CS, Rus V, Nguyen P, Linsley P, Gause WC. Differential effect of CTLA4Ig on murine graft-versus-host disease (GVHD) development: CTLA4Ig prevents both

acute and chronic GVHD development but reverses only chronic GVHD. Journal of immunology. 1996;157(9):4258-67. PubMed PMID: 8892665.
38. Koura DT, Horan JT, Langston AA, Qayed M, Mehta A, Khoury HJ, Harvey RD, Suessmuth Y, Couture C, Carr J, Grizzle A, Johnson HR, Cheeseman JA, Conger JA, Robertson J, Stempora L, Johnson BE, Garrett A, Kirk AD, Larsen CP, Waller EK, Kean LS. In vivo T cell costimulation blockade with abatacept for acute graft-versus-host disease prevention: a first-in-disease trial. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2013;19(11):1638-49. Epub 2013/09/21. doi: 10.1016/j.bbmt.2013.09.003. PubMed PMID: 24047754.
39. Pree I, Bigenzahn S, Fuchs D, Koporc Z, Nierlich P, Winkler C, Brandacher G, Sykes M, Muehlbacher F, Langer F, Wekerle T. CTLA4Ig promotes the induction of hematopoietic chimerism and tolerance independently of Indoleamine-2,3-dioxygenase. Transplantation. 2007;83(5):663-7. doi: 10.1097/01.tp.0000255594.23445.29. PubMed PMID: 17353791; PMCID: PMC2992942.
40. Blaha P, Bigenzahn S, Koporc Z, Sykes M, Muehlbacher F, Wekerle T. Short-term immunosuppression facilitates induction of mixed chimerism and tolerance after bone marrow transplantation without cytoreductive conditioning. Transplantation. 2005;80(2):237-43. PubMed PMID: 16041269.
41. Wekerle T, Kurtz J, Bigenzahn S, Takeuchi Y, Sykes M. Mechanisms of transplant tolerance induction using costimulatory blockade. Current opinion in immunology. 2002;14(5):592-600. PubMed PMID: 12183158.
42. Wekerle T, Kurtz J, Sayegh M, Ito H, Wells A, Bensinger S, Shaffer J, Turka L, Sykes M. Peripheral deletion after bone marrow transplantation with costimulatory blockade has features of both activation-induced cell death and passive cell death. Journal of immunology. 2001;166(4):2311-6. PubMed PMID: 11160287.
43. Wekerle T, Kurtz J, Ito H, Ronquillo JV, Dong V, Zhao G, Shaffer J, Sayegh MH, Sykes M. Allogeneic bone marrow transplantation with co-stimulatory blockade induces macrochimerism and tolerance without cytoreductive host treatment. Nature medicine. 2000;6(4):464-9. doi: 10.1038/74731. PubMed PMID: 10742157.
44. Wekerle T, Sayegh MH, Ito H, Hill J, Chandraker A, Pearson DA, Swenson KG, Zhao G, Sykes M. Anti-CD154 or CTLA4Ig obviates the need for thymic irradiation in a non-myeloablative conditioning regimen for the induction of mixed hematopoietic chimerism and tolerance. Transplantation. 1999;68(9):1348-55. PubMed PMID: 10573075.
45. Wekerle T, Sayegh MH, Hill J, Zhao Y, Chandraker A, Swenson KG, Zhao G, Sykes M. Extrathymic T cell deletion and allogeneic stem cell engraftment induced with costimulatory blockade is followed by central T cell tolerance. The Journal of experimental medicine. 1998;187(12):2037-44. PubMed PMID: 9625763; PMCID: PMC2212372.
46. Adams AB, Durham MM, Kean L, Shirasugi N, Ha J, Williams MA, Rees PA, Cheung MC, Mittelstaedt S, Bingaman AW, Archer DR, Pearson TC, Waller EK, Larsen CP. Costimulation blockade, busulfan, and bone marrow promote titratable macrochimerism, induce transplantation tolerance, and correct genetic hemoglobinopathies with minimal myelosuppression. Journal of immunology. 2001;167(2):1103-11. PubMed PMID: 11441122.
47. Adams AB, Pearson TC, Larsen CP. Conventional immunosuppression and co-stimulation blockade. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2001;356(1409):703-5. doi: 10.1098/rstb.2001.0854. PubMed PMID: 11375073; PMCID: PMC1088457.

48. Adams AB, Shirasugi N, Durham MM, Strobert E, Anderson D, Rees P, Cowan S, Xu H, Blinder Y, Cheung M, Hollenbaugh D, Kenyon NS, Pearson TC, Larsen CP. Calcineurin inhibitor-free CD28 blockade-based protocol protects allogeneic islets in nonhuman primates. Diabetes. 2002;51(2):265-70. PubMed PMID: 11812731.
49. Durham MM, Bingaman AW, Adams AB, Ha J, Waitze SY, Pearson TC, Larsen CP. Cutting edge: administration of anti-CD40 ligand and donor bone marrow leads to hemopoietic chimerism and donor-specific tolerance without cytoreductive conditioning. Journal of immunology. 2000;165(1):1-4. PubMed PMID: 10861026.
50. Kean LS, Durham MM, Adams AB, Hsu LL, Perry JR, Dillehay D, Pearson TC, Waller EK, Larsen CP, Archer DR. A cure for murine sickle cell disease through stable mixed chimerism and tolerance induction after nonmyeloablative conditioning and major histocompatibility complex-mismatched bone marrow transplantation. Blood. 2002;99(5):1840-9. PubMed PMID: 11861303.
51. Kean LS, Manci EA, Perry J, Balkan C, Coley S, Holtzclaw D, Adams AB, Larsen CP, Hsu LL, Archer DR. Chimerism and cure: hematologic and pathologic correction of murine sickle cell disease. Blood. 2003;102(13):4582-93. doi: 10.1182/blood-2003-03-0712. PubMed PMID: 12933586.
52. Larsen CP, Pearson TC, Adams AB, Tso P, Shirasugi N, Strobert E, Anderson D, Cowan S, Price K, Naemura J, Emswiler J, Greene J, Turk LA, Bajorath J, Townsend R, Hagerty D, Linsley PS, Peach RJ. Rational development of LEA29Y (belatacept), a high-affinity variant of CTLA4-Ig with potent immunosuppressive properties. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2005;5(3):443-53. doi: 10.1111/j.1600-6143.2005.00749.x. PubMed PMID: 15707398.
53. Levisetti MG, Padrid PA, Szot GL, Mittal N, Meehan SM, Wardrip CL, Gray GS, Bruce DS, Thistlethwaite JR, Jr., Bluestone JA. Immunosuppressive effects of human CTLA4Ig in a non-human primate model of allogeneic pancreatic islet transplantation. Journal of immunology. 1997;159(11):5187-91. PubMed PMID: 9548454.
54. Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G, Lang P, Grinyo J, Halloran PF, Solez K, Hagerty D, Levy E, Zhou W, Natarajan K, Charpentier B, Belatacept Study G. Costimulation blockade with belatacept in renal transplantation. The New England journal of medicine. 2005;353(8):770-81. doi: 10.1056/NEJMoa050085. PubMed PMID: 16120857.
55. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, Moal MC, Mondragon-Ramirez GA, Kothari J, Polinsky MS, Meier-Kriesche HU, Munier S, Larsen CP. Belatacept and Long-Term Outcomes in Kidney Transplantation. The New England journal of medicine. 2016;374(4):333-43. doi: 10.1056/NEJMoa1506027. PubMed PMID: 26816011.
56. Rostaing L, Vincenti F, Grinyo J, Rice KM, Bresnahan B, Steinberg S, Gang S, Gaite LE, Moal MC, Mondragon-Ramirez GA, Kothari J, Pupim L, Larsen CP. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(11):2875-83. doi: 10.1111/ajt.12460. PubMed PMID: 24047110.
57. Vanrenterghem Y, Bresnahan B, Campistol J, Durrbach A, Grinyo J, Neumayer HH, Lang P, Larsen CP, Mancilla-Urrea E, Pestana JM, Block A, Duan T, Glicklich A, Gujrathi S, Vincenti F. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). Transplantation. 2011;91(9):976-83. doi: 10.1097/TP.0b013e31820c10eb. PubMed PMID: 21372756.

58. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity. 1995;3(5):541-7. PubMed PMID: 7584144.
59. Sansom DM. CD28, CTLA-4 and their ligands: who does what and to whom? Immunology. 2000;101(2):169-77. PubMed PMID: 11012769; PMCID: PMC2327073.
60. Schmidt EM, Wang CJ, Ryan GA, Clough LE, Qureshi OS, Goodall M, Abbas AK, Sharpe AH, Sansom DM, Walker LS. Ctla-4 controls regulatory T cell peripheral homeostasis and is required for suppression of pancreatic islet autoimmunity. Journal of immunology. 2009;182(1):274-82. PubMed PMID: 19109158.
61. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, Nomura T, Sakaguchi S. CTLA-4 control over Foxp3+ regulatory T cell function. Science. 2008;322(5899):271-5. doi: 10.1126/science.1160062. PubMed PMID: 18845758.
62. Waterhouse P, Penninger JM, Timms E, Wakeham A, Shahinian A, Lee KP, Thompson CB, Griesser H, Mak TW. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science. 1995;270(5238):985-8. PubMed PMID: 7481803.
63. Tang Q, Henriksen KJ, Boden EK, Tooley AJ, Ye J, Subudhi SK, Zheng XX, Strom TB, Bluestone JA. Cutting edge: CD28 controls peripheral homeostasis of CD4+CD25+ regulatory T cells. Journal of immunology. 2003;171(7):3348-52. PubMed PMID: 14500627.
64. Zhang R, Huynh A, Whitcher G, Chang J, Maltzman JS, Turka LA. An obligate cell-intrinsic function for CD28 in Tregs. The Journal of clinical investigation. 2013;123(2):580-93. doi: 10.1172/JCI65013. PubMed PMID: 23281398; PMCID: PMC3561819.
65. Bluestone JA, Liu W, Yabu JM, Laszik ZG, Putnam A, Belingheri M, Gross DM, Townsend RM, Vincenti F. The effect of costimulatory and interleukin 2 receptor blockade on regulatory T cells in renal transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2008;8(10):2086-96. doi: 10.1111/j.1600-6143.2008.02377.x. PubMed PMID: 18828769; PMCID: PMC3087374.
66. Riella LV, Liu T, Yang J, Chock S, Shimizu T, Mfarrej B, Batal I, Xiao X, Sayegh MH, Chandraker A. Deleterious effect of CTLA4-Ig on a Treg-dependent transplant model. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(4):846-55. doi: 10.1111/j.1600-6143.2011.03929.x. PubMed PMID: 22300534.
67. Zheng HB, Watkins B, Tkachev V, Yu S, Tran D, Furlan S, Zeleski K, Singh K, Hamby K, Hotchkiss C, Lane J, Gumber S, Adams AB, Cendales L, Kirk AD, Kaur A, Blazar BR, Larsen CP, Kean LS. The Knife's Edge of Tolerance: Inducing Stable Multilineage Mixed Chimerism but With a Significant Risk of CMV Reactivation and Disease in Rhesus Macaques. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016. doi: 10.1111/ajt.14006. PubMed PMID: 27500470.
68. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. The New England journal of medicine. 2006;355(10):1018-28. doi: 10.1056/NEJMoa063842. PubMed PMID: 16908486.
69. Hanke T. Lessons from TGN1412. Lancet. 2006;368(9547):1569-70; author reply 70. doi: 10.1016/S0140-6736(06)69651-7. PubMed PMID: 17084746.
70. Suchard SJ, Davis PM, Kansal S, Stetsko DK, Brosius R, Tamura J, Schneeweis L, Bryson J, Salcedo T, Wang H, Yang Z, Fleener CA, Ignatovich O, Plummer C, Grant S, Nadler SG. A monovalent anti-human CD28 domain antibody antagonist: preclinical

efficacy and safety. Journal of immunology. 2013;191(9):4599-610. doi: 10.4049/jimmunol.1300470. PubMed PMID: 24081989.
71. Liu D, Suchard SJ, Nadler SG, Ford ML. Inhibition of Donor-Reactive CD8+ T Cell Responses by Selective CD28 Blockade Is Independent of Reduced ICOS Expression. PloS one. 2015;10(6):e0130490. doi: 10.1371/journal.pone.0130490. PubMed PMID: 26098894; PMCID: PMC4476729.
72. Liu D, Krummey SM, Badell IR, Wagener M, Schneeweis LA, Stetsko DK, Suchard SJ, Nadler SG, Ford ML. 2B4 (CD244) induced by selective CD28 blockade functionally regulates allograft-specific CD8+ T cell responses. The Journal of experimental medicine. 2014;211(2):297-311. doi: 10.1084/jem.20130902. PubMed PMID: 24493803; PMCID: PMC3920565.
73. Shi R, Honczarenko M, Zhang S, Fleener C, Mora J, Lee SK, Wang R, Liu X, Shevell DE, Yang Z, Wang H, Murthy B. Pharmacokinetic, Pharmacodynamic, and Safety Profile of a Novel Anti-CD28 Domain Antibody Antagonist in Healthy Subjects. J Clin Pharmacol. 2016. doi: 10.1002/jcph.791. PubMed PMID: 27402064.
74. Yang Z, Wang H, Salcedo TW, Suchard SJ, Xie JH, Schneeweis LA, Fleener CA, Calore JD, Shi R, Zhang SX, Rodrigues AD, Car BD, Marathe PH, Nadler SG. Integrated Pharmacokinetic/Pharmacodynamic Analysis for Determining the Minimal Anticipated Biological Effect Level of a Novel Anti-CD28 Receptor Antagonist BMS-931699. J Pharmacol Exp Ther. 2015;355(3):506-15. doi: 10.1124/jpet.115.227249. PubMed PMID: 26442523.
75. Mary C, Coulon F, Poirier N, Dilek N, Martinet B, Blancho G, Vanhove B. Antagonist properties of monoclonal antibodies targeting human CD28: role of valency and the heavy-chain constant domain. mAbs. 2013;5(1):47-55. doi: 10.4161/mabs.22697. PubMed PMID: 23221503; PMCID: PMC3564885.
76. Poirier N, Mary C, Dilek N, Hervouet J, Minault D, Blancho G, Vanhove B. Preclinical efficacy and immunological safety of FR104, an antagonist anti-CD28 monovalent Fab' antibody. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(10):2630-40. doi: 10.1111/j.1600-6143.2012.04164.x. PubMed PMID: 22759318.
77. Poirier N, Dilek N, Mary C, Ville S, Coulon F, Branchereau J, Tillou X, Charpy V, Pengam S, Nerriere-Daguin V, Hervouet J, Minault D, Le Bas-Bernardet S, Renaudin K, Vanhove B, Blancho G. FR104, an antagonist anti-CD28 monovalent fab' antibody, prevents alloimmunization and allows calcineurin inhibitor minimization in nonhuman primate renal allograft. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(1):88-100. doi: 10.1111/ajt.12964. PubMed PMID: 25488654.
78. Vierboom MP, Breedveld E, Kap YS, Mary C, Poirier N, t Hart BA, Vanhove B. Clinical efficacy of a new CD28-targeting antagonist of T cell co-stimulation in a non-human primate model of collagen-induced arthritis. Clinical and experimental immunology. 2016;183(3):405-18. doi: 10.1111/cei.12739. PubMed PMID: 26540618; PMCID: PMC4750591.
79. Haanstra KG, Dijkman K, Bashir N, Bauer J, Mary C, Poirier N, Baker P, Crossan CL, Scobie L, t Hart BA, Vanhove B. Selective blockade of CD28-mediated T cell costimulation protects rhesus monkeys against acute fatal experimental autoimmune encephalomyelitis. Journal of immunology. 2015;194(4):1454-66. doi: 10.4049/jimmunol.1402563. PubMed PMID: 25589073.
80. Ville S, Poirier N, Branchereau J, Charpy V, Pengam S, Nerriere-Daguin V, Le Bas-Bernardet S, Coulon F, Mary C, Chenouard A, Hervouet J, Minault D, Nedellec S, Renaudin K, Vanhove B, Blancho G. Anti-CD28 Antibody and Belatacept Exert

