[Frontiers in Bioscience 14, 4173-4188, January 1, 2009]

CD137, implications in immunity and potential for therapy

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1. ABSTRACT

CD137 is a member of the TNF receptor family and a potent T cell costimulatory molecule. Crosslinking of CD137 on activated T cells has shown promise in enhancing anti-tumor immune responses in murine models, and agonistic anti-CD137 antibodies are currently being tested in phase I clinical trials. Surprisingly, these very same agonistic anti-CD137 antibodies have also been found to ameliorate autoimmune disease under certain circumstances. At the current state of knowledge these circumstances cannot be clearly defined. Therefore, anti-CD137 antibodies in man will need to be used with caution. CD137 ligand is expressed by antigen presenting cells. Antagonistic anti-CD137 ligand antibodies have shown efficacy in dampening disease in murine autoimmune models. A similar effect would be expected from antagonistic anti-CD137 antibodies, soluble CD137, or any other compound interfering with CD137 / CD137 ligand interaction. CD137 ligand is expressed as a transmembrane protein on the cell surface and it too can transmit signals into antigen presenting cells. Agonistic anti-CD137 ligand antibodies or a recombinant CD137 protein could stimulate the activity of antigen presenting cells.

2. INTRODUCTION

CD137 (4-1BB, *induced by lymphocyte activation* (ILA), TNFRSF9) and its ligand (CD137 ligand, 4-1BB ligand, TNFSF9) are members of the tumor necrosis factor (TNF) receptor and TNF superfamilies, respectively. Both molecules are expressed on the surfaces of a variety of leukocytes and non-immune cells as transmembrane proteins, and both proteins can transduce signals into the cells they are expressed on, a process referred to as bidirectional signal transduction.

A complex multitude of immunoregulatory activities has been identified for the CD137 receptor/ligand system (Figure 1). Crosslinking of CD137 on activated T cells enhances proliferation, IL-2 secretion, cell survival, cytolytic activity and the immunological memory. CD137 ligand signaling also enhances natural killer (NK) cell activity, leading to a general increase in the strength of an immune response, thereby enabling rejection of tumors in murine models (1). Under certain, poorly understood circumstances CD137 signaling may also inhibit T cell responses, in particular $CD4^+$ T cell-mediated functions (2). Reverse signaling, i.e. signal transduction through CD137

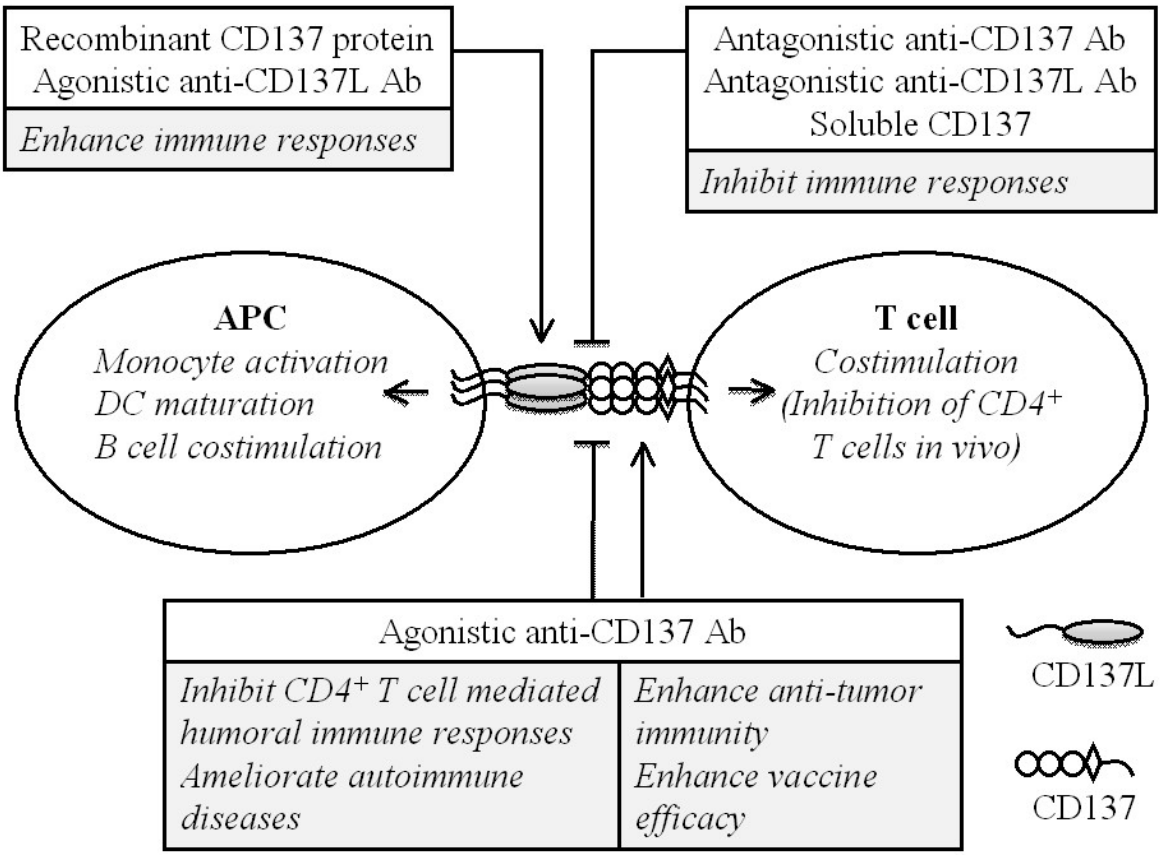

Figure 1. Schematic representation of proteins and their potential therapeutic applications involved in CD137/CD137 ligand bidirectional signaling. APC: antigen presenting cell, DC: dendritic cell, CD137L: CD137 ligand, Ab: antibody. Arrow: stimulation, blocking line: inhibition.

ligand activates monocytes, resulting in cytokine secretion, prolonged survival and migration. Further, it costimulates proliferation and immunoglobulin secretion of B cells, and it induces dendritic cell (DC) maturation (3). In T cells the CD137 ligand signal has been found in some situations to induce apoptosis and in other situations cell activation (4, 5). These many activities of CD137 provide opportunities for various therapeutic manipulations. However, the diversity of CD137 or CD137 ligand activities, and the context dependency of these activities entail the danger of harmful side effects. This review explores potential therapeutic intervention points using reagents targeting CD137 or CD137 ligand, and aims to assess benefits and risks associated with the different options.

3. BIOLOGY OF THE CD137 RECEPTOR / LIGAND SYSTEM

3.1. Expression of CD137

CD137, was first identified in the murine system in a screen for receptors on concanavalin A-activated T cells (6) and designated 4-1BB. The human homologue was isolated independently from activated human T cells and termed originally *induced by lymphocyte activation (ILA)* (7).

Expression of CD137 is strictly activation dependent in primary cells. CD137 is not detectable on resting T cells. However, when T cells are activated, expression of CD137 is strongly induced on both $CD4^+$ and $CD8^+$ T cells (8-10). Other immune cells that express CD137 include monocytes, NK cells, DC, follicular dendritic cells (FDC) and regulatory T cells (Treg) (11-16). Expression of CD137 is not restricted in immune cells. Chondrocytes, neurons, astrocytes, microglia and endothelial cells can also express CD137 on their surface (17-21). In addition, CD137 could be related to diseases such as cancer as expression of CD137 has been reported in osteosarcoma (22).

CD137 is a type-I transmembrane protein which belongs to the TNF receptor superfamily. The gene of murine CD137 is located on mouse chromosome 4. CD137 is made up of eight exons and seven introns. The nucleotide sequence of CD137 contains a single reading frame that encodes a polypeptide of 256 amino acids (aa) with a calculated molecular weight of 27 kDa (23). The first 23 aa constitute a signal peptide followed by a 63 aa extracellular domain. Amino acids 186-211 constitute the hydrophobic transmembrane domain which lies in exon 7. The remaining 45 aa form the cytoplasmic domain which is necessary for signal transduction. Human CD137 is located

on chromosome 1p36 (24). It contains 255 aa and has a predicted molecular weight of 27 kDa. There is 60% amino acid identity between human and murine CD137, including five conserved regions in the cytoplasmic domain, indicating that they may be important for CD137 functions.

3.2. Expression of CD137 ligand

The ligand of CD137, CD137 ligand is a type-II transmembrane glycoprotein consisting of 254 aa in man and 309 aa in mouse (25, 26). CD137 ligand is expressed mainly on antigen presenting cells (APCs), including B cells, DC and monocytes/macrophages. Human and murine transformed B cells express CD137 ligand protein constitutively while activation may be required for primary B cells (27-30). CD137 ligand is also expressed constitutively on peripheral monocytes and monocyte/macrophage cell lines (13, 30-32). In DC, CD137 ligand is expressed at low levels in both murine and human system. However, it can be enhanced by proinflammatory stimuli, including IL-1, CD40 ligand, LPS and double stranded RNA (13, 32-34).

Besides APCs, CD137 ligand is also present on murine and human T cell lines while the expression of CD137 ligand in murine and human primary T cells was either not detectable or only at low levels (5, 13, 25, 28, 30, 35). A number of human carcinoma cell lines derived from the colon, lung, breast, ovary and prostate have also been reported to express CD137 ligand (35).

3.3. Costimulatory activities of CD137

CD137 has been identified as a potent T cell costimulatory molecule. Upon signals from the T cell receptor (TCR) and CD28, CD137 expression is upregulated on the T cell surface. Interaction of CD137 with its ligand or agonistic anti-CD137 antibodies induces proliferation and cytokine production of activated T cells (10, 25, 26, 36). Enhanced cell survival has also been observed as engagement of CD137 by CD137 ligand leads to inhibition of activation-induced cell death (AICD), which correlates with the upregulation of anti-apoptotic protein Bcl-xL (37, 38).

The costimulation of T cells through CD137 is CD28-independent but can synergize with CD28. CD137 ligand-expressing APCs were able to stimulate T cells purified from $CD28^{-/-}$ mice, suggesting that CD137 provides costimulatory signals to T cells independently from CD28 signaling (29). Like murine CD137 ligand, human CD137 ligand can also stimulate CD28-deficient T cells, resulting in cell division, inflammatory cytokine production, enhancement of cytolytic effector function, as well as the upregulation of anti-apoptotic gene expression (39). Other studies have shown that CD28 and CD137 synergize in the induction of IL-2 by T cells, and a recombinant CTLA-Ig protein partially blocked CD137 ligand-dependent IL-2 production (40). In addition, artificial APC coexpressing ligands for CD28 and CD137 synergistically enhanced T cell proliferation and survival, compared with CD28 alone (41). Taken together, these findings indicate that CD137 ligand can promote CD28-independent T cell activation, but the combination of CD28 and CD137-mediated costimulation is more effective than either signal alone.

Consistent with the *in vitro* findings, studies from murine models of tumors, viral infection, graft versus host disease (GVHD) and transplantation have clearly suggested a potent costimulatory role of CD137 on $CD8^+$ T cells. In an *in vivo* adoptive transfer model, blocking of CD137 by a CD137-Fc fusion protein significantly reduced $CD8^+$ T cell clonal expansion. This was due to a reduction in T cell division and enhanced apoptosis of $CD8^+$ T cells (42). Administration of anti-CD137 antibodies *in vivo* promoted rejection of cardiac and skin allografts in a GVHD model by amplifying the generation of H2d-specific cytotoxic T cells (43). The same antibody was able to prevent tumor progression and was even effective in eradicating established tumors by the induction of potent $CD8^+$ T cell-mediated immune responses (44).

3.4. CD137 as a coinhibitory molecule

In contrast to the costimulatory effects of CD137 *in vitro* and *in vivo*, several recent studies show that a CD137 agonist might also be inhibitory to some immune responses *in vivo*. As mentioned earlier, administration of anti-CD137 antibodies into tumor-bearing or allografted mice induced a potent $CD8^+$ T cell immunity. However, when the same antibody was injected into immunized mice, it suppressed development of T-dependent humoral immunity (Table 1). In other words, mice injected with anti-CD137 antibody were unable to generate a $CD4^+$ T cell-dependent humoral immune response to the T-dependent antigens used for immunization (45).