Differential Effects on Mechanisms of Renal Allograft Rejection. J Am Soc Nephrol. 2016. doi: 10.1681/ASN.2015070774. PubMed PMID: 27160407.
81. Hippen KL, Watkins B, Tkachev V, Lemire AM, Lehnen C, Riddle MJ, Singh K, Panoskaltsis-Mortari A, Vanhove B, Tolar J, Kean LS, Blazar BR. Preclinical testing of anti-human CD28 Fab' antibody in a novel nonhuman primate (NHP) small animal rodent model of xenogenic graft-versus-host disease (GVHD). Transplantation. 2016. doi: 10.1097/TP.0000000000001465. PubMed PMID: 27607527.
82. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. Immunological reviews. 2009;229(1):152-72. doi: 10.1111/j.1600-065X.2009.00782.x. PubMed PMID: 19426221; PMCID: PMC3826168.
83. Pullen SS, Labadia ME, Ingraham RH, McWhirter SM, Everdeen DS, Alber T, Crute JJ, Kehry MR. High-affinity interactions of tumor necrosis factor receptor-associated factors (TRAFs) and CD40 require TRAF trimerization and CD40 multimerization. Biochemistry. 1999;38(31):10168-77. doi: 10.1021/bi9909905. PubMed PMID: 10433725.
84. Foy TM, Shepherd DM, Durie FH, Aruffo A, Ledbetter JA, Noelle RJ. In vivo CD40-gp39 interactions are essential for thymus-dependent humoral immunity. II. Prolonged suppression of the humoral immune response by an antibody to the ligand for CD40, gp39. The Journal of experimental medicine. 1993;178(5):1567-75. PubMed PMID: 7693850; PMCID: PMC2191245.
85. Van den Eertwegh AJ, Noelle RJ, Roy M, Shepherd DM, Aruffo A, Ledbetter JA, Boersma WJ, Claassen E. In vivo CD40-gp39 interactions are essential for thymus-dependent humoral immunity. I. In vivo expression of CD40 ligand, cytokines, and antibody production delineates sites of cognate T-B cell interactions. The Journal of experimental medicine. 1993;178(5):1555-65. PubMed PMID: 7693849; PMCID: PMC2191254.
86. Hancock WW, Sayegh MH, Zheng XG, Peach R, Linsley PS, Turka LA. Costimulatory function and expression of CD40 ligand, CD80, and CD86 in vascularized murine cardiac allograft rejection. Proceedings of the National Academy of Sciences of the United States of America. 1996;93(24):13967-72. PubMed PMID: 8943044; PMCID: PMC19478.
87. Larsen CP, Alexander DZ, Hollenbaugh D, Elwood ET, Ritchie SC, Aruffo A, Hendrix R, Pearson TC. CD40-gp39 interactions play a critical role during allograft rejection. Suppression of allograft rejection by blockade of the CD40-gp39 pathway. Transplantation. 1996;61(1):4-9. PubMed PMID: 8560571.
88. Fehr T, Takeuchi Y, Kurtz J, Wekerle T, Sykes M. Early regulation of CD8 T cell alloreactivity by CD4+CD25- T cells in recipients of anti-CD154 antibody and allogeneic BMT is followed by rapid peripheral deletion of donor-reactive CD8+ T cells, precluding a role for sustained regulation. European journal of immunology. 2005;35(9):2679-90. doi: 10.1002/eji.200526190. PubMed PMID: 16082727.
89. Kawai T, Sogawa H, Boskovic S, Abrahamian G, Smith RN, Wee SL, Andrews D, Nadazdin O, Koyama I, Sykes M, Winn HJ, Colvin RB, Sachs DH, Cosimi AB. CD154 blockade for induction of mixed chimerism and prolonged renal allograft survival in nonhuman primates. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2004;4(9):1391-8. doi: 10.1111/j.1600-6143.2004.00523.x. PubMed PMID: 15307826.
90. Kurtz J, Shaffer J, Lie A, Anosova N, Benichou G, Sykes M. Mechanisms of early peripheral CD4 T-cell tolerance induction by anti-CD154 monoclonal antibody and allogeneic bone marrow transplantation: evidence for anergy and deletion but not

regulatory cells. Blood. 2004;103(11):4336-43. doi: 10.1182/blood-2003-08-2642. PubMed PMID: 14962909.
91. Niimi M, Pearson TC, Larsen CP, Alexander DZ, Hollenbaugh D, Aruffo A, Linsley PS, Thomas E, Campbell K, Fanslow WC, Geha RS, Morris PJ, Wood KJ. The role of the CD40 pathway in alloantigen-induced hyporesponsiveness in vivo. Journal of immunology. 1998;161(10):5331-7. PubMed PMID: 9820506.
92. Taylor PA, Lees CJ, Waldmann H, Noelle RJ, Blazar BR. Requirements for the promotion of allogeneic engraftment by anti-CD154 (anti-CD40L) monoclonal antibody under nonmyeloablative conditions. Blood. 2001;98(2):467-74. PubMed PMID: 11435318.
93. Blazar BR, Taylor PA, Noelle RJ, Vallera DA. CD4(+) T cells tolerized ex vivo to host alloantigen by anti-CD40 ligand (CD40L:CD154) antibody lose their graft-versus-host disease lethality capacity but retain nominal antigen responses. The Journal of clinical investigation. 1998;102(3):473-82. doi: 10.1172/JCI3741. PubMed PMID: 9691083; PMCID: PMC508907.
94. Blazar BR, Taylor PA, Panoskaltsis-Mortari A, Buhlman J, Xu J, Flavell RA, Korngold R, Noelle R, Vallera DA. Blockade of CD40 ligand-CD40 interaction impairs CD4+ T cell-mediated alloreactivity by inhibiting mature donor T cell expansion and function after bone marrow transplantation. Journal of immunology. 1997;158(1):29-39. PubMed PMID: 8977172.
95. Smook ML, Heeringa P, Damoiseaux JG, Daemen MJ, de Winther MP, Gijbels MJ, Beckers L, Lutgens E, Tervaert JW. Leukocyte CD40L deficiency affects the CD25(+) CD4 T cell population but does not affect atherosclerosis. Atherosclerosis. 2005;183(2):275-82. doi: 10.1016/j.atherosclerosis.2005.03.051. PubMed PMID: 16002076.
96. Bour-Jordan H, Salomon BL, Thompson HL, Szot GL, Bernhard MR, Bluestone JA. Costimulation controls diabetes by altering the balance of pathogenic and regulatory T cells. The Journal of clinical investigation. 2004;114(7):979-87. doi: 10.1172/JCI20483. PubMed PMID: 15467837; PMCID: PMC518661.
97. Ochando JC, Yopp AC, Yang Y, Garin A, Li Y, Boros P, Llodra J, Ding Y, Lira SA, Krieger NR, Bromberg JS. Lymph node occupancy is required for the peripheral development of alloantigen-specific Foxp3+ regulatory T cells. Journal of immunology. 2005;174(11):6993-7005. PubMed PMID: 15905542.
98. Zhai Y, Meng L, Gao F, Wang Y, Busuttil RW, Kupiec-Weglinski JW. CD4+ T regulatory cell induction and function in transplant recipients after CD154 blockade is TLR4 independent. Journal of immunology. 2006;176(10):5988-94. PubMed PMID: 16670307.
99. Ferrer IR, Wagener ME, Song M, Kirk AD, Larsen CP, Ford ML. Antigen-specific induced Foxp3+ regulatory T cells are generated following CD40/CD154 blockade. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(51):20701-6. doi: 10.1073/pnas.1105500108. PubMed PMID: 22143783; PMCID: PMC3251074.
100. Pinelli DF, Wagener ME, Liu D, Yamniuk A, Tamura J, Grant S, Larsen CP, Suri A, Nadler SG, Ford ML. An anti-CD154 domain antibody prolongs graft survival and induces Foxp3(+) iTreg in the absence and presence of CTLA-4 Ig. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(11):3021-30. doi: 10.1111/ajt.12417. PubMed PMID: 24007441; PMCID: PMC4287239.
101. Zhang N, Schroppel B, Lal G, Jakubzick C, Mao X, Chen D, Yin N, Jessberger R, Ochando JC, Ding Y, Bromberg JS. Regulatory T cells sequentially migrate from inflamed tissues to draining lymph nodes to suppress the alloimmune response.

Immunity. 2009;30(3):458-69. doi: 10.1016/j.immuni.2008.12.022. PubMed PMID: 19303390; PMCID: PMC2737741.
102. Larsen CP, Page A, Linzie KH, Russell M, Deane T, Stempora L, Strobert E, Penedo MC, Ward T, Wiseman R, O'Connor D, Miller W, Sen S, Singh K, Kean LS. An MHC-defined primate model reveals significant rejection of bone marrow after mixed chimerism induction despite full MHC matching. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(11):2396-409. doi: 10.1111/j.1600-6143.2010.03272.x. PubMed PMID: 20849552; PMCID: PMC2980834.
103. Kim EJ, Kwun J, Gibby AC, Hong JJ, Farris AB, 3rd, Iwakoshi NN, Villinger F, Kirk AD, Knechtle SJ. Costimulation blockade alters germinal center responses and prevents antibody-mediated rejection. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2014;14(1):59-69. doi: 10.1111/ajt.12526. PubMed PMID: 24354871; PMCID: PMC3985346.
104. Kirk AD, Burkly LC, Batty DS, Baumgartner RE, Berning JD, Buchanan K, Fechner JH, Jr., Germond RL, Kampen RL, Patterson NB, Swanson SJ, Tadaki DK, TenHoor CN, White L, Knechtle SJ, Harlan DM. Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. Nature medicine. 1999;5(6):686-93. doi: 10.1038/9536. PubMed PMID: 10371508.
105. Kirk AD, Harlan DM, Armstrong NN, Davis TA, Dong Y, Gray GS, Hong X, Thomas D, Fechner JH, Jr., Knechtle SJ. CTLA4-Ig and anti-CD40 ligand prevent renal allograft rejection in primates. Proceedings of the National Academy of Sciences of the United States of America. 1997;94(16):8789-94. PubMed PMID: 9238056; PMCID: PMC23132.
106. May AE, Kalsch T, Massberg S, Herouy Y, Schmidt R, Gawaz M. Engagement of glycoprotein IIb/IIIa (alpha(IIb)beta3) on platelets upregulates CD40L and triggers CD40L-dependent matrix degradation by endothelial cells. Circulation. 2002;106(16):2111-7. PubMed PMID: 12379582.
107. Henn V, Slupsky JR, Grafe M, Anagnostopoulos I, Forster R, Muller-Berghaus G, Kroczek RA. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature. 1998;391(6667):591-4. doi: 10.1038/35393. PubMed PMID: 9468137.
108. Charafeddine AH, Kim EJ, Maynard DM, Yi H, Weaver TA, Gunay-Aygun M, Russell M, Gahl WA, Kirk AD. Platelet-derived CD154: ultrastructural localization and clinical correlation in organ transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(11):3143-51. doi: 10.1111/j.1600-6143.2012.04241.x. PubMed PMID: 22947105; PMCID: PMC3484197.
109. Kawai T, Andrews D, Colvin RB, Sachs DH, Cosimi AB. Thromboembolic complications after treatment with monoclonal antibody against CD40 ligand. Nature medicine. 2000;6(2):114. doi: 10.1038/72162. PubMed PMID: 10655072.
110. Badell IR, Thompson PW, Turner AP, Russell MC, Avila JG, Cano JA, Robertson JM, Leopardi FV, Strobert EA, Iwakoshi NN, Reimann KA, Ford ML, Kirk AD, Larsen CP. Nondepleting anti-CD40-based therapy prolongs allograft survival in nonhuman primates. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(1):126-35. doi: 10.1111/j.1600-6143.2011.03736.x. PubMed PMID: 21920020; PMCID: PMC3259281.
111. Gilson CR, Milas Z, Gangappa S, Hollenbaugh D, Pearson TC, Ford ML, Larsen CP. Anti-CD40 monoclonal antibody synergizes with CTLA4-Ig in promoting long-term