The inhibitory effect of the anti-CD137 antibody was also observed in mice with autoimmune diseases. In NZB/NZW lupus-prone mice, anti-CD137 treatment has been shown to be effective in controlling the development of systemic lupus erythematosus (SLE). Administration of anti-CD137 antibodies inhibited production of anti-DNA antibodies. Mice in the treatment group no longer maintained pathogenic IgG autoantibody production and achieved an extension of lifespan from 10 months to more than 2 years (46). Anti-CD137 antibodies can also affect the development of collagen-induced arthritis (CIA). Injection of anti-CD137 antibody into DBA/1J mice immunized with bovine collagen II has been shown to prevent disease development and to inhibit humoral immune response against collagen II. Furthermore, it induced a protective memory in the mice, enabling resistance to subsequent challenges with the same antigen (47). Similar results were obtained by other groups in the CIA model and in a model for experimental autoimmune uveoretinitis (EAU), where administration of anti-CD137 antibody inhibited disease development and reduced even established disease. In both models a massive expansion of $CD11c^+CD8^+$ cells and accumulation of indoleamine 2,3-dioxygenase (IDO), which is a downstream effector of IFN-γ were found. Addition of either anti-IFN-γ or 1-methyltryptophan, a inhibitor of IDO, reversed the inhibitory effect of anti-CD137 on disease activity (48, 49).

Table 1. Effects of CD137 and CD137 ligand signaling in autoimmune diseases

Disease	Experimental Model	Observations	Impact on disease	Ref.
HSK	HSV-1 infection of CD137-deficient mice	Decreased recruitment of infiltrating T cells to infected corneas due to decreased CD62L expression on T cells Downregulation of IL-6 and IFN-γ production	Amelioration	81
RA	Administration of anti-CD137 antibodies to CIA model	Inhibition of humoral immune response against collagen II	Amelioration	47,48
Lacrimal gland disease	CD137-deficient lpr mice	Increased infiltration of pathogenic $CD4^+$ T cells into lacrimal gland Increased IL-4 production	Exacerbation	82
SLE	CD137-deficient lpr mice	Increased proliferation of $CD4^+$ T cells, resulting in Increased activation of auto-reactive B cells Increased serum autoantibody titres Increased proportion of double-negative T cells in the spleen	Exacerbation	84
SLE	Administration of anti-CD137 antibodies to NZB/NZW lupus-prone mice	Decreased production of anti-DNA antibodies	Amelioration	45
Type I diabetes	NOD mice containing allele for CD137 derived from diabetes resistant strain	Increased biological activity of CD137, as compared to regular NOD mice	Amelioration	85
EAU	Administration of anti-CD137 antibodies to B10RIII mice immunized with receptor retinoid binding protein	Inhibition of $CD4^+$ T cell responses	Amelioration	49
cGVHD	Administration of anti-CD137 antibodies to mouse parent-into-F_1 model for cGVHD	Abrogated immune complex deposition in kidney, prevented glomerulonephritis in the recipients, increased survival, ameliorated advanced cGVHD Blocked the production of anti-DNA IgG and total IgE	Amelioration	103

The effect of CD137 signaling on another subset of T cells, the $CD4^+CD25^+$ Treg, has not been resolved as contradictory data have been obtained by different groups. CD137 was expressed constitutively on freshly isolated $CD4^+CD25^+$ cells at low levels and its expression could be upregulated upon activation. Addition of an anti-CD137 antibody *in vitro* abrogated $CD4^+CD25^+$ cell-induced suppression on $CD4^+CD25^-$ cells. The same antibody was also effective in reversing a Treg-induced delay of GVHD *in vivo*, resulting in accelerated disease progression and death. The same results could be obtained when using $CD4^+CD25^-$ cells from CD137-deficient mice, indicating a direct role of CD137 in the regulation of Treg cell functions (14). Consistent with these findings, Morris *et al.* found that CD137 signaling interferes with $CD4^+CD25^+$ Treg-mediated tolerance in a murine experimental autoimmune thyroiditis model (50). In sharp contrast to the above findings showing an inhibitory effect of CD137 on $CD4^+CD25^+$ T cells, Zheng *et al.* recently reported that the CD137 signal was strongly costimulatory for $CD4^+CD25^+$ T cells, both *in vitro* and *in vivo*. Furthermore, the CD137-expanded $CD4^+CD25^+$ T cells were functional, as they remained suppressive to other T cells in coculture (51).

Several theories have been proposed to explain the unexpected finding that the same anti-CD137 antibody apparently can enhance anti-tumor, anti-transplant and anti-viral immune responses, and yet in other cases inhibit autoimmune responses. There is evidence that $CD4^+$ and $CD8^+$ T cells respond differently to CD137 costimulation. $CD8^+$ but not $CD4^+$ T cells responses generated against lymphocytic choriomeningitis virus (LCMV) and influenza virus are diminished in CD137 ligand-deficient mice (52, 53). Thus, one theory claims that CD137 agonists enhance $CD8^+$ T cell activity while their effect on $CD4^+$ T cells is or at least can be inhibitory.

Stimulation by CD137 agonists *in vivo* enhanced the initial proliferation of $CD4^+$ T cells, but it subsequently accelerated their death (54). Induction of IDO leading to apoptosis of antigen-specific $CD4^+$ T cells may be part of the underlying mechanism. IDO is a tryptophan-catabolizing enzyme expressed by macrophages and other cell types. Expression of IDO induces depletion of tryptophan and production of tryptophan metabolites such as kynurenine, which may kill antigen-activated $CD4^+$ T cells, leading to inhibition of autoimmune disease (55). In both, the CIA and EAU models, administration of anti-CD137 antibodies induced antigen-dependent clonal expansion of $CD11c^+CD8^+$ T cells that produce IFN-γ, resulting in an accumulation of a high level of IDO in DC and macrophages. Both, anti-IFN-γ and 1-MT reversed the anti-CD137 antibody effect, indicating that CD137 induced the suppression of antigen-specific $CD4^+$ T cells in an IDO-dependent manner (48). An alternative mechanism that could explain the suppressive effects of CD137 agonists on $CD4^+$ T cells would be the indirect interaction between anti-CD137 antibodies and $CD4^+$ T cells. As CD137 is expressed by a variety of cell types including DC and NK cells *in vivo*, it is possible that CD137 stimulation of these cells contributes to its suppressive effects on $CD4^+$ or $CD4^+CD25^+$ T cells.

If the theory outlined above is correct CD137 agonists would ameliorate diseases that are mainly mediated by $CD4^+$ T cells while they would worsen autoimmune conditions that are mediated by $CD8^+$ T cells. Accordingly, the therapeutic use of CD137 agonists would be beneficial for treatment of autoimmune diseases in case they are caused by $CD4^+$ T cells, and for cancer, if the anti-cancer immune response is mediated by $CD8^+$ T cells.

Whether T cells become activated or inhibited by CD137 agonists may depend on the biological context of the stimulation and the conditions, among them time of stimulation. Administration of anti-CD137 antibody one day after LCMV or influenza infection led to a breakdown of antiviral immunity and decreased survival of the mice while the antibody enhanced antiviral immunity and survival when it was given after day three (56). Whether

timing is critical for the anti-tumor and anti-viral effects of CD137 agonists or is specific to this infection model is not known. Interestingly, in this infection model not only the $CD4^+$ T cells but also the $CD8^+$ T cells that were eliminated following an early administration of anti-CD137 antibody (56).

3.5. Reverse signaling through CD137 ligand

The ligands of the TNF receptor family members, the members of the TNF family, are also expressed as cell surface molecules and many of them can also transduce signals into the cells they are expressed on. In such cases the receptor/ligand systems mediate bidirectional signaling and both molecules function simultaneously as ligands and as receptors (57). Reverse signaling refers to signal transduction of the so-called ligands which carry the name 'ligand' for historical rather than functional reasons. Bidirectional signaling is rare but not unique to the TNF receptor/ligand family members as it also occurs in the ephrin/Eph receptor family and also for B7-CD28 (58, 59).

Signal transduction through CD137 ligand is one of the best studied cases of reverse signal transduction (3). Best known are the effects of reverse CD137 ligand signaling in APCs. In monocytes CD137 ligand signaling induces activation and migration, prolongs survival and leads to cell growth (20, 31, 60-63). CD137 ligand associates with CD14 and possibly other Toll like receptors, and synergistically regulates TNF release (64).

In DC reverse signaling enhances maturation of immature DC, leading to higher expression of CD80, CD86, MHC class II and IL-12, migration of DC and enhanced capacity to stimulate T cell responses (32, 33, 65).

Little is known of the effects of reverse CD137 signaling in B cells except for costimulation of proliferation and immunoglobulin secretion (16). Interestingly, CD137 is expressed on FDC in germinal centers where B cells migrate after first antigen contact and where they undergo affinity maturation. FDC-expressed CD137 may participate in costimulation of B cells that bind more tightly to FDC-displayed antigen, once they have rearranged their B cell receptors to higher affinity ones (15, 16).

Reverse signaling also takes place in T cells, and contrary to the situation in APC, the CD137 ligand signal has been shown to inhibit proliferation and to induce apoptosis in human T cells (4, 31, 66). A recent study however, found that CD137 ligand signaling in murine T cells induces IFN-γ release, contributing to immune de-viation and an inhibition of Th2-mediated allergic lung inflammation (5).

In monocytes part of the signaling pathway initiated by CD137 ligand has been elucidated. Protein tyrosine kinases, p38 mitogen activated protein kinase, extracellular signal-regulated kinase 1,2, MAP/ERK kinase, phosphoinositide-3-kinase and protein kinase A are involved, demonstrating that the exotic concept of reverse signaling relies on very conventional molecules (67).

3.6. Soluble CD137

A naturally occurring and endogenous inhibitor of CD137 activities is soluble CD137 (sCD137). sCD137 was first identified in 1995 when Serateh *et al.* found two isoforms of CD137 mRNA from mouse splenocytes and thymocytes. Both isoforms were expressed in an activation-dependent manner and the smaller isoform was a mRNA splice variant lacking the exon encoding the transmembrane domain (68). Human sCD137 protein was also identified and shown to be released by activated lymphocytes. Like murine sCD137, human sCD137 is generated by differential splicing and three mRNA variants have been identified (69). Expression of sCD137 does not strictly correlate with expression of membrane-bound CD137. A study using human peripheral blood mononuclear cells showed that levels of sCD137 correlate with AICD, indicating that sCD137 may provide a negative control mechanism for immune responses (70). Indeed, *in vitro* studies have shown that sCD137 antagonizes the activity of mCD137 and abolishes CD137-mediated immunological activities. In murine splenocytes, soluble recombinant CD137 protein could significantly inhibit T cell proliferation and IL-2 production in a culture of anti-CD3 stimulated splenocytes and in a primary mixed leukocyte reaction (36, 71).

Interestingly, elevated sCD137 levels have been reported in sera of patients with various hematological malignancies and autoimmune diseases, such as chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), multiple sclerosis, SLE and Behcet's disease (72-75).

The fact that expression of sCD137 does not correlate with proliferation, but rather with AICD indicates that sCD137 could be indicative of a specific immune activation stage. The elevated levels of sCD137 in diseases implicates its participation in a negative feedback control of the ongoing immune responses (69). It could be that sCD137 antagonizes CD137 by either competitive binding to CD137 ligand or by inserting into pre-existing CD137 trimers on the cell surface. Because of the bidirectional signaling of CD137/CD137 ligand interaction, the inhibitory effect of sCD137 to CD137 could block the signal into both T lymphocyte and APC simultaneously (3). In that case, sCD137 may be helpful to treat autoimmune diseases by disrupting autoreactive lymphocyte activation.