graft survival in murine models of transplantation. Journal of immunology. 2009;183(3):1625-35. doi: 10.4049/jimmunol.0900339. PubMed PMID: 19592649; PMCID: PMC2828346.
112. Lowe M, Badell IR, Thompson P, Martin B, Leopardi F, Strobert E, Price AA, Abdulkerim HS, Wang R, Iwakoshi NN, Adams AB, Kirk AD, Larsen CP, Reimann KA. A novel monoclonal antibody to CD40 prolongs islet allograft survival. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(8):2079-87. doi: 10.1111/j.1600-6143.2012.04054.x. PubMed PMID: 22845909; PMCID: PMC3410651.
113. Rothstein DM, Livak MF, Kishimoto K, Ariyan C, Qian HY, Fecteau S, Sho M, Deng S, Zheng XX, Sayegh MH, Basadonna GP. Targeting signal 1 through CD45RB synergizes with CD40 ligand blockade and promotes long term engraftment and tolerance in stringent transplant models. Journal of immunology. 2001;166(1):322-9. PubMed PMID: 11123308.
114. Thompson P, Cardona K, Russell M, Badell IR, Shaffer V, Korbutt G, Rayat GR, Cano J, Song M, Jiang W, Strobert E, Rajotte R, Pearson T, Kirk AD, Larsen CP. CD40-specific costimulation blockade enhances neonatal porcine islet survival in nonhuman primates. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2011;11(5):947-57. doi: 10.1111/j.1600-6143.2011.03509.x. PubMed PMID: 21521467; PMCID: PMC4845096.
115. Page A, Srinivasan S, Singh K, Russell M, Hamby K, Deane T, Sen S, Stempora L, Leopardi F, Price AA, Strobert E, Reimann KA, Kirk AD, Larsen CP, Kean LS. CD40 blockade combines with CTLA4Ig and sirolimus to produce mixed chimerism in an MHC-defined rhesus macaque transplant model. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(1):115-25. doi: 10.1111/j.1600-6143.2011.03737.x. PubMed PMID: 21929643; PMCID: PMC3259212.
116. Adams AB, Shirasugi N, Jones TR, Durham MM, Strobert EA, Cowan S, Rees P, Hendrix R, Price K, Kenyon NS, Hagerty D, Townsend R, Hollenbaugh D, Pearson TC, Larsen CP. Development of a chimeric anti-CD40 monoclonal antibody that synergizes with LEA29Y to prolong islet allograft survival. Journal of immunology. 2005;174(1):542-50. PubMed PMID: 15611281.
117. Haanstra KG, Ringers J, Sick EA, Ramdien-Murli S, Kuhn EM, Boon L, Jonker M. Prevention of kidney allograft rejection using anti-CD40 and anti-CD86 in primates. Transplantation. 2003;75(5):637-43. doi: 10.1097/01.TP.0000054835.58014.C2. PubMed PMID: 12640302.
118. Pearson TC, Trambley J, Odom K, Anderson DC, Cowan S, Bray R, Lin A, Hollenbaugh D, Aruffo A, Siadak AW, Strobert E, Hennigar R, Larsen CP. Anti-CD40 therapy extends renal allograft survival in rhesus macaques. Transplantation. 2002;74(7):933-40. doi: 10.1097/01.TP.0000020751.87264.61. PubMed PMID: 12394833.
119. Aoyagi T, Yamashita K, Suzuki T, Uno M, Goto R, Taniguchi M, Shimamura T, Takahashi N, Miura T, Okimura K, Itoh T, Shimizu A, Furukawa H, Todo S. A human anti-CD40 monoclonal antibody, 4D11, for kidney transplantation in cynomolgus monkeys: induction and maintenance therapy. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(8):1732-41. doi: 10.1111/j.1600-6143.2009.02693.x. PubMed PMID: 19519810.
120. Imai A, Suzuki T, Sugitani A, Itoh T, Ueki S, Aoyagi T, Yamashita K, Taniguchi M, Takahashi N, Miura T, Shimamura T, Furukawa H, Todo S. A novel fully human anti-

CD40 monoclonal antibody, 4D11, for kidney transplantation in cynomolgus monkeys. Transplantation. 2007;84(8):1020-8. doi: 10.1097/01.tp.0000286058.79448.c7. PubMed PMID: 17989608.
121. Xie JH, Yamniuk AP, Borowski V, Kuhn R, Susulic V, Rex-Rabe S, Yang X, Zhou X, Zhang Y, Gillooly K, Brosius R, Ravishankar R, Waggie K, Mink K, Price L, Rehfuss R, Tamura J, An Y, Cheng L, Abramczyk B, Ignatovich O, Drew P, Grant S, Bryson JW, Suchard S, Salter-Cid L, Nadler S, Suri A. Engineering of a novel anti-CD40L domain antibody for treatment of autoimmune diseases. Journal of immunology. 2014;192(9):4083-92. doi: 10.4049/jimmunol.1303239. PubMed PMID: 24670803.
122. Hutloff A, Dittrich AM, Beier KC, Eljaschewitsch B, Kraft R, Anagnostopoulos I, Kroczek RA. ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. Nature. 1999;397(6716):263-6. doi: 10.1038/16717. PubMed PMID: 9930702.
123. Simpson TR, Quezada SA, Allison JP. Regulation of CD4 T cell activation and effector function by inducible costimulator (ICOS). Current opinion in immunology. 2010;22(3):326-32. doi: 10.1016/j.coi.2010.01.001. PubMed PMID: 20116985.
124. Dong C, Juedes AE, Temann UA, Shresta S, Allison JP, Ruddle NH, Flavell RA. ICOS co-stimulatory receptor is essential for T-cell activation and function. Nature. 2001;409(6816):97-101. doi: 10.1038/35051100. PubMed PMID: 11343121.
125. Gonzalo JA, Tian J, Delaney T, Corcoran J, Rottman JB, Lora J, Al-garawi A, Kroczek R, Gutierrez-Ramos JC, Coyle AJ. ICOS is critical for T helper cell-mediated lung mucosal inflammatory responses. Nature immunology. 2001;2(7):597-604. doi: 10.1038/89739. PubMed PMID: 11429543.
126. Rottman JB, Smith T, Tonra JR, Ganley K, Bloom T, Silva R, Pierce B, Gutierrez-Ramos JC, Ozkaynak E, Coyle AJ. The costimulatory molecule ICOS plays an important role in the immunopathogenesis of EAE. Nature immunology. 2001;2(7):605-11. doi: 10.1038/89750. PubMed PMID: 11429544.
127. Bauquet AT, Jin H, Paterson AM, Mitsdoerffer M, Ho IC, Sharpe AH, Kuchroo VK. The costimulatory molecule ICOS regulates the expression of c-Maf and IL-21 in the development of follicular T helper cells and TH-17 cells. Nature immunology. 2009;10(2):167-75. doi: 10.1038/ni.1690. PubMed PMID: 19098919; PMCID: PMC2742982.
128. Xu H, Li X, Liu D, Li J, Zhang X, Chen X, Hou S, Peng L, Xu C, Liu W, Zhang L, Qi H. Follicular T-helper cell recruitment governed by bystander B cells and ICOS-driven motility. Nature. 2013;496(7446):523-7. doi: 10.1038/nature12058. PubMed PMID: 23619696.
129. McAdam AJ, Greenwald RJ, Levin MA, Chernova T, Malenkovich N, Ling V, Freeman GJ, Sharpe AH. ICOS is critical for CD40-mediated antibody class switching. Nature. 2001;409(6816):102-5. doi: 10.1038/35051107. PubMed PMID: 11343122.
130. Schenk AD, Gorbacheva V, Rabant M, Fairchild RL, Valujskikh A. Effector functions of donor-reactive CD8 memory T cells are dependent on ICOS induced during division in cardiac grafts. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(1):64-73. doi: 10.1111/j.1600-6143.2008.02460.x. PubMed PMID: 18976292; PMCID: PMC3289995.
131. Ozkaynak E, Gao W, Shemmeri N, Wang C, Gutierrez-Ramos JC, Amaral J, Qin S, Rottman JB, Coyle AJ, Hancock WW. Importance of ICOS-B7RP-1 costimulation in acute and chronic allograft rejection. Nature immunology. 2001;2(7):591-6. doi: 10.1038/89731. PubMed PMID: 11429542.
132. Nanji SA, Hancock WW, Luo B, Schur CD, Pawlick RL, Zhu LF, Anderson CC, Shapiro AM. Costimulation blockade of both inducible costimulator and CD40 ligand

induces dominant tolerance to islet allografts and prevents spontaneous autoimmune diabetes in the NOD mouse. Diabetes. 2006;55(1):27-33. PubMed PMID: 16380473.
133. Nanji SA, Hancock WW, Anderson CC, Adams AB, Luo B, Schur CD, Pawlick RL, Wang L, Coyle AJ, Larsen CP, Shapiro AM. Multiple combination therapies involving blockade of ICOS/B7RP-1 costimulation facilitate long-term islet allograft survival. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2004;4(4):526-36. doi: 10.1111/j.1600-6143.2004.00384.x. PubMed PMID: 15023144.
134. Taylor PA, Panoskaltsis-Mortari A, Freeman GJ, Sharpe AH, Noelle RJ, Rudensky AY, Mak TW, Serody JS, Blazar BR. Targeting of inducible costimulator (ICOS) expressed on alloreactive T cells down-regulates graft-versus-host disease (GVHD) and facilitates engraftment of allogeneic bone marrow (BM). Blood. 2005;105(8):3372-80. doi: 10.1182/blood-2004-10-3869. PubMed PMID: 15618467.
135. Sato M, Storb R, Loretz C, Stone D, Mielcarek M, Sale GE, Rezvani AR, Graves SS. Inducible costimulator (ICOS) up-regulation on activated T cells in chronic graft-versus-host disease after dog leukocyte antigen-nonidentical hematopoietic cell transplantation: a potential therapeutic target. Transplantation. 2013;96(1):34-41. doi: 10.1097/TP.0b013e318295c025. PubMed PMID: 23694952; PMCID: PMC3696413.
136. Ogawa S, Nagamatsu G, Watanabe M, Watanabe S, Hayashi T, Horita S, Nitta K, Nihei H, Tezuka K, Abe R. Opposing effects of anti-activation-inducible lymphocyte-immunomodulatory molecule/inducible costimulator antibody on the development of acute versus chronic graft-versus-host disease. Journal of immunology. 2001;167(10):5741-8. PubMed PMID: 11698447.
137. Flynn R, Du J, Veenstra RG, Reichenbach DK, Panoskaltsis-Mortari A, Taylor PA, Freeman GJ, Serody JS, Murphy WJ, Munn DH, Sarantopoulos S, Luznik L, Maillard I, Koreth J, Cutler C, Soiffer RJ, Antin JH, Ritz J, Dubovsky JA, Byrd JC, MacDonald KP, Hill GR, Blazar BR. Increased T follicular helper cells and germinal center B cells are required for cGVHD and bronchiolitis obliterans. Blood. 2014;123(25):3988-98. doi: 10.1182/blood-2014-03-562231. PubMed PMID: 24820310; PMCID: PMC4064335.
138. Lo DJ, Anderson DJ, Song M, Leopardi F, Farris AB, Strobert E, Chapin S, Devens B, Karrer E, Kirk AD. A pilot trial targeting the ICOS-ICOS-L pathway in nonhuman primate kidney transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(4):984-92. doi: 10.1111/ajt.13100. PubMed PMID: 25703015; PMCID: PMC4628789.
139. Chen AI, McAdam AJ, Buhlmann JE, Scott S, Lupher ML, Jr., Greenfield EA, Baum PR, Fanslow WC, Calderhead DM, Freeman GJ, Sharpe AH. Ox40-ligand has a critical costimulatory role in dendritic cell:T cell interactions. Immunity. 1999;11(6):689-98. PubMed PMID: 10626891.
140. Kopf M, Ruedl C, Schmitz N, Gallimore A, Lefrang K, Ecabert B, Odermatt B, Bachmann MF. OX40-deficient mice are defective in Th cell proliferation but are competent in generating B cell and CTL Responses after virus infection. Immunity. 1999;11(6):699-708. PubMed PMID: 10626892.
141. Kinnear G, Wood KJ, Marshall D, Jones ND. Anti-OX40 prevents effector T-cell accumulation and CD8+ T-cell mediated skin allograft rejection. Transplantation. 2010;90(12):1265-71. doi: 10.1097/TP.0b013e3181fe5396. PubMed PMID: 21037534.
142. Kinnear G, Wood KJ, Fallah-Arani F, Jones ND. A diametric role for OX40 in the response of effector/memory CD4+ T cells and regulatory T cells to alloantigen. Journal of immunology. 2013;191(3):1465-75. doi: 10.4049/jimmunol.1300553. PubMed PMID: 23817421; PMCID: PMC3721124.

143. Tsukada N, Akiba H, Kobata T, Aizawa Y, Yagita H, Okumura K. Blockade of CD134 (OX40)-CD134L interaction ameliorates lethal acute graft-versus-host disease in a murine model of allogeneic bone marrow transplantation. Blood. 2000;95(7):2434-9. PubMed PMID: 10733518.
144. Blazar BR, Sharpe AH, Chen AI, Panoskaltsis-Mortari A, Lees C, Akiba H, Yagita H, Killeen N, Taylor PA. Ligation of OX40 (CD134) regulates graft-versus-host disease (GVHD) and graft rejection in allogeneic bone marrow transplant recipients. Blood. 2003;101(9):3741-8. doi: 10.1182/blood-2002-10-3048. PubMed PMID: 12521997.
145. Sanchez J, Casano J, Alvarez MA, Roman-Gomez J, Martin C, Martinez F, Gomez P, Serrano J, Herrera C, Torres A. Kinetic of regulatory CD25high and activated CD134+ (OX40) T lymphocytes during acute and chronic graft-versus-host disease after allogeneic bone marrow transplantation. British journal of haematology. 2004;126(5):697-703. doi: 10.1111/j.1365-2141.2004.05108.x. PubMed PMID: 15327522.
146. Miura Y, Thoburn CJ, Bright EC, Arai S, Hess AD. Regulation of OX40 gene expression in graft-versus-host disease. Transplant Proc. 2005;37(1):57-61. doi: 10.1016/j.transproceed.2005.01.014. PubMed PMID: 15808546.
147. Moncrieffe H, Coles M, Stockinger B. The influence of CD4 T-cell subsets on control of CD4 T-cell-mediated graft-versus-host disease. Immunology. 2008;125(4):459-68. doi: 10.1111/j.1365-2567.2008.02866.x. PubMed PMID: 18498346; PMCID: PMC2612549.
148. Ge X, Brown J, Sykes M, Boussiotis VA. CD134-allodepletion allows selective elimination of alloreactive human T cells without loss of virus-specific and leukemia-specific effectors. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(5):518-30. doi: 10.1016/j.bbmt.2008.02.010. PubMed PMID: 18410894; PMCID: PMC2423190.
149. Demirci G, Amanullah F, Kewalaramani R, Yagita H, Strom TB, Sayegh MH, Li XC. Critical role of OX40 in CD28 and CD154-independent rejection. Journal of immunology. 2004;172(3):1691-8. PubMed PMID: 14734751.
150. Vu MD, Xiao X, Gao W, Degauque N, Chen M, Kroemer A, Killeen N, Ishii N, Li XC. OX40 costimulation turns off Foxp3+ Tregs. Blood. 2007;110(7):2501-10. doi: 10.1182/blood-2007-01-070748. PubMed PMID: 17575071; PMCID: PMC1988917.
151. Jensen MC, Riddell SR. Designing chimeric antigen receptors to effectively and safely target tumors. Current opinion in immunology. 2015;33:9-15. doi: 10.1016/j.coi.2015.01.002. PubMed PMID: 25621840; PMCID: PMC4397136.
152. Ruella M, June CH. Chimeric Antigen Receptor T cells for B Cell Neoplasms: Choose the Right CAR for You. Curr Hematol Malig Rep. 2016;11(5):368-84. doi: 10.1007/s11899-016-0336-z. PubMed PMID: 27475429.
153. Schoenbrunn A, Frentsch M, Kohler S, Keye J, Dooms H, Moewes B, Dong J, Loddenkemper C, Sieper J, Wu P, Romagnani C, Matzmohr N, Thiel A. A converse 4-1BB and CD40 ligand expression pattern delineates activated regulatory T cells (Treg) and conventional T cells enabling direct isolation of alloantigen-reactive natural Foxp3+ Treg. Journal of immunology. 2012;189(12):5985-94. doi: 10.4049/jimmunol.1201090. PubMed PMID: 23162126.
154. Pollok KE, Kim YJ, Hurtado J, Zhou Z, Kim KK, Kwon BS. 4-1BB T-cell antigen binds to mature B cells and macrophages, and costimulates anti-mu-primed splenic B cells. European journal of immunology. 1994;24(2):367-74. doi: 10.1002/eji.1830240215. PubMed PMID: 8299685.
155. Pollok KE, Kim YJ, Zhou Z, Hurtado J, Kim KK, Pickard RT, Kwon BS. Inducible T cell antigen 4-1BB. Analysis of expression and function. Journal of immunology. 1993;150(3):771-81. PubMed PMID: 7678621.

156. Dawicki W, Watts TH. Expression and function of 4-1BB during CD4 versus CD8 T cell responses in vivo. European journal of immunology. 2004;34(3):743-51. doi: 10.1002/eji.200324278. PubMed PMID: 14991604.
157. Lee SW, Vella AT, Kwon BS, Croft M. Enhanced CD4 T cell responsiveness in the absence of 4-1BB. Journal of immunology. 2005;174(11):6803-8. PubMed PMID: 15905521.
158. Shuford WW, Klussman K, Tritchler DD, Loo DT, Chalupny J, Siadak AW, Brown TJ, Emswiler J, Raecho H, Larsen CP, Pearson TC, Ledbetter JA, Aruffo A, Mittler RS. 4-1BB costimulatory signals preferentially induce CD8+ T cell proliferation and lead to the amplification in vivo of cytotoxic T cell responses. The Journal of experimental medicine. 1997;186(1):47-55. PubMed PMID: 9206996; PMCID: PMC2198949.
159. Blazar BR, Kwon BS, Panoskaltsis-Mortari A, Kwak KB, Peschon JJ, Taylor PA. Ligation of 4-1BB (CDw137) regulates graft-versus-host disease, graft-versus-leukemia, and graft rejection in allogeneic bone marrow transplant recipients. Journal of immunology. 2001;166(5):3174-83. PubMed PMID: 11207270.
160. Blazar BR, Lees CJ, Martin PJ, Noelle RJ, Kwon B, Murphy W, Taylor PA. Host T cells resist graft-versus-host disease mediated by donor leukocyte infusions. Journal of immunology. 2000;165(9):4901-9. PubMed PMID: 11046015.
161. Martins SL, St John LS, Champlin RE, Wieder ED, McMannis J, Molldrem JJ, Komanduri KV. Functional assessment and specific depletion of alloreactive human T cells using flow cytometry. Blood. 2004;104(12):3429-36. doi: 10.1182/blood-2004-05-1918. PubMed PMID: 15284108.
162. Kim J, Choi WS, La S, Suh JH, Kim BS, Cho HR, Kwon BS, Kwon B. Stimulation with 4-1BB (CD137) inhibits chronic graft-versus-host disease by inducing activation-induced cell death of donor CD4+ T cells. Blood. 2005;105(5):2206-13. doi: 10.1182/blood-2004-06-2080. PubMed PMID: 15522958.
163. DeBenedette MA, Wen T, Bachmann MF, Ohashi PS, Barber BH, Stocking KL, Peschon JJ, Watts TH. Analysis of 4-1BB ligand (4-1BBL)-deficient mice and of mice lacking both 4-1BBL and CD28 reveals a role for 4-1BBL in skin allograft rejection and in the cytotoxic T cell response to influenza virus. Journal of immunology. 1999;163(9):4833-41. PubMed PMID: 10528184.
164. Asai T, Choi BK, Kwon PM, Kim WY, Kim JD, Vinay DS, Gebhardt BM, Kwon BS. Blockade of the 4-1BB (CD137)/4-1BBL and/or CD28/CD80/CD86 costimulatory pathways promotes corneal allograft survival in mice. Immunology. 2007;121(3):349-58. doi: 10.1111/j.1365-2567.2007.02581.x. PubMed PMID: 17376197; PMCID: PMC2265952.
165. Wang J, Guo Z, Dong Y, Kim O, Hart J, Adams A, Larsen CP, Mittler RS, Newell KA. Role of 4-1BB in allograft rejection mediated by CD8+ T cells. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2003;3(5):543-51. PubMed PMID: 12752310.
166. Saiki H, Suzuki J, Kosuge H, Haraguchi G, Ishihara T, Haga T, Maejima Y, Isobe M, Uede T. Blockade of the 4-1BB pathway attenuates graft arterial disease in cardiac allografts. Int Heart J. 2008;49(1):105-18. PubMed PMID: 18360069.
167. Cho HR, Kwon B, Yagita H, La S, Lee EA, Kim JE, Akiba H, Kim J, Suh JH, Vinay DS, Ju SA, Kim BS, Mittler RS, Okumura K, Kwon BS. Blockade of 4-1BB (CD137)/4-1BB ligand interactions increases allograft survival. Transplant international : official journal of the European Society for Organ Transplantation. 2004;17(7):351-61. doi: 10.1007/s00147-004-0726-3. PubMed PMID: 15349720.
168. Chalkley JJ, Berger JR. Progressive multifocal leukoencephalopathy in multiple sclerosis. Curr Neurol Neurosci Rep. 2013;13(12):408. doi: 10.1007/s11910-013-0408-6. PubMed PMID: 24136456.

169. Bamias G, Clark DJ, Rivera-Nieves J. Leukocyte traffic blockade as a therapeutic strategy in inflammatory bowel disease. Curr Drug Targets. 2013;14(12):1490-500. PubMed PMID: 23621509; PMCID: PMC3779486.
170. Joshi A, Bauer R, Kuebler P, White M, Leddy C, Compton P, Garovoy M, Kwon P, Walicke P, Dedrick R. An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis. J Clin Pharmacol. 2006;46(1):10-20. doi: 10.1177/0091270005283282. PubMed PMID: 16397279.
171. Calabrese LH, Molloy E, Berger J. Sorting out the risks in progressive multifocal leukoencephalopathy. Nat Rev Rheumatol. 2015;11(2):119-23. doi: 10.1038/nrrheum.2014.167. PubMed PMID: 25314016.
172. Kothary N, Diak IL, Brinker A, Bezabeh S, Avigan M, Dal Pan G. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. J Am Acad Dermatol. 2011;65(3):546-51. doi: 10.1016/j.jaad.2010.05.033. PubMed PMID: 21514689.
173. Carson KR, Focosi D, Major EO, Petrini M, Richey EA, West DP, Bennett CL. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. The lancet oncology. 2009;10(8):816-24. doi: 10.1016/S1470-2045(09)70161-5. PubMed PMID: 19647202.
174. Stoppa AM, Maraninchi D, Blaise D, Viens P, Hirn M, Olive D, Reiffers J, Milpied N, Gaspard MH, Mawas C. Anti-LFA1 monoclonal antibody (25.3) for treatment of steroid-resistant grade III-IV acute graft-versus-host disease. Transplant international : official journal of the European Society for Organ Transplantation. 1991;4(1):3-7. PubMed PMID: 2059297.
175. Le Mauff B, Hourmant M, Rougier JP, Hirn M, Dantal J, Baatard R, Cantarovich D, Jacques Y, Soulillou JP. Effect of anti-LFA1 (CD11a) monoclonal antibodies in acute rejection in human kidney transplantation. Transplantation. 1991;52(2):291-6. PubMed PMID: 1871802.
176. Blazar BR, Carroll SF, Vallera DA. Prevention of murine graft-versus-host disease and bone marrow alloengraftment across the major histocompatibility barrier after donor graft preincubation with anti-LFA1 immunotoxin. Blood. 1991;78(11):3093-102. PubMed PMID: 1954395.
177. Blazar BR, Taylor PA, Panoskaltsis-Mortari A, Gray GS, Vallera DA. Coblockade of the LFA1:ICAM and CD28/CTLA4:B7 pathways is a highly effective means of preventing acute lethal graft-versus-host disease induced by fully major histocompatibility complex-disparate donor grafts. Blood. 1995;85(9):2607-18. PubMed PMID: 7537122.
178. Tchorsh-Yutsis D, Hecht G, Aronovich A, Shezen E, Klionsky Y, Rosen C, Bitcover R, Eventov-Friedman S, Katchman H, Cohen S, Tal O, Milstein O, Yagita H, Blazar BR, Reisner Y. Pig embryonic pancreatic tissue as a source for transplantation in diabetes: transient treatment with anti-LFA1, anti-CD48, and FTY720 enables long-term graft maintenance in mice with only mild ongoing immunosuppression. Diabetes. 2009;58(7):1585-94. doi: 10.2337/db09-0112. PubMed PMID: 19401429; PMCID: PMC2699862.
179. Kwun J, Farris AB, Song H, Mahle WT, Burlingham WJ, Knechtle SJ. Impact of Leukocyte Function-Associated Antigen-1 Blockade on Endogenous Allospecific T Cells to Multiple Minor Histocompatibility Antigen Mismatched Cardiac Allograft. Transplantation. 2015;99(12):2485-93. doi: 10.1097/TP.0000000000000805. PubMed PMID: 26102611.
180. Ramsey H, Pilat N, Hock K, Klaus C, Unger L, Schwarz C, Baranyi U, Gattringer M, Schwaiger E, Wrba F, Wekerle T. Anti-LFA-1 or rapamycin overcome costimulation

blockade-resistant rejection in sensitized bone marrow recipients. Transplant international : official journal of the European Society for Organ Transplantation. 2013;26(2):206-18. doi: 10.1111/tri.12021. PubMed PMID: 23240587.
181. Kitchens WH, Haridas D, Wagener ME, Song M, Ford ML. Combined costimulatory and leukocyte functional antigen-1 blockade prevents transplant rejection mediated by heterologous immune memory alloresponses. Transplantation. 2012;93(10):997-1005. doi: 10.1097/TP.0b013e31824e75d7. PubMed PMID: 22475765; PMCID: PMC3703766.
182. Reisman NM, Floyd TL, Wagener ME, Kirk AD, Larsen CP, Ford ML. LFA-1 blockade induces effector and regulatory T-cell enrichment in lymph nodes and synergizes with CTLA-4Ig to inhibit effector function. Blood. 2011;118(22):5851-61. doi: 10.1182/blood-2011-04-347252. PubMed PMID: 21972294; PMCID: PMC3228500.
183. Setoguchi K, Schenk AD, Ishii D, Hattori Y, Baldwin WM, 3rd, Tanabe K, Fairchild RL. LFA-1 antagonism inhibits early infiltration of endogenous memory CD8 T cells into cardiac allografts and donor-reactive T cell priming. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2011;11(5):923-35. doi: 10.1111/j.1600-6143.2011.03492.x. PubMed PMID: 21466654; PMCID: PMC3215941.
184. Kitchens WH, Larsen CP, Ford ML. Integrin antagonists for transplant immunosuppression: panacea or peril? Immunotherapy. 2011;3(3):305-7. doi: 10.2217/imt.10.113. PubMed PMID: 21395371; PMCID: PMC4642442.
185. Badell IR, Russell MC, Thompson PW, Turner AP, Weaver TA, Robertson JM, Avila JG, Cano JA, Johnson BE, Song M, Leopardi FV, Swygert S, Strobert EA, Ford ML, Kirk AD, Larsen CP. LFA-1-specific therapy prolongs allograft survival in rhesus macaques. The Journal of clinical investigation. 2010;120(12):4520-31. doi: 10.1172/JCI43895. PubMed PMID: 21099108; PMCID: PMC2994340.
186. Posselt AM, Bellin MD, Tavakol M, Szot GL, Frassetto LA, Masharani U, Kerlan RK, Fong L, Vincenti FG, Hering BJ, Bluestone JA, Stock PG. Islet transplantation in type 1 diabetics using an immunosuppressive protocol based on the anti-LFA-1 antibody efalizumab. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(8):1870-80. doi: 10.1111/j.1600-6143.2010.03073.x. PubMed PMID: 20659093; PMCID: PMC2911648.
187. Wang Y, Li D, Jones D, Bassett R, Sale GE, Khalili J, Komanduri KV, Couriel DR, Champlin RE, Molldrem JJ, Ma Q. Blocking LFA-1 activation with lovastatin prevents graft-versus-host disease in mouse bone marrow transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(12):1513-22. doi: 10.1016/j.bbmt.2009.08.013. PubMed PMID: 19896074; PMCID: PMC4809421.
188. Vincenti F, Mendez R, Pescovitz M, Rajagopalan PR, Wilkinson AH, Butt K, Laskow D, Slakey DP, Lorber MI, Garg JP, Garovoy M. A phase I/II randomized open-label multicenter trial of efalizumab, a humanized anti-CD11a, anti-LFA-1 in renal transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2007;7(7):1770-7. doi: 10.1111/j.1600-6143.2007.01845.x. PubMed PMID: 17564637.
189. Beus JM, Hashmi SS, Selvaraj SA, Duan D, Stempora LL, Monday SA, Cheeseman JA, Hamby KM, Speck SH, Larsen CP, Kirk AD, Kean LS. Heterologous immunity triggered by a single, latent virus in Mus musculus: combined costimulation- and adhesion- blockade decrease rejection. PloS one. 2013;8(8):e71221. doi: 10.1371/journal.pone.0071221. PubMed PMID: 23940724; PMCID: PMC3733932.