4. INVOLVEMENT OF THE CD137 RECEPTOR / LIGAND SYSTEM IN DISEASE

4.1. Involvement of CD137 in cancer

CD137 expression has been reported in several cancers. Human carcinoma cell lines derived from osteosarcoma (22) and lung cancer (76) have been shown to express CD137 constitutively. In the case of lung cancer, CD137 has also been detected in tumor tissue samples, but not in corresponding controls from healthy tissues (76).

In a number of solid tumors, CD137 was not detected on the cancerous cells, but rather, on the cells of the blood vessel walls in these tumors. A study involving immunohistochemical staining of frozen tissue sections

found that 32% of malignant and 14% of benign tumor tissues contained blood vessels that stained positive for CD137 (77). In contrast, none of the paired normal tissues contained blood vessels that expressed CD137. Tumor tissues containing CD137-positive blood vessels included fibrosarcoma, nephroblastoma and ameloblastoma. A possible reason for the presence of CD137 on tumor blood vessels may be an increased ability to recruit monocytes to the tumor site (20). Monocytes can subsequently differentiate into macrophages, and as tumor associated macrophages can promote tumor angiogenesis and support tumor growth and metastasis (78).

In addition to its membrane-bound counterpart, sCD137 has also been associated with several cancers. Sera from patients with various haematological malignancies had significantly higher sCD137 concentrations than those from healthy donors (72). For example, 22.6% of sera samples from non-Hodgkin's lymphoma (NHL) were sCD137-positive. In particular, samples from patients with CLL displayed the strongest association with elevated sCD137 levels, with 78.6% of such samples being sCD137-positive.

The reasons for enhanced sCD137 serum concentrations in leukemia and lymphoma patients remain unclear. While the increased sCD137 levels may simply indicate the presence of an active anti-tumor immune response, it is also possible that sCD137 is produced by tumor cells to quench an anti-tumor immune response. Other questions that remain to be answered include why sCD137 is present in a subset of patients but not in all, and whether sCD137 levels can be utilized as a prognostic or diagnostic marker for hematological cancers.

4.2. Involvement of CD137 ligand in cancer

Unlike CD137, the presence of CD137 ligand has only been reported in cell lines that originated from colon, lung, breast, ovarian or prostate cancer (35), but not in actual tumor tissues. Therefore, in the absence of such evidence, the association between CD137 ligand and cancer remains to be substantiated.

However, enhanced levels of sCD137 ligand are clearly correlated with a number of hematological malignancies. A comparison between sera samples from patients with NHL, myelodysplastic syndrome and acute myelogenous leukemia (AML), and from healthy individuals revealed that the former contained significantly higher sCD137 ligand concentrations (79). Amongst them, the highest levels of sCD137 ligand were detected in sera from AML patients. It was proposed that leukemic cells might release CD137 ligand from their surfaces in order to limit the costimulation of host T lymphocytes, thus allowing the cancer cells to evade local immune surveillance. This would result in increased amounts of sCD137 ligand being present in the serum. In addition, the authors also proposed that the release of sCD137 ligand to distal sites might be involved in some of the pathophysiology of the disease, although further study is required to validate this point.

In a subsequent study, it was found that serum levels of sCD137 ligand correlated with unfavorable subtypes in AML, while such a correlation was not observed in NHL (80). In the case of AML, higher sCD137 levels were also associated with shorter disease progression-free survival times indicating that serum levels of sCD137 ligand might be an additional prognostic marker to estimate the risk of disease progression in the case of AML.

4.3. Disruption of CD137/CD137 ligand signaling prevents autoimmune diseases

The disruption of CD137/CD137 ligand signaling ameliorates the severity of certain autoimmune diseases (Table 1). For example, herpetic stromal keratitis (HSK) is caused by herpes simplex virus (HSV)-1 infection, which results in the destruction of corneal tissue by T cells (81). Complications that can develop from the infection include glaucoma, corneal melting and irreversible corneal scarring, leading to blindness. To determine whether CD137 plays a role in the pathogenesis of HSK, the authors infected corneas of $CD137^{-/-}$ and wild type mice with HSV-1. As compared to their wild-type littermates, infected CD137-deficient mice displayed significantly lower disease incidence and severity in HSK. Similar results were obtained when infected wild-type mice were injected with an antagonistic anti-CD137 ligand antibody compared to control IgG, thus verifying that the above observations were indeed due to the absence of CD137 signaling.

Infected $CD137^{-/-}$ mice also produced lower levels of cytokines such as IL-6 and IFN-γ that are involved in the pathogenesis of HSK. An analysis of the T cells in infected wild-type mice showed that CD137 was expressed on approximately 65% of the infiltrating T cells in the cornea, but not on peripheral T cells. This indicates that CD137 plays a role in the pathogenesis of HSK. In addition, infiltrating T cells in HSV-1-infected $CD137^{-/-}$ mice expressed less CD62L (L-selectin) than their wild-type counterparts. CD62L is constitutively expressed on many leukocytes, and facilitates their recruitment to sites of injury and inflammation. Taking the above observations together, the authors suggested that the lack of CD137/CD137 ligand signaling might have resulted in the downregulation of CD62L on T cells. This in turn impaired the recruitment of T cells to the HSV-1-infected corneas, leading to the amelioration of disease severity. Based on these findings, the disruption of CD137/CD137 ligand signaling might have clinical applications in the treatment of HSK.

The same group also studied the role of CD137 in RA, which is a systemic inflammatory disease characterized by a massive recruitment of immune cells to the joint (48). These cells secrete various catabolic enzymes and cytokines, which cause the destruction of cartilage and bone. Using the CIA model in DBA/1 mice, the authors found that the administration of anti-CD137 ligand antibodies at the time of immunization resulted in a milder disease as compared to treatment with control IgG. This was accompanied by an inhibition of IL-6 production in the joint, anti-collagen antibody production and $CD4^{+}$ T cell

responses, indicating that the disruption of CD137/CD137 ligand signaling inhibits the inflammatory process in CIA.