190. Anderson DJ, Lo DJ, Leopardi F, Song M, Turgeon NA, Strobert EA, Jenkins JB, Wang R, Reimann KA, Larsen CP, Kirk AD. Anti-Leukocyte Function-Associated Antigen 1 Therapy in a Nonhuman Primate Renal Transplant Model of Costimulation Blockade-Resistant Rejection. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016;16(5):1456-64. doi: 10.1111/ajt.13628. PubMed PMID: 26602755.
191. Kitchens WH, Haridas D, Wagener ME, Song M, Kirk AD, Larsen CP, Ford ML. Integrin antagonists prevent costimulatory blockade-resistant transplant rejection by CD8(+) memory T cells. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(1):69-80. doi: 10.1111/j.1600-6143.2011.03762.x. PubMed PMID: 21942986; PMCID: PMC3467016.
192. Turgeon NA, Avila JG, Cano JA, Hutchinson JJ, Badell IR, Page AJ, Adams AB, Sears MH, Bowen PH, Kirk AD, Pearson TC, Larsen CP. Experience with a novel efalizumab-based immunosuppressive regimen to facilitate single donor islet cell transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(9):2082-91. doi: 10.1111/j.1600-6143.2010.03212.x. PubMed PMID: 20883542; PMCID: PMC3335736.
193. Paul LC, Davidoff A, Benediktsson H, Issekutz TB. The efficacy of LFA-1 and VLA-4 antibody treatment in rat vascularized cardiac allograft rejection. Transplantation. 1993;55(5):1196-9. PubMed PMID: 8497903.
194. Stegall MD, Ostrowska A, Haynes J, Karrer F, Kam I, Gill RG. Prolongation of islet allograft survival with an antibody to vascular cell adhesion molecule 1. Surgery. 1995;118(2):366-9; discussion 9-70. PubMed PMID: 7543705.
195. Molossi S, Elices M, Arrhenius T, Diaz R, Coulber C, Rabinovitch M. Blockade of very late antigen-4 integrin binding to fibronectin with connecting segment-1 peptide reduces accelerated coronary arteriopathy in rabbit cardiac allografts. The Journal of clinical investigation. 1995;95(6):2601-10. doi: 10.1172/JCI117962. PubMed PMID: 7539456; PMCID: PMC295943.
196. Yang H, Issekutz TB, Wright JR, Jr. Prolongation of rat islet allograft survival by treatment with monoclonal antibodies against VLA-4 and LFA-1. Transplantation. 1995;60(1):71-6. PubMed PMID: 7624946.
197. Shiohara T, Moriya N, Gotoh C, Saizawa K, Nagashima M. Locally administered monoclonal antibodies to lymphocyte function-associated antigen 1 and to L3T4 prevent cutaneous graft-vs-host disease. Journal of immunology. 1988;141(7):2261-7. PubMed PMID: 3049803.
198. Harning R, Pelletier J, Lubbe K, Takei F, Merluzzi VJ. Reduction in the severity of graft-versus-host disease and increased survival in allogenic mice by treatment with monoclonal antibodies to cell adhesion antigens LFA-1 alpha and MALA-2. Transplantation. 1991;52(5):842-5. PubMed PMID: 1658992.
199. Schlegel PG, Vaysburd M, Chen Y, Butcher EC, Chao NJ. Inhibition of T cell costimulation by VCAM-1 prevents murine graft-versus-host disease across minor histocompatibility barriers. Journal of immunology. 1995;155(8):3856-65. PubMed PMID: 7561092.
200. Khatri BO. Fingolimod in the treatment of relapsing-remitting multiple sclerosis: long-term experience and an update on the clinical evidence. Ther Adv Neurol Disord. 2016;9(2):130-47. doi: 10.1177/1756285616628766. PubMed PMID: 27006700; PMCID: PMC4784254.
201. Ziemssen T, Derfuss T, de Stefano N, Giovannoni G, Palavra F, Tomic D, Vollmer T, Schippling S. Optimizing treatment success in multiple sclerosis. J Neurol.

2016;263(6):1053-65. doi: 10.1007/s00415-015-7986-y. PubMed PMID: 26705122; PMCID: PMC4893374.
202. Ueda H, Takahara S, Azuma H, Kusaka M, Suzuki S, Katsuoka Y. Effect of a novel immunosuppressant, FTY720, on allograft survival after renal transplant in rats. Eur Surg Res. 2000;32(5):279-83. doi: 8776. PubMed PMID: 11111172.
203. Hoitsma AJ, Woodle ES, Abramowicz D, Proot P, Vanrenterghem Y, Group FTYPITS. FTY720 combined with tacrolimus in de novo renal transplantation: 1-year, multicenter, open-label randomized study. Nephrol Dial Transplant. 2011;26(11):3802-5. doi: 10.1093/ndt/gfr503. PubMed PMID: 21911597.
204. Huu DL, Matsushita T, Jin G, Hamaguchi Y, Hasegawa M, Takehara K, Fujimoto M. FTY720 ameliorates murine sclerodermatous chronic graft-versus-host disease by promoting expansion of splenic regulatory cells and inhibiting immune cell infiltration into skin. Arthritis Rheum. 2013;65(6):1624-35. doi: 10.1002/art.37933. PubMed PMID: 23508350.
205. Taylor PA, Kelly RM, Bade ND, Smith MJ, Stefanski HE, Blazar BR. FTY720 markedly increases alloengraftment but does not eliminate host anti-donor T cells that cause graft rejection on its withdrawal. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012;18(9):1341-52. doi: 10.1016/j.bbmt.2012.06.007. PubMed PMID: 22728248; PMCID: PMC3520609.
206. Weckbecker G, Pally C, Beerli C, Burkhart C, Wieczorek G, Metzler B, Morris RE, Wagner J, Bruns C. Effects of the novel protein kinase C inhibitor AEB071 (Sotrastaurin) on rat cardiac allograft survival using single agent treatment or combination therapy with cyclosporine, everolimus or FTY720. Transplant international : official journal of the European Society for Organ Transplantation. 2010;23(5):543-52. doi: 10.1111/j.1432-2277.2009.01015.x. PubMed PMID: 20003043.
207. Lopes CT, Gallo AP, Palma PV, Cury PM, Bueno V. Skin allograft survival and analysis of renal parameters after FTY720 + tacrolimus treatment in mice. Transplant Proc. 2008;40(3):856-60. doi: 10.1016/j.transproceed.2008.02.051. PubMed PMID: 18455036.
208. Taylor PA, Ehrhardt MJ, Lees CJ, Tolar J, Weigel BJ, Panoskaltsis-Mortari A, Serody JS, Brinkmann V, Blazar BR. Insights into the mechanism of FTY720 and compatibility with regulatory T cells for the inhibition of graft-versus-host disease (GVHD). Blood. 2007;110(9):3480-8. doi: 10.1182/blood-2007-05-087940. PubMed PMID: 17606761; PMCID: PMC2200903.
209. Suzuki S, Enosawa S, Kakefuda T, Shinomiya T, Amari M, Naoe S, Hoshino Y, Chiba K. A novel immunosuppressant, FTY720, with a unique mechanism of action, induces long-term graft acceptance in rat and dog allotransplantation. Transplantation. 1996;61(2):200-5. PubMed PMID: 8600623.
210. Yanagawa Y, Sugahara K, Kataoka H, Kawaguchi T, Masubuchi Y, Chiba K. FTY720, a novel immunosuppressant, induces sequestration of circulating mature lymphocytes by acceleration of lymphocyte homing in rats. II. FTY720 prolongs skin allograft survival by decreasing T cell infiltration into grafts but not cytokine production in vivo. Journal of immunology. 1998;160(11):5493-9. PubMed PMID: 9605152.
211. Chiba K, Yanagawa Y, Masubuchi Y, Kataoka H, Kawaguchi T, Ohtsuki M, Hoshino Y. FTY720, a novel immunosuppressant, induces sequestration of circulating mature lymphocytes by acceleration of lymphocyte homing in rats. I. FTY720 selectively decreases the number of circulating mature lymphocytes by acceleration of lymphocyte homing. Journal of immunology. 1998;160(10):5037-44. PubMed PMID: 9590253.
212. Hashimoto D, Asakura S, Matsuoka K, Sakoda Y, Koyama M, Aoyama K, Tanimoto M, Teshima T. FTY720 enhances the activation-induced apoptosis of donor T

cells and modulates graft-versus-host disease. European journal of immunology. 2007;37(1):271-81. doi: 10.1002/eji.200636123. PubMed PMID: 17154260.
213. Lee RS, Kuhr CS, Sale GE, Zellmer E, Hogan WJ, Storb R, Little MT. FTY720 does not abrogate acute graft-versus-host disease in the dog leukocyte antigen-nonidentical unrelated canine model. Transplantation. 2003;76(8):1155-8. doi: 10.1097/01.TP.0000083891.14089.B8. PubMed PMID: 14578745.
214. Kim YM, Sachs T, Asavaroengchai W, Bronson R, Sykes M. Graft-versus-host disease can be separated from graft-versus-lymphoma effects by control of lymphocyte trafficking with FTY720. The Journal of clinical investigation. 2003;111(5):659-69. doi: 10.1172/JCI16950. PubMed PMID: 12618520; PMCID: PMC151899.
215. Blaha P, Bigenzahn S, Koporc Z, Schmid M, Langer F, Selzer E, Bergmeister H, Wrba F, Kurtz J, Kiss C, Roth E, Muehlbacher F, Sykes M, Wekerle T. The influence of immunosuppressive drugs on tolerance induction through bone marrow transplantation with costimulation blockade. Blood. 2003;101(7):2886-93. doi: 10.1182/blood-2002-10-3014. PubMed PMID: 12433677.
216. Xun CQ, Little MT, Zellmer E, Yu C, Zaucha JM, Sale GE, Storer B, Storb R. What role for FTY720, a novel immunosuppressive agent, in canine nonmyeloablative hematopoietic stem cell transplantation? Transplantation. 2002;73(2):310-3. PubMed PMID: 11821753.
217. Murai M, Yoneyama H, Ezaki T, Suematsu M, Terashima Y, Harada A, Hamada H, Asakura H, Ishikawa H, Matsushima K. Peyer's patch is the essential site in initiating murine acute and lethal graft-versus-host reaction. Nature immunology. 2003;4(2):154-60. doi: 10.1038/ni879. PubMed PMID: 12524535.
218. Murai M, Yoneyama H, Harada A, Yi Z, Vestergaard C, Guo B, Suzuki K, Asakura H, Matsushima K. Active participation of CCR5(+)CD8(+) T lymphocytes in the pathogenesis of liver injury in graft-versus-host disease. The Journal of clinical investigation. 1999;104(1):49-57. doi: 10.1172/JCI6642. PubMed PMID: 10393698; PMCID: PMC408408.
219. Wysocki CA, Burkett SB, Panoskaltsis-Mortari A, Kirby SL, Luster AD, McKinnon K, Blazar BR, Serody JS. Differential roles for CCR5 expression on donor T cells during graft-versus-host disease based on pretransplant conditioning. Journal of immunology. 2004;173(2):845-54. PubMed PMID: 15240671.
220. Welniak LA, Wang Z, Sun K, Kuziel W, Anver MR, Blazar BR, Murphy WJ. An absence of CCR5 on donor cells results in acceleration of acute graft-vs-host disease. Experimental hematology. 2004;32(3):318-24. doi: 10.1016/j.exphem.2003.12.003. PubMed PMID: 15003318.
221. Reshef R, Luger SM, Hexner EO, Loren AW, Frey NV, Nasta SD, Goldstein SC, Stadtmauer EA, Smith J, Bailey S, Mick R, Heitjan DF, Emerson SG, Hoxie JA, Vonderheide RH, Porter DL. Blockade of lymphocyte chemotaxis in visceral graft-versus-host disease. The New England journal of medicine. 2012;367(2):135-45. doi: 10.1056/NEJMoa1201248. PubMed PMID: 22784116; PMCID: PMC3568501.
222. Chavin KD, Lau HT, Bromberg JS. Prolongation of allograft and xenograft survival in mice by anti-CD2 monoclonal antibodies. Transplantation. 1992;54(2):286-91. PubMed PMID: 1353913.
223. Lo DJ, Weaver TA, Stempora L, Mehta AK, Ford ML, Larsen CP, Kirk AD. Selective targeting of human alloresponsive CD8+ effector memory T cells based on CD2 expression. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2011;11(1):22-33. doi: 10.1111/j.1600-6143.2010.03317.x. PubMed PMID: 21070604; PMCID: PMC3057516.

224. Weaver TA, Charafeddine AH, Agarwal A, Turner AP, Russell M, Leopardi FV, Kampen RL, Stempora L, Song M, Larsen CP, Kirk AD. Alefacept promotes co-stimulation blockade based allograft survival in nonhuman primates. Nature medicine. 2009;15(7):746-9. doi: 10.1038/nm.1993. PubMed PMID: 19584865; PMCID: PMC2772128.
225. Stenger EO, Chiang KY, Haight A, Qayed M, Kean L, Horan J. Use of Alefacept for Preconditioning in Multiply Transfused Pediatric Patients with Nonmalignant Diseases. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015;21(10):1845-52. doi: 10.1016/j.bbmt.2015.06.005. PubMed PMID: 26095669.
226. Rigby MR, Harris KM, Pinckney A, DiMeglio LA, Rendell MS, Felner EI, Dostou JM, Gitelman SE, Griffin KJ, Tsalikian E, Gottlieb PA, Greenbaum CJ, Sherry NA, Moore WV, Monzavi R, Willi SM, Raskin P, Keyes-Elstein L, Long SA, Kanaparthi S, Lim N, Phippard D, Soppe CL, Fitzgibbon ML, McNamara J, Nepom GT, Ehlers MR. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. The Journal of clinical investigation. 2015;125(8):3285-96. doi: 10.1172/JCI81722. PubMed PMID: 26193635; PMCID: PMC4623571.
227. Rigby MR, DiMeglio LA, Rendell MS, Felner EI, Dostou JM, Gitelman SE, Patel CM, Griffin KJ, Tsalikian E, Gottlieb PA, Greenbaum CJ, Sherry NA, Moore WV, Monzavi R, Willi SM, Raskin P, Moran A, Russell WE, Pinckney A, Keyes-Elstein L, Howell M, Aggarwal S, Lim N, Phippard D, Nepom GT, McNamara J, Ehlers MR, Team TDS. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol. 2013;1(4):284-94. doi: 10.1016/S2213-8587(13)70111-6. PubMed PMID: 24622414; PMCID: PMC3957186.
228. Wood KJ, Bushell A, Hester J. Regulatory immune cells in transplantation. Nature reviews Immunology. 2012;12(6):417-30. doi: 10.1038/nri3227. PubMed PMID: 22627860.
229. Daud AI, Loo K, Pauli ML, Sanchez-Rodriguez R, Sandoval PM, Taravati K, Tsai K, Nosrati A, Nardo L, Alvarado MD, Algazi AP, Pampaloni MH, Lobach IV, Hwang J, Pierce RH, Gratz IK, Krummel MF, Rosenblum MD. Tumor immune profiling predicts response to anti-PD-1 therapy in human melanoma. The Journal of clinical investigation. 2016;126(9):3447-52. doi: 10.1172/JCI87324. PubMed PMID: 27525433; PMCID: PMC5004965.
230. Huynh A, DuPage M, Priyadharshini B, Sage PT, Quiros J, Borges CM, Townamchai N, Gerriets VA, Rathmell JC, Sharpe AH, Bluestone JA, Turka LA. Control of PI(3) kinase in Treg cells maintains homeostasis and lineage stability. Nature immunology. 2015;16(2):188-96. doi: 10.1038/ni.3077. PubMed PMID: 25559257; PMCID: PMC4297515.
231. Taylor PA, Panoskaltsis-Mortari A, Swedin JM, Lucas PJ, Gress RE, Levine BL, June CH, Serody JS, Blazar BR. L-Selectin(hi) but not the L-selectin(lo) CD4+25+ T-regulatory cells are potent inhibitors of GVHD and BM graft rejection. Blood. 2004;104(12):3804-12. doi: 10.1182/blood-2004-05-1850. PubMed PMID: 15292057.
232. Steiner D, Brunicki N, Bachar-Lustig E, Taylor PA, Blazar BR, Reisner Y. Overcoming T cell-mediated rejection of bone marrow allografts by T-regulatory cells: synergism with veto cells and rapamycin. Experimental hematology. 2006;34(6):802-8. doi: 10.1016/j.exphem.2006.02.017. PubMed PMID: 16728286.
233. Steiner D, Brunicki N, Blazar BR, Bachar-Lustig E, Reisner Y. Tolerance induction by third-party "off-the-shelf" CD4+CD25+ Treg cells. Experimental hematology. 2006;34(1):66-71. doi: 10.1016/j.exphem.2005.10.011. PubMed PMID: 16413392.

234. Brunstein CG, Miller JS, McKenna DH, Hippen KL, DeFor TE, Sumstad D, Curtsinger J, Verneris MR, MacMillan ML, Levine BL, Riley JL, June CH, Le C, Weisdorf DJ, McGlave PB, Blazar BR, Wagner JE. Umbilical cord blood-derived T regulatory cells to prevent GVHD: kinetics, toxicity profile, and clinical effect. Blood. 2016;127(8):1044-51. doi: 10.1182/blood-2015-06-653667. PubMed PMID: 26563133; PMCID: PMC4768428.
235. Hippen KL, Riley JL, June CH, Blazar BR. Clinical perspectives for regulatory T cells in transplantation tolerance. Seminars in immunology. 2011;23(6):462-8. doi: 10.1016/j.smim.2011.07.008. PubMed PMID: 21820917; PMCID: PMC3230779.
236. Hippen KL, Merkel SC, Schirm DK, Sieben CM, Sumstad D, Kadidlo DM, McKenna DH, Bromberg JS, Levine BL, Riley JL, June CH, Scheinberg P, Douek DC, Miller JS, Wagner JE, Blazar BR. Massive ex vivo expansion of human natural regulatory T cells (T(regs)) with minimal loss of in vivo functional activity. Science translational medicine. 2011;3(83):83ra41. doi: 10.1126/scitranslmed.3001809. PubMed PMID: 21593401; PMCID: PMC3551476.
237. Golovina TN, Mikheeva T, Brusko TM, Blazar BR, Bluestone JA, Riley JL. Retinoic acid and rapamycin differentially affect and synergistically promote the ex vivo expansion of natural human T regulatory cells. PloS one. 2011;6(1):e15868. doi: 10.1371/journal.pone.0015868. PubMed PMID: 21253593; PMCID: PMC3017077.
238. Brunstein CG, Miller JS, Cao Q, McKenna DH, Hippen KL, Curtsinger J, Defor T, Levine BL, June CH, Rubinstein P, McGlave PB, Blazar BR, Wagner JE. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. Blood. 2011;117(3):1061-70. doi: 10.1182/blood-2010-07-293795. PubMed PMID: 20952687; PMCID: PMC3035067.
239. June CH, Blazar BR, Riley JL. Engineering lymphocyte subsets: tools, trials and tribulations. Nature reviews Immunology. 2009;9(10):704-16. doi: 10.1038/nri2635. PubMed PMID: 19859065; PMCID: PMC3412112.
240. Riley JL, June CH, Blazar BR. Human T regulatory cell therapy: take a billion or so and call me in the morning. Immunity. 2009;30(5):656-65. doi: 10.1016/j.immuni.2009.04.006. PubMed PMID: 19464988; PMCID: PMC2742482.
241. Martelli MF, Di Ianni M, Ruggeri L, Falzetti F, Carotti A, Terenzi A, Pierini A, Massei MS, Amico L, Urbani E, Del Papa B, Zei T, Iacucci Ostini R, Cecchini D, Tognellini R, Reisner Y, Aversa F, Falini B, Velardi A. HLA-haploidentical transplantation with regulatory and conventional T-cell adoptive immunotherapy prevents acute leukemia relapse. Blood. 2014;124(4):638-44. doi: 10.1182/blood-2014-03-564401. PubMed PMID: 24923299.
242. Martelli MF, Di Ianni M, Ruggeri L, Pierini A, Falzetti F, Carotti A, Terenzi A, Reisner Y, Aversa F, Falini B, Velardi A. "Designed" grafts for HLA-haploidentical stem cell transplantation. Blood. 2014;123(7):967-73. doi: 10.1182/blood-2013-10-531764. PubMed PMID: 24363403.
243. Di Ianni M, Falzetti F, Carotti A, Terenzi A, Castellino F, Bonifacio E, Del Papa B, Zei T, Ostini RI, Cecchini D, Aloisi T, Perruccio K, Ruggeri L, Balucani C, Pierini A, Sportoletti P, Aristei C, Falini B, Reisner Y, Velardi A, Aversa F, Martelli MF. Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation. Blood. 2011;117(14):3921-8. doi: 10.1182/blood-2010-10-311894. PubMed PMID: 21292771.
244. Barao I, Hanash AM, Hallett W, Welniak LA, Sun K, Redelman D, Blazar BR, Levy RB, Murphy WJ. Suppression of natural killer cell-mediated bone marrow cell rejection by CD4+CD25+ regulatory T cells. Proceedings of the National Academy of Sciences of the United States of America. 2006;103(14):5460-5. doi: 10.1073/pnas.0509249103. PubMed PMID: 16567639; PMCID: PMC1459377.

245. Cohen JL, Trenado A, Vasey D, Klatzmann D, Salomon BL. CD4(+)CD25(+) immunoregulatory T Cells: new therapeutics for graft-versus-host disease. The Journal of experimental medicine. 2002;196(3):401-6. PubMed PMID: 12163568; PMCID: PMC2193933.
246. Edinger M, Hoffmann P, Ermann J, Drago K, Fathman CG, Strober S, Negrin RS. CD4+CD25+ regulatory T cells preserve graft-versus-tumor activity while inhibiting graft-versus-host disease after bone marrow transplantation. Nature medicine. 2003;9(9):1144-50. doi: 10.1038/nm915. PubMed PMID: 12925844.
247. Hoffmann P, Ermann J, Edinger M, Fathman CG, Strober S. Donor-type CD4(+)CD25(+) regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation. The Journal of experimental medicine. 2002;196(3):389-99. PubMed PMID: 12163567; PMCID: PMC2193938.
248. Taylor PA, Lees CJ, Blazar BR. The infusion of ex vivo activated and expanded CD4(+)CD25(+) immune regulatory cells inhibits graft-versus-host disease lethality. Blood. 2002;99(10):3493-9. PubMed PMID: 11986199.
249. Gudmundsdottir H, Turka LA. A closer look at homeostatic proliferation of CD4+ T cells: costimulatory requirements and role in memory formation. Journal of immunology. 2001;167(7):3699-707. PubMed PMID: 11564785.
250. Valujskikh A, Pantenburg B, Heeger PS. Primed allospecific T cells prevent the effects of costimulatory blockade on prolonged cardiac allograft survival in mice. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2002;2(6):501-9. PubMed PMID: 12118893.
251. Adams AB, Pearson TC, Larsen CP. Heterologous immunity: an overlooked barrier to tolerance. Immunological reviews. 2003;196:147-60. PubMed PMID: 14617203.
252. Adams AB, Williams MA, Jones TR, Shirasugi N, Durham MM, Kaech SM, Wherry EJ, Onami T, Lanier JG, Kokko KE, Pearson TC, Ahmed R, Larsen CP. Heterologous immunity provides a potent barrier to transplantation tolerance. The Journal of clinical investigation. 2003;111(12):1887-95. doi: 10.1172/JCI17477. PubMed PMID: 12813024; PMCID: PMC161424.
253. Padovan E, Casorati G, Dellabona P, Meyer S, Brockhaus M, Lanzavecchia A. Expression of two T cell receptor alpha chains: dual receptor T cells. Science. 1993;262(5132):422-4. PubMed PMID: 8211163.
254. Vu MD, Clarkson MR, Yagita H, Turka LA, Sayegh MH, Li XC. Critical, but conditional, role of OX40 in memory T cell-mediated rejection. Journal of immunology. 2006;176(3):1394-401. PubMed PMID: 16424166.
255. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. The EMBO journal. 1992;11(11):3887-95. PubMed PMID: 1396582; PMCID: PMC556898.
256. Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, Sasayama S, Mizoguchi A, Hiai H, Minato N, Honjo T. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291(5502):319-22. doi: 10.1126/science.291.5502.319. PubMed PMID: 11209085.
257. Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, Freeman GJ, Ahmed R. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature. 2006;439(7077):682-7. doi: 10.1038/nature04444. PubMed PMID: 16382236.
258. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, Linsley PS, Thompson CB, Riley JL. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol. 2005;25(21):9543-53. doi: 10.1128/MCB.25.21.9543-9553.2005. PubMed PMID: 16227604; PMCID: PMC1265804.

259. Wang L, Han R, Hancock WW. Programmed cell death 1 (PD-1) and its ligand PD-L1 are required for allograft tolerance. European journal of immunology. 2007;37(10):2983-90. doi: 10.1002/eji.200737583. PubMed PMID: 17899549.
260. Ito T, Ueno T, Clarkson MR, Yuan X, Jurewicz MM, Yagita H, Azuma M, Sharpe AH, Auchincloss H, Jr., Sayegh MH, Najafian N. Analysis of the role of negative T cell costimulatory pathways in CD4 and CD8 T cell-mediated alloimmune responses in vivo. Journal of immunology. 2005;174(11):6648-56. PubMed PMID: 15905503.
261. Koehn BH, Ford ML, Ferrer IR, Borom K, Gangappa S, Kirk AD, Larsen CP. PD-1-dependent mechanisms maintain peripheral tolerance of donor-reactive CD8+ T cells to transplanted tissue. Journal of immunology. 2008;181(8):5313-22. PubMed PMID: 18832687; PMCID: PMC2572818.
262. Blazar BR, Carreno BM, Panoskaltsis-Mortari A, Carter L, Iwai Y, Yagita H, Nishimura H, Taylor PA. Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-gamma-dependent mechanism. Journal of immunology. 2003;171(3):1272-7. PubMed PMID: 12874215.
263. Schilbach K, Schick J, Wehrmann M, Wollny G, Simon P, Schlegel PG, Eyrich M. PD-1-PD-L1 pathway is involved in suppressing alloreactivity of heart infiltrating t cells during murine gvhd across minor histocompatibility antigen barriers. Transplantation. 2007;84(2):214-22. doi: 10.1097/01.tp.0000268074.77929.54. PubMed PMID: 17667813.
264. Koestner W, Hapke M, Herbst J, Klein C, Welte K, Fruehauf J, Flatley A, Vignali DA, Hardtke-Wolenski M, Jaeckel E, Blazar BR, Sauer MG. PD-L1 blockade effectively restores strong graft-versus-leukemia effects without graft-versus-host disease after delayed adoptive transfer of T-cell receptor gene-engineered allogeneic CD8+ T cells. Blood. 2011;117(3):1030-41. doi: 10.1182/blood-2010-04-283119. PubMed PMID: 21063028; PMCID: PMC3035065.
265. Fujiwara H, Maeda Y, Kobayashi K, Nishimori H, Matsuoka K, Fujii N, Kondo E, Tanaka T, Chen L, Azuma M, Yagita H, Tanimoto M. Programmed death-1 pathway in host tissues ameliorates Th17/Th1-mediated experimental chronic graft-versus-host disease. Journal of immunology. 2014;193(5):2565-73. doi: 10.4049/jimmunol.1400954. PubMed PMID: 25080485.
266. Sandner SE, Clarkson MR, Salama AD, Sanchez-Fueyo A, Domenig C, Habicht A, Najafian N, Yagita H, Azuma M, Turka LA, Sayegh MH. Role of the programmed death-1 pathway in regulation of alloimmune responses in vivo. Journal of immunology. 2005;174(6):3408-15. PubMed PMID: 15749874.
267. Yang J, Popoola J, Khandwala S, Vadivel N, Vanguri V, Yuan X, Dada S, Guleria I, Tian C, Ansari MJ, Shin T, Yagita H, Azuma M, Sayegh MH, Chandraker A. Critical role of donor tissue expression of programmed death ligand-1 in regulating cardiac allograft rejection and vasculopathy. Circulation. 2008;117(5):660-9. doi: 10.1161/CIRCULATIONAHA.107.741025. PubMed PMID: 18212277.
268. Yang J, Riella LV, Chock S, Liu T, Zhao X, Yuan X, Paterson AM, Watanabe T, Vanguri V, Yagita H, Azuma M, Blazar BR, Freeman GJ, Rodig SJ, Sharpe AH, Chandraker A, Sayegh MH. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. Journal of immunology. 2011;187(3):1113-9. doi: 10.4049/jimmunol.1100056. PubMed PMID: 21697455; PMCID: PMC3140607.
269. Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, Sharpe AH. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. The Journal of experimental medicine. 2009;206(13):3015-29. doi: 10.1084/jem.20090847. PubMed PMID: 20008522; PMCID: PMC2806460.