4.4. Disruption of CD137/CD137 ligand signaling leads to increased disease severity

In contrast, the disruption of CD137/CD137 ligand signaling increased the severity of certain diseases (Table 1). In a study by Vinay *et al.,* (2007) the MRL/lympho-proliferation (lpr) mouse model was used to investigate the role of CD137 signaling in lacrimal gland disease (82). In addition to a SLE-like disease phenotype, lpr mice also develop lacrimal gland disease, which resembles the Sjogren syndrome in humans. Given that $CD4^+$ T cells play an important role in the pathogenesis of ocular diseases, and that $CD137^{-/-}$ mice display enhanced $CD4^+$ T cell proliferation (83), the authors hypothesized that $CD137^{-/-}$ mice on a lpr background should exhibit increased disease severity as compared to wild-type lpr littermates.

Indeed, it was observed that lpr/$CD137^{-/-}$ mice exhibited increased infiltration of $CD4^+$ T cells in their lacrimal glands, and consequently, increased disease severity. There appeared also to be a bias towards Th2 responses in these mice, as evidenced by the upregulation of IL-4 production in the infiltrating $CD4^+$ T cells. Therefore, the authors concluded that the absence of endogenous CD137 in lpr mice exacerbated lacrimal gland disease by promoting the infiltration of pathogenic $CD4^+$ T cells into the lacrimal glands, and by upregulating the secretion of IL-4.

The same group also studied the role of endogenous CD137 in the development of SLE (84). In SLE patients the immune system is in a chronic state of activation and B cells produce high levels of pathogenic autoantibodies against nuclear antigens such as DNA and nucleosomes resulting in severe tissue damage. These autoreactive B cells are activated by $CD4^+$ T cells, the proliferation of which is enhanced by the absence of CD137/CD137 ligand signaling. In comparison with their wild-type littermates, lpr/$CD137^{-/-}$ mice exhibited signs of increased disease severity, including more severe skin lesions, higher serum autoantibody titres and increased renal damage. CD137-deficient lpr mice also had an increased proportion of double negative T cells ($CD3^+CD4^-CD8^-$) in spleen and enhanced B cell function.

CD137 is also likely to play a role in the development of Type I diabetes in non-obese diabetic (NOD) mice (85). In a process controlled by insulin-dependent diabetes (Idd) genes, approximately 80% of female NOD mice acquire diabetes spontaneously. A diabetes-resistant B10 strain, in which only approximately 5% of females develop diabetes, could be derived from the parental NOD strain. On the mouse chromosome 4, three distinct regions (Idd9.1, Idd9.2 and Idd9.3) have been shown to affect Type I diabetes, and in particular, a B10-derived resistance allele at Idd9.3 alone can provide approximately 50% resistance to diabetes. Since CD137 is one of the genes that localizes to Idd9.3, it was hypothesized that CD137 might play a role in the development of diabetes.

The study by Cannons *et al.,* (2005) suggests that this might be the case (85). First of all, CD137 in mice containing a B10-derived allele at Idd9.3 (NOD.B10 Idd9.3) differs at three aa positions from CD137 the parental NOD mice. These genetic changes result in T cells in the strain with the B10 allele (i.e. the diabetes-resistant strain) having higher proliferation rates and IL-2 production when stimulated with anti-CD3 and CD137 ligand. This effect is specific to CD137-mediated signaling, since there was no difference between NOD and NOD.B10 Idd9.3 mice in their response to anti-CD3 and anti-CD28 stimulation. This functional hyperactivity of T cells in NOD.B10 Idd9.3 mice was not due to different CD137 expression levels. This suggests that the three aa substitutions make CD137 biologically more active in the diabetes-resistant strain, and consequently, that CD137 signaling may normally limit immune responses that contribute to the development of diabetes. As in the case of lacrimal gland disease and SLE, the disruption of CD137/CD137 ligand signaling is likely to exacerbate the severity of Type I diabetes.

4.5. sCD137 and sCD137 ligand in autoimmune diseases

Several groups have reported that sCD137 and sCD137 ligand levels are associated with certain autoimmune diseases. In the case of MS it was observed that patients with clinically active MS had higher concentrations of sCD137 in their sera than healthy individuals, or patients with clinically stable MS, or inflammatory and non-inflammatory neurodisorders (73, 74). The enhanced sCD137 levels observed in patients with clinically active MS do not merely reflect a state of heightened immune activation since there was no corresponding increase in the amounts of cytokines (IL-2, TNF-α) and immunoglobulins (IgG and IgM), which were used as markers of cellular and humoral responses, respectively. Instead, Sharief *et al.,* (2002) speculated that sCD137 might play a role in the regulation of lymphocyte function in clinically active MS (73, 74).

Besides sCD137, plasma sCD137 ligand levels were also shown to be elevated in patients with MS (74, 75). However, causes and effects of enhanced sCD137 and sCD137 ligand remain yet to be determined.

Patients with RA also displayed enhanced levels of sCD137 (69, 74) and sCD137 ligand (74) in their sera. Serum levels of both sCD137 and sCD137 ligand correlated with serological parameters such as total serum lactate rheumatoid factor and erythrosedimentation rate which were indicative of RA severity. Patients in an inactive stage of RA after receiving immunosuppressive therapy exhibited decreased serum levels of sCD137 and sCD137 ligand, as compared to the onset of disease. While there is clearly a link between sCD137 and sCD137 ligand levels and RA severity, the functional roles of the two soluble proteins in modulating disease progression remain unclear. Nevertheless, these findings indicate that serum levels of sCD137 and sCD137 ligand may be utilized as diagnostic markers to assess disease severity in RA (74). In addition to the two diseases mentioned above, elevated

levels of serum sCD137 and sCD137 ligand have also been observed in SLE and Behcet's disease (74).

4.6. CD137 signaling in IgE-mediated allergic responses

CD137 expression on eosinophils is associated with IgE-mediated allergic responses (86). Specifically, blood and tissue eosinophils from patients with IgE-mediated asthma and atopic dermatitis expressed CD137, whereas those from healthy individuals did not express CD137. In addition, eosinophils from patients with non-IgE-mediated asthma and idiopathic eosinophilia also did not express detectable levels of CD137. The difference in CD137 expression was due to factors secreted by T cells from patients with IgE-mediated asthma and atopic dermatitis. However, the authors were unable to identify which cytokine(s) was/were responsible for inducing CD137 in the eosinophils.