270. Saha A, Aoyama K, Taylor PA, Koehn BH, Veenstra RG, Panoskaltsis-Mortari A, Munn DH, Murphy WJ, Azuma M, Yagita H, Fife BT, Sayegh MH, Najafian N, Socie G, Ahmed R, Freeman GJ, Sharpe AH, Blazar BR. Host programmed death ligand 1 is dominant over programmed death ligand 2 expression in regulating graft-versus-host disease lethality. Blood. 2013;122(17):3062-73. doi: 10.1182/blood-2013-05-500801. PubMed PMID: 24030385; PMCID: PMC3811178.
271. Asakura S, Hashimoto D, Takashima S, Sugiyama H, Maeda Y, Akashi K, Tanimoto M, Teshima T. Alloantigen expression on non-hematopoietic cells reduces graft-versus-leukemia effects in mice. The Journal of clinical investigation. 2010;120(7):2370-8. doi: 10.1172/JCI39165. PubMed PMID: 20530875; PMCID: PMC2898583.
272. Matte-Martone C, Venkatesan S, Tan HS, Athanasiadis I, Chang J, Pavisic J, Shlomchik WD. Graft-versus-leukemia (GVL) against mouse blast-crisis chronic myelogenous leukemia (BC-CML) and chronic-phase chronic myelogenous leukemia (CP-CML): shared mechanisms of T cell killing, but programmed death ligands render CP-CML and not BC-CML GVL resistant. Journal of immunology. 2011;187(4):1653-63. doi: 10.4049/jimmunol.1100311. PubMed PMID: 21768400; PMCID: PMC3150287.
273. Saha A, O'Connor RS, Thangavelu G, Lovitch SB, Dandamudi DB, Wilson CB, Vincent BG, Tkachev V, Pawlicki JM, Furlan SN, Kean LS, Aoyama K, Taylor PA, Panoskaltsis-Mortari A, Foncea R, Ranganathan P, Devine SM, Burrill JS, Guo L, Sacristan C, Snyder NW, Blair IA, Milone MC, Dustin ML, Riley JL, Bernlohr DA, Murphy WJ, Fife BT, Munn DH, Miller JS, Serody JS, Freeman GJ, Sharpe AH, Turka LA, Blazar BR. Programmed death ligand-1 expression on donor T cells drives graft-versus-host disease lethality. The Journal of clinical investigation. 2016;126(7):2642-60. doi: 10.1172/JCI85796. PubMed PMID: 27294527; PMCID: PMC4922691.
274. Yi T, Li X, Yao S, Wang L, Chen Y, Zhao D, Johnston HF, Young JS, Liu H, Todorov I, Forman SJ, Chen L, Zeng D. Host APCs augment in vivo expansion of donor natural regulatory T cells via B7H1/B7.1 in allogeneic recipients. Journal of immunology. 2011;186(5):2739-49. doi: 10.4049/jimmunol.1002939. PubMed PMID: 21263067; PMCID: PMC3786569.
275. Deng R, Cassady K, Li X, Yao S, Zhang M, Racine J, Lin J, Chen L, Zeng D. B7H1/CD80 interaction augments PD-1-dependent T cell apoptosis and ameliorates graft-versus-host disease. Journal of immunology. 2015;194(2):560-74. doi: 10.4049/jimmunol.1402157. PubMed PMID: 25488990; PMCID: PMC4282988.
276. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity. 2007;27(1):111-22. doi: 10.1016/j.immuni.2007.05.016. PubMed PMID: 17629517; PMCID: PMC2707944.
277. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong AN, Park JJ, McQuade JL, Shoushtari AN, Tsai KK, Eroglu Z, Klein O, Hassel JC, Sosman JA, Guminski A, Sullivan RJ, Ribas A, Carlino MS, Davies MA, Sandhu SK, Long GV. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2016. doi: 10.1093/annonc/mdw443. PubMed PMID: 27687304.
278. Krecke N, Zimmer A, Friesenhahn-Ochs B, Muller CS, Vogt T, Pfohler C. Sneaky side effects and ineffectiveness of an immunotherapy with ipilimumab in a case of metastatic melanoma. Dermatoendocrinol. 2016;8(1):e1199307. doi: 10.1080/19381980.2016.1199307. PubMed PMID: 27574531; PMCID: PMC4977105.
279. Koelzer VH, Buser T, Willi N, Rothschild SI, Wicki A, Schiller P, Cathomas G, Zippelius A, Mertz KD. Grover's-like drug eruption in a patient with metastatic melanoma

under ipilimumab therapy. J Immunother Cancer. 2016;4:47. doi: 10.1186/s40425-016-0151-z. PubMed PMID: 27532022; PMCID: PMC4986338.
280. Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, Voegeli M, Cathomas G, Zippelius A, Mertz KD. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer. 2016;4:13. doi: 10.1186/s40425-016-0117-1. PubMed PMID: 26981243; PMCID: PMC4791920.
281. Verschuren EC, van den Eertwegh AJ, Wonders J, Slangen RM, van Delft F, van Bodegraven A, Neefjes-Borst A, de Boer NK. Clinical, Endoscopic, and Histologic Characteristics of Ipilimumab-Associated Colitis. Clin Gastroenterol Hepatol. 2016;14(6):836-42. doi: 10.1016/j.cgh.2015.12.028. PubMed PMID: 26748223.
282. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, Guminski A, Puzanov I, Lawrence DP, Buchbinder EI, Mudigonda T, Spencer K, Bender C, Lee J, Kaufman HL, Menzies AM, Hassel JC, Mehnert JM, Sosman JA, Long GV, Clark JI. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncol. 2016;2(2):234-40. doi: 10.1001/jamaoncol.2015.4368. PubMed PMID: 26633184.
283. Davids MS, Kim HT, Bachireddy P, Costello C, Liguori R, Savell A, Lukez AP, Avigan D, Chen YB, McSweeney P, LeBoeuf NR, Rooney MS, Bowden M, Zhou CW, Granter SR, Hornick JL, Rodig SJ, Hirakawa M, Severgnini M, Hodi FS, Wu CJ, Ho VT, Cutler C, Koreth J, Alyea EP, Antin JH, Armand P, Streicher H, Ball ED, Ritz J, Bashey A, Soiffer RJ, Leukemia, Lymphoma Society Blood Cancer Research P. Ipilimumab for Patients with Relapse after Allogeneic Transplantation. The New England journal of medicine. 2016;375(2):143-53. doi: 10.1056/NEJMoa1601202. PubMed PMID: 27410923.
284. Singh AK, Porrata LF, Aljitawi O, Lin T, Shune L, Ganguly S, McGuirk JP, Abhyankar S. Fatal GvHD induced by PD-1 inhibitor pembrolizumab in a patient with Hodgkin's lymphoma. Bone marrow transplantation. 2016;51(9):1268-70. doi: 10.1038/bmt.2016.111. PubMed PMID: 27111048.
285. Yang Y, Jacoby E, Fry TJ. Challenges and opportunities of allogeneic donor-derived CAR T cells. Current opinion in hematology. 2015;22(6):509-15. doi: 10.1097/MOH.0000000000000181. PubMed PMID: 26390167; PMCID: PMC4636084.
286. Kochenderfer JN, Dudley ME, Carpenter RO, Kassim SH, Rose JJ, Telford WG, Hakim FT, Halverson DC, Fowler DH, Hardy NM, Mato AR, Hickstein DD, Gea-Banacloche JC, Pavletic SZ, Sportes C, Maric I, Feldman SA, Hansen BG, Wilder JS, Blacklock-Schuver B, Jena B, Bishop MR, Gress RE, Rosenberg SA. Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. Blood. 2013;122(25):4129-39. doi: 10.1182/blood-2013-08-519413. PubMed PMID: 24055823; PMCID: PMC3862276.
287. Jacoby E, Yang Y, Qin H, Chien CD, Kochenderfer JN, Fry TJ. Murine allogeneic CD19 CAR T cells harbor potent antileukemic activity but have the potential to mediate lethal GVHD. Blood. 2016;127(10):1361-70. doi: 10.1182/blood-2015-08-664250. PubMed PMID: 26660684; PMCID: PMC4786842.
288. Jones BS, Lamb LS, Goldman F, Di Stasi A. Improving the safety of cell therapy products by suicide gene transfer. Front Pharmacol. 2014;5:254. doi: 10.3389/fphar.2014.00254. PubMed PMID: 25505885; PMCID: PMC4245885.
289. Gargett T, Brown MP. The inducible caspase-9 suicide gene system as a "safety switch" to limit on-target, off-tumor toxicities of chimeric antigen receptor T cells. Front Pharmacol. 2014;5:235. doi: 10.3389/fphar.2014.00235. PubMed PMID: 25389405; PMCID: PMC4211380.

290. Okamura T, Fujio K, Sumitomo S, Yamamoto K. Roles of LAG3 and EGR2 in regulatory T cells. Ann Rheum Dis. 2012;71 Suppl 2:i96-100. doi: 10.1136/annrheumdis-2011-200588. PubMed PMID: 22460149.
291. Okamura T, Fujio K, Shibuya M, Sumitomo S, Shoda H, Sakaguchi S, Yamamoto K. CD4+CD25-LAG3+ regulatory T cells controlled by the transcription factor Egr-2. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(33):13974-9. doi: 10.1073/pnas.0906872106. PubMed PMID: 19666526; PMCID: PMC2729005.
292. Chen SY, Hsu WT, Chen YL, Chien CH, Chiang BL. Lymphocyte-activation gene 3(+) (LAG3(+)) forkhead box protein 3(-) (FOXP3(-)) regulatory T cells induced by B cells alleviates joint inflammation in collagen-induced arthritis. J Autoimmun. 2016;68:75-85. doi: 10.1016/j.jaut.2016.02.002. PubMed PMID: 26908164.
293. Do JS, Visperas A, Sanogo YO, Bechtel JJ, Dvorina N, Kim S, Jang E, Stohlman SA, Shen B, Fairchild RL, Baldwin Iii WM, Vignali DA, Min B. An IL-27/Lag3 axis enhances Foxp3+ regulatory T cell-suppressive function and therapeutic efficacy. Mucosal immunology. 2016;9(1):137-45. doi: 10.1038/mi.2015.45. PubMed PMID: 26013006; PMCID: PMC4662649.
294. Sega EI, Leveson-Gower DB, Florek M, Schneidawind D, Luong RH, Negrin RS. Role of lymphocyte activation gene-3 (Lag-3) in conventional and regulatory T cell function in allogeneic transplantation. PloS one. 2014;9(1):e86551. doi: 10.1371/journal.pone.0086551. PubMed PMID: 24475140; PMCID: PMC3903521.
295. Wang L, Fraser CC, Kikly K, Wells AD, Han R, Coyle AJ, Chen L, Hancock WW. B7-H3 promotes acute and chronic allograft rejection. European journal of immunology. 2005;35(2):428-38. doi: 10.1002/eji.200425518. PubMed PMID: 15682454.
296. Ueno T, Yeung MY, McGrath M, Yang S, Zaman N, Snawder B, Padera RF, Magee CN, Gorbatov R, Hashiguchi M, Azuma M, Freeman GJ, Sayegh MH, Najafian N. Intact B7-H3 signaling promotes allograft prolongation through preferential suppression of Th1 effector responses. European journal of immunology. 2012;42(9):2343-53. doi: 10.1002/eji.201242501. PubMed PMID: 22733595; PMCID: PMC3822046.
297. Veenstra RG, Flynn R, Kreymborg K, McDonald-Hyman C, Saha A, Taylor PA, Osborn MJ, Panoskaltsis-Mortari A, Schmitt-Graeff A, Lieberknect E, Murphy WJ, Serody JS, Munn DH, Freeman GJ, Allison JP, Mak TW, van den Brink M, Zeiser R, Blazar BR. B7-H3 expression in donor T cells and host cells negatively regulates acute graft-versus-host disease lethality. Blood. 2015;125(21):3335-46. doi: 10.1182/blood-2014-09-603357. PubMed PMID: 25814530; PMCID: PMC4440885.
298. Mahnke K, Ring S, Johnson TS, Schallenberg S, Schonfeld K, Storn V, Bedke T, Enk AH. Induction of immunosuppressive functions of dendritic cells in vivo by CD4+CD25+ regulatory T cells: role of B7-H3 expression and antigen presentation. European journal of immunology. 2007;37(8):2117-26. doi: 10.1002/eji.200636841. PubMed PMID: 17615586.
299. Yamaura K, Watanabe T, Boenisch O, Yeung M, Yang S, Magee CN, Padera R, Datta S, Schatton T, Kamimura Y, Azuma M, Najafian N. In vivo function of immune inhibitory molecule B7-H4 in alloimmune responses. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(10):2355-62. doi: 10.1111/j.1600-6143.2010.03250.x. PubMed PMID: 21143433.
300. Bengsch B, Seigel B, Ruhl M, Timm J, Kuntz M, Blum HE, Pircher H, Thimme R. Coexpression of PD-1, 2B4, CD160 and KLRG1 on exhausted HCV-specific CD8+ T cells is linked to antigen recognition and T cell differentiation. PLoS pathogens. 2010;6(6):e1000947. doi: 10.1371/journal.ppat.1000947. PubMed PMID: 20548953; PMCID: PMC2883597.