In CD137-expressing eosinophils, the engagement of CD137 by agonistic antibodies led to the abrogation of GM-CSF- and IL-5-mediated survival. That could be the reason for the higher eosinophil numbers in patients with non-IgE-mediated asthma and idiopathic eosinophilia where eosinophils do not express CD137, as opposed to patients with IgE-mediated asthma and atopic dermatitis. Nevertheless, the role of CD137 signaling in eosinophils under inflammatory conditions remains unclear and requires further investigation.

4.7. CD137 signaling in allergic airway disease

Studies have shown that CD137 signaling does modulate the progression of allergic airway diseases. However, its effects vary greatly depending on the disease model. When mice are sensitized with inactivated *Schistosoma mansoni* eggs followed by intranasal challenge with *S. mansoni*-soluble egg antigen they develop allergic airway inflammation. Treatment with agonistic anti-CD137 antibody during the sensitization process resulted in an amelioration of disease symptoms, as characterized by reductions in airway infiltration by T cells and eosinophils, Th2 cytokine production and reduced serum IgE levels, as well as a reduction of airway hyperresponsiveness in airways and lungs. These effects were attributed to reduced Th2 cell function caused by CD137 signaling, and would indicate a potential role for agonistic anti-CD137 antibodies in immunotherapy for allergic airway diseases.

However, the opposite, i.e. an exacerbation of disease activity by agonistic CD137 antibodies was found in a model of airway hyper-responsiveness (AHR) that was mediated by NKT cells. NKT cell activation was induced by the α-galactosylceramide (α-GalCer), a ligand for the TCR of NKT cells resulting in AHR and airway inflammation. CD137 was not expressed on resting NKT cells but was induced by α-GalCer (87). Administration of agonistic anti-CD137 antibodies costimulated NKT cell activity resulting in enhanced IL-4, IL-13 and IFN-γ levels in the bronchoalveolar lavage, and exacerbated AHR and inflammatory cell accumulation in this model.

In summary, the two studies show that much remains to be elucidated with regards to the role of CD137 in allergic airway diseases. Therefore, there is a need to exercise caution when developing anti-CD137 antibodies for therapeutic purposes.

5. POTENTIAL THERAPEUTIC APPLICATIONS OF TARGETING THE CD137 RECEPTOR / LIGAND SYSTEM

5.1. Agonistic anti-CD137 antibodies for enhancing immune responses

The potential usefulness of agonistic anti-CD137 for tumor immunotherapy became obvious with the discovery of CD137 activities. Indeed, enhancement of anti-tumor immune responses is the best characterized activity of CD137 (Figure 1). The efficacy of agonistic anti-CD137 antibodies has been demonstrated in a wide range of murine tumor models by a number of different labs (1, 88). Monoclonal anti-CD137 antibodies have been humanized and are currently being tested in phase I clinical trials (89, 90). No results have been reported so far. The mechanism of actions for immunostimulatory anti-CD137 antibodies is assumed to be T cell costimulation, in particular costimulation of $CD8^+$ T cells. While there is ample evidence supporting this view it may not be the only mechanism. CD137 is also expressed by NK cells and NK cell activity is essential at least in a mastocytoma model (12). Whether dependency on NK cell activity is a general feature of CD137 agonists is not known. Also, CD137 is expressed on DC and crosslinking of CD137 has been reported to enhance DC activity (13).

While crosslinking of CD137 on NK and DC potentially contributes to a therapeutic effect of agonistic anti-CD137 antibodies, it is not clear what effects crosslinking of CD137 on endothelial cells or FDC might have. For endothelial cells induction of intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 has been reported (21). Expression of CD137 on FDC has so far only been shown in man and therefore it is unknown whether potential beneficial or adverse effects of CD137 agonists on FDC are visible in the murine models (15, 16).

Besides agonistic anti-CD137 antibodies an aptamer activating CD137 has been developed and found to costimulate T cell activation and to mediate tumor rejection in mice (91).

CD137 agonists have been remarkably effective in murine tumor models, leading to the eradication of even established tumors. But the list of drug candidates that displayed impressive efficacy in murine models only to fail disappointingly in clinical trials is quite long. Combination therapy may be a solution. Indeed combining agonistic anti-CD137 antibodies with anti-CD134 antibodies resulted in stronger $CD8^+$ T cell responses and protected mice more efficiently from tumors (92-94). Further, the combination of agonistic anti-CD137 antibodies with anti-death receptor 5 and anti-CD40 antibodies resulted in a significantly enhanced anti-tumor effect compared to using anti-CD137 antibody alone (95). No studies have been published on the combination of anti-CD137 antibodies with chemotherapy.

Such a combination would need to be carefully balanced as chemotherapy reduces leukocyte activities while an anti-CD137 antibody effect relies on them.

Agonistic anti-CD137 antibodies have also been shown to enhance the efficacy of vaccines against influenza and poxvirus (96, 97). Inclusion of a CD137 ligand-expressing vector in a vaccine, or engineered expression of CD137 ligand on monocytes enhanced their ability to induce anti-HIV responses (98, 99). The adjuvant effect of the anti-CD137 antibody was restricted to the cellular response while the humoral response was not enhanced. These data suggest that CD137 agonists may be useful components in vaccines for preventing viral infections, and possibly in therapeutic vaccines.

While all these activities are very promising one needs to keep in mind that there are still significant gaps in our understanding of the CD137 biology. As mentioned in chapter 3.4, CD137 agonists are often potent costimulators of $CD8^+$ T cell activities, however, their effects on $CD4^+$ T cells are less clear. Crosslinking of CD137 on $CD4^+$ T cells can lead to induction of apoptosis and an inhibition of immune responses (2, 100, 101).

5.2. Agonistic anti-CD137 antibodies for inhibiting immune responses

That the very same antibody that can enhance anti-tumor and anti-pathogen immune responses should also be able to inhibit autoimmune responses sounds quite surprising. However, exactly that is what data indicate for agonistic CD137 antibodies (Figure 1). The above mentioned agonistic anti-CD137 antibodies have been shown to reduce CIA, SLE, EAU, allergic lung inflammation and inflammatory bowel disease in mice (chapter 3.4) (2). The opposite, i.e. an enhancement of autoreactivity would have been expected based on the results from the murine tumor models data.