301. Blackburn SD, Shin H, Haining WN, Zou T, Workman CJ, Polley A, Betts MR, Freeman GJ, Vignali DA, Wherry EJ. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nature immunology. 2009;10(1):29-37. doi: 10.1038/ni.1679. PubMed PMID: 19043418; PMCID: PMC2605166.
302. Raziorrouh B, Schraut W, Gerlach T, Nowack D, Gruner NH, Ulsenheimer A, Zachoval R, Wachtler M, Spannagl M, Haas J, Diepolder HM, Jung MC. The immunoregulatory role of CD244 in chronic hepatitis B infection and its inhibitory potential on virus-specific CD8+ T-cell function. Hepatology. 2010;52(6):1934-47. doi: 10.1002/hep.23936. PubMed PMID: 21064032.
303. Wherry EJ, Ha SJ, Kaech SM, Haining WN, Sarkar S, Kalia V, Subramaniam S, Blattman JN, Barber DL, Ahmed R. Molecular signature of CD8+ T cell exhaustion during chronic viral infection. Immunity. 2007;27(4):670-84. doi: 10.1016/j.immuni.2007.09.006. PubMed PMID: 17950003.
304. Brown DR, Calpe S, Keszei M, Wang N, McArdel S, Terhorst C, Sharpe AH. Cutting edge: an NK cell-independent role for Slamf4 in controlling humoral autoimmunity. Journal of immunology. 2011;187(1):21-5. doi: 10.4049/jimmunol.1100510. PubMed PMID: 21622868; PMCID: PMC3119727.
305. Kim JR, Mathew SO, Patel RK, Pertusi RM, Mathew PA. Altered expression of signalling lymphocyte activation molecule (SLAM) family receptors CS1 (CD319) and 2B4 (CD244) in patients with systemic lupus erythematosus. Clinical and experimental immunology. 2010;160(3):348-58. doi: 10.1111/j.1365-2249.2010.04116.x. PubMed PMID: 20345977; PMCID: PMC2883105.
306. Sabatos CA, Chakravarti S, Cha E, Schubart A, Sanchez-Fueyo A, Zheng XX, Coyle AJ, Strom TB, Freeman GJ, Kuchroo VK. Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance. Nature immunology. 2003;4(11):1102-10. doi: 10.1038/ni988. PubMed PMID: 14556006.
307. Sanchez-Fueyo A, Tian J, Picarella D, Domenig C, Zheng XX, Sabatos CA, Manlongat N, Bender O, Kamradt T, Kuchroo VK, Gutierrez-Ramos JC, Coyle AJ, Strom TB. Tim-3 inhibits T helper type 1-mediated auto- and alloimmune responses and promotes immunological tolerance. Nature immunology. 2003;4(11):1093-101. doi: 10.1038/ni987. PubMed PMID: 14556005.
308. Veenstra RG, Taylor PA, Zhou Q, Panoskaltsis-Mortari A, Hirashima M, Flynn R, Liu D, Anderson AC, Strom TB, Kuchroo VK, Blazar BR. Contrasting acute graft-versus-host disease effects of Tim-3/galectin-9 pathway blockade dependent upon the presence of donor regulatory T cells. Blood. 2012;120(3):682-90. doi: 10.1182/blood-2011-10-387977. PubMed PMID: 22677125; PMCID: PMC3401220.
309. Wang F, He W, Yuan J, Wu K, Zhou H, Zhang W, Chen ZK. Activation of Tim-3-Galectin-9 pathway improves survival of fully allogeneic skin grafts. Transplant immunology. 2008;19(1):12-9. doi: 10.1016/j.trim.2008.01.008. PubMed PMID: 18346632.
310. Wang F, He W, Zhou H, Yuan J, Wu K, Xu L, Chen ZK. The Tim-3 ligand galectin-9 negatively regulates CD8+ alloreactive T cell and prolongs survival of skin graft. Cell Immunol. 2007;250(1-2):68-74. doi: 10.1016/j.cellimm.2008.01.006. PubMed PMID: 18353298.
311. He W, Fang Z, Wang F, Wu K, Xu Y, Zhou H, Du D, Gao Y, Zhang WN, Niki T, Hirashima M, Yuan J, Chen ZK. Galectin-9 significantly prolongs the survival of fully mismatched cardiac allografts in mice. Transplantation. 2009;88(6):782-90. doi: 10.1097/TP.0b013e3181b47f25. PubMed PMID: 19920777.
312. Boenisch O, D'Addio F, Watanabe T, Elyaman W, Magee CN, Yeung MY, Padera RF, Rodig SJ, Murayama T, Tanaka K, Yuan X, Ueno T, Jurisch A, Mfarrej B, Akiba H, Yagita H, Najafian N. TIM-3: a novel regulatory molecule of alloimmune

activation. Journal of immunology. 2010;185(10):5806-19. doi: 10.4049/jimmunol.0903435. PubMed PMID: 20956339; PMCID: PMC3619947.
313. Gupta S, Thornley TB, Gao W, Larocca R, Turka LA, Kuchroo VK, Strom TB. Allograft rejection is restrained by short-lived TIM-3+PD-1+Foxp3+ Tregs. The Journal of clinical investigation. 2012;122(7):2395-404. doi: 10.1172/JCI45138. PubMed PMID: 22684103; PMCID: PMC3386804.
314. Tao YF, Lin F, Yan XY, Gao XG, Teng F, Fu ZR, Wang ZX. Galectin-9 in Combination With EX-527 Prolongs the Survival of Cardiac Allografts in Mice After Cardiac Transplantation. Transplant Proc. 2015;47(6):2003-9. doi: 10.1016/j.transproceed.2015.04.091. PubMed PMID: 26293089.
315. Cai L, Zhou H, Fang Z, Yuan J, Niki T, Hirashima M, He W, Chen ZK. Galectin-9 in combination with rapamycin induces cardiac allograft tolerance in mice. Transplantation. 2013;96(4):379-86. doi: 10.1097/TP.0b013e31829b07b5. PubMed PMID: 23838998.
316. Shimmura-Tomita M, Wang M, Taniguchi H, Akiba H, Yagita H, Hori J. Galectin-9-mediated protection from allo-specific T cells as a mechanism of immune privilege of corneal allografts. PloS one. 2013;8(5):e63620. doi: 10.1371/journal.pone.0063620. PubMed PMID: 23667648; PMCID: PMC3646846.
317. Chen Y, Fukuda T, Thakar MS, Kornblit BT, Storer BE, Santos EB, Storb R, Sandmaier BM. Immunomodulatory effects induced by cytotoxic T lymphocyte antigen 4 immunoglobulin with donor peripheral blood mononuclear cell infusion in canine major histocompatibility complex-haplo-identical non-myeloablative hematopoietic cell transplantation. Cytotherapy. 2011;13(10):1269-80. doi: 10.3109/14653249.2011.586997. PubMed PMID: 21846291; PMCID: PMC3195840.
318. Graves SS, Stone D, Loretz C, Peterson L, McCune JS, Mielcarek M, Storb R. Establishment of long-term tolerance to SRBC in dogs by recombinant canine CTLA4-Ig. Transplantation. 2009;88(3):317-22. doi: 10.1097/TP.0b013e3181ae3285. PubMed PMID: 19667932; PMCID: PMC2753482.
319. Graves SS, Stone DM, Loretz C, Peterson LJ, Lesnikova M, Hwang B, Georges GE, Nash R, Storb R. Antagonistic and agonistic anti-canine CD28 monoclonal antibodies: tools for allogeneic transplantation. Transplantation. 2011;91(8):833-40. doi: 10.1097/TP.0b013e31820f07ff. PubMed PMID: 21343872; PMCID: PMC3180996.
320. Mathes DW, Hwang B, Graves SS, Edwards J, Chang J, Storer BE, Butts-Miwongtum T, Sale GE, Nash RA, Storb R. Tolerance to vascularized composite allografts in canine mixed hematopoietic chimeras. Transplantation. 2011;92(12):1301-8. doi: 10.1097/TP.0b013e318237d6d4. PubMed PMID: 22082819; PMCID: PMC3310209.
321. Rosinski SL, Storb R, Strong RK, Sale GE, Stone DM, Gewe MM, Friend DJ, Abrams VK, Randolph-Habecker J, Graves SS. Anti-CD28 Antibody-Initiated Cytokine Storm in Canines. Transplant Direct. 2015;1(2). doi: 10.1097/TXD.0000000000000516. PubMed PMID: 25988188; PMCID: PMC4433175.
322. Jochum C, Beste M, Zellmer E, Graves SS, Storb R. CD154 blockade and donor-specific transfusions in DLA-identical marrow transplantation in dogs conditioned with 1-Gy total body irradiation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2007;13(2):164-71. doi: 10.1016/j.bbmt.2006.10.031. PubMed PMID: 17241922; PMCID: PMC1831459.
323. Kean LS, Singh K, Blazar BR, Larsen CP. Nonhuman primate transplant models finally evolve: detailed immunogenetic analysis creates new models and strengthens the old. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(4):812-9. doi: 10.1111/j.1600-6143.2011.03873.x. PubMed PMID: 22177005; PMCID: PMC3482466.

324. Guinan EC, Boussiotis VA, Neuberg D, Brennan LL, Hirano N, Nadler LM, Gribben JG. Transplantation of anergic histoincompatible bone marrow allografts. The New England journal of medicine. 1999;340(22):1704-14. doi: 10.1056/NEJM199906033402202. PubMed PMID: 10352162.
325. Eastwood D, Findlay L, Poole S, Bird C, Wadhwa M, Moore M, Burns C, Thorpe R, Stebbings R. Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4+ effector memory T-cells. Br J Pharmacol. 2010;161(3):512-26. doi: 10.1111/j.1476-5381.2010.00922.x. PubMed PMID: 20880392; PMCID: PMC2990151.
326. Pallardy M, Hunig T. Primate testing of TGN1412: right target, wrong cell. Br J Pharmacol. 2010;161(3):509-11. doi: 10.1111/j.1476-5381.2010.00925.x. PubMed PMID: 20880391; PMCID: PMC2990150.
327. Pitcher CJ, Hagen SI, Walker JM, Lum R, Mitchell BL, Maino VC, Axthelm MK, Picker LJ. Development and homeostasis of T cell memory in rhesus macaque. Journal of immunology. 2002;168(1):29-43. PubMed PMID: 11751943.
328. Poirier N, Mary C, Le Bas-Bernardet S, Daguin V, Belarif L, Chevalier M, Hervouet J, Minault D, Ville S, Charpy V, Blancho G, Vanhove B. Advantages of Papio anubis for preclinical testing of immunotoxicity of candidate therapeutic antagonist antibodies targeting CD28. mAbs. 2014;6(3):697-707. doi: 10.4161/mabs.28375. PubMed PMID: 24598534; PMCID: PMC4011914.
329. Kenyon NS, Chatzipetrou M, Masetti M, Ranuncoli A, Oliveira M, Wagner JL, Kirk AD, Harlan DM, Burkly LC, Ricordi C. Long-term survival and function of intrahepatic islet allografts in rhesus monkeys treated with humanized anti-CD154. Proceedings of the National Academy of Sciences of the United States of America. 1999;96(14):8132-7. PubMed PMID: 10393960; PMCID: PMC22200.
330. Kawai T, Cosimi AB, Colvin RB, Powelson J, Eason J, Kozlowski T, Sykes M, Monroy R, Tanaka M, Sachs DH. Mixed allogeneic chimerism and renal allograft tolerance in cynomolgus monkeys. Transplantation. 1995;59(2):256-62. PubMed PMID: 7839449.
331. Kimikawa M, Sachs DH, Colvin RB, Bartholomew A, Kawai T, Cosimi AB. Modifications of the conditioning regimen for achieving mixed chimerism and donor-specific tolerance in cynomolgus monkeys. Transplantation. 1997;64(5):709-16. PubMed PMID: 9311707.
332. Boumpas DT, Furie R, Manzi S, Illei GG, Wallace DJ, Balow JE, Vaishnaw A, Group BGLNT. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum. 2003;48(3):719-27. doi: 10.1002/art.10856. PubMed PMID: 12632425.
333. Johnson ZP, Eady RD, Ahmad SF, Agravat S, Morris T, Else J, Lank SM, Wiseman RW, O'Connor DH, Penedo MC, Larsen CP, Kean LS. Immunogenetic Management Software: a new tool for visualization and analysis of complex immunogenetic datasets. Immunogenetics. 2012;64(4):329-36. Epub 2011/11/15. doi: 10.1007/s00251-011-0587-8. PubMed PMID: 22080300; PMCID: 3514553.
334. Wiseman RW, Karl JA, Bimber BN, O'Leary CE, Lank SM, Tuscher JJ, Detmer AM, Bouffard P, Levenkova N, Turcotte CL, Szekeres E, Jr., Wright C, Harkins T, O'Connor DH. Major histocompatibility complex genotyping with massively parallel pyrosequencing. Nature medicine. 2009;15(11):1322-6. doi: 10.1038/nm.2038. PubMed PMID: 19820716; PMCID: PMC2824247.
335. Zimin AV, Cornish AS, Maudhoo MD, Gibbs RM, Zhang X, Pandey S, Meehan DT, Wipfler K, Bosinger SE, Johnson ZP, Tharp GK, Marcais G, Roberts M, Ferguson B, Fox HS, Treangen T, Salzberg SL, Yorke JA, Norgren RB, Jr. A new rhesus macaque

assembly and annotation for next-generation sequencing analyses. Biol Direct. 2014;9(1):20. doi: 10.1186/1745-6150-9-20. PubMed PMID: 25319552; PMCID: PMC4214606.
336. Furlan SN, Watkins B, Tkachev V, Cooley S, Panoskaltsis-Mortari A, Betz K, Brown M, Hunt DJ, Schell JB, Zeleski K, Yu A, Giver C, Waller E, Miller JS, Blazar BR, Kean LS. Systems analysis uncovers inflammatory Th/Tc17-driven modules during acute GVHD in monkey and man. Blood. 2016. doi: 10.1182/blood-2016-07-726547. PubMed PMID: 27758873.
337. Furlan SN, Watkins B, Tkachev V, Flynn R, Cooley S, Ramakrishnan S, Singh K, Giver C, Hamby K, Stempora L, Garrett A, Chen J, Betz KM, Ziegler CG, Tharp GK, Bosinger SE, Promislow DE, Miller JS, Waller EK, Blazar BR, Kean LS. Transcriptome analysis of GVHD reveals aurora kinase A as a targetable pathway for disease prevention. Science translational medicine. 2015;7(315):315ra191. doi: 10.1126/scitranslmed.aad3231. PubMed PMID: 26606970; PMCID: PMC4876606.
338. Billingham RE, Brent L, Medawar PB. Actively acquired tolerance of foreign cells. Nature. 1953;172(4379):603-6. PubMed PMID: 13099277.