The dichotomy of the activities of CD137 agonists is exemplified by GVHD. An agonistic anti-CD137 antibody has enhanced GVHD (43, 102), and has inhibited it in another case (103). It is hypothesized that these different activities may be due to the acute versus chronic nature of the GVHD in the different experimental models. When the anti-CD137 antibody ameliorated GVHD it was postulated that the underlying mechanism may have been the elimination of $CD4^+$ T cells by the antibody (103).

Another experimental system where CD137 agonists enhanced rather than ameliorated autoimmune disease was reported by Sytwu *et al.*, 2003 (104). Transgenic NOD mice overexpressing an agonistic anti-CD137 single chain variable fragment developed more severe diabetes and developed it earlier than the non-transgenic control animals and suffered from a higher mortality.

5.3. Cautionary notes

If CD137 agonists could indeed enhance protective and reduce harmful immune responses they would be most valuable drugs. But whether they have such a dual beneficial effect in patients is quite questionable. The activities of CD137 stimulation are hardly resolved and understood in experiments using inbred mice which have an identical genetic background, an almost identical immune system and are matched in terms of physiological states, ages, sex, etc. In a human patient population of diverse genetic and immunological background and different physiological and pathological conditions the effects of agonistic anti-CD137 antibodies are very difficult to predict.

The prevailing theory holds that CD137 agonists can be used for treatment of cancer and autoimmune diseases that are mainly mediated by $CD4^+$ T cells while CD137 agonists may worsen autoimmune conditions that are mediated by $CD8^+$ T cells. Consequently, the former can be treated while the latter ones cannot be treated by CD137 agonists. This distinction between 'treatable' $CD4^+$ T cell-mediated conditions and 'need-to-avoid' $CD8^+$ T cell-mediated conditions is even difficult to maintain in inbred experimental animals under highly controlled conditions. Whether it will be possible in a diverse human population that is subject to all kinds of environmental challenges which will stimulate $CD4^+$ as well as $CD8^+$ T cells remains to be seen. In addition, while the experimental animals have a comparatively homogeneous disease, the pathologies between patients can differ profoundly.

Although most evidence supports a costimulation of $CD8^+$ T cells by CD137 agonists and a potent effect in tumor immunotherapy, it is very challenging to predict under what conditions they will enhance or inhibit immune responses in patients.

5.4. Antagonistic anti-CD137 or anti-CD137 ligand antibodies for inhibiting immune responses

Antagonistic anti-CD137 or anti-CD137 ligand antibodies should be able to inhibit immune responses and therefore be of use in the treatment of autoimmune diseases (Figure 1). Antagonistic anti-CD137 antibodies have not yet been tested in animal models, but neutralization of CD137 ligand in a CIA model ameliorated disease (48). In this model, the anti-CD137 ligand antibody was less potent than an agonistic anti-CD137 antibody. But this higher potency may come at a price as agonistic anti-CD137 antibodies can enhance or inhibit immune responses as outlined above. Antagonistic anti-CD137 or anti-CD137 ligand antibodies would be expected to have only immunoinhibitory activities and should therefore be safer drugs. However, the scarcity of experimental data with anti-CD137 ligand antibodies makes predictions on their potential benefits difficult.

5.5. Recombinant CD137 protein or agonistic anti-CD137 ligand antibodies for enhancing immune responses

Since the CD137 receptor/ligand system has the capacity of bidirectional signaling, reagents that crosslink and thereby activate CD137 ligand are also able to regulate immune functions. So far, recombinant CD137 proteins and

anti-CD137 ligand antibodies have been used as CD137 ligand agonists (Figure 1).

Most studies have been done *in vitro*, therefore a prediction on how CD137 ligand agonists can be employed therapeutically can only be tentative at present (3). Best characterized are the effects of CD137 ligand signaling in APC, leading to monocyte activation (60-63), DC maturation (32, 33, 65) and B cell costimulation (16). These activities imply that a CD137 ligand agonist may enhance immune responses and could be beneficial as an adjuvant in immunotherapy of cancer and infectious diseases.

Agonistic anti-CD137 ligand antibodies that induce activities which rely on CD137 ligand signaling may at the same time inhibit activities which rely on CD137 signaling since they compete with CD137 to bind to CD137 ligand. A problem with using CD137 ligand agonists is that expression of CD137 ligand can be difficult to detect, and accordingly, it is impossible to predict *in vivo* effects, and it may be difficult to explain obtained results.

Interestingly, agonistic anti-CD137 and agonistic anti-CD137 ligand antibodies may synergistically enhance immune responses. The former would stimulate T cell activity while the latter would enhance DC activity.

5.6. Agonistic anti-CD137 ligand antibodies for inhibiting immune responses

In contrast to APC where CD137 ligand signaling induces activation, CD137 ligand signaling inhibits T cell proliferation and induces cell death by apoptosis (4, 31, 66). Agonistic anti-CD137 ligand antibodies have also been shown to induce immune deviation. $CD8^+$ T cells released IFN-γ in response to activation of CD137 ligand, and IFN-γ in turn reduced $CD4^+$ T cell activity, thereby ameliorating Th2-mediated allergic asthma in mice (5).

Whether these inhibitory activities of CD137 ligand or its stimulatory activities on APC, as discussed in section 5.5, would prevail *in vivo* cannot be answered at the current state of knowledge. Therefore, due to the scarcity of available data it is presently highly speculative whether CD137 ligand agonists would be useful in downregulating unwanted T cell responses.

5.7. Soluble CD137

Soluble CD137 occurs naturally and by analogy with other members of the TNF receptor family soluble CD137 would antagonize the activities of cell surface expressed CD137. Indeed, two recombinant CD137 proteins inhibited splenocyte proliferation and IL-2 secretion (36, 71). Soluble CD137 can compete with cell surface expressed CD137 for binding to CD137 ligand and would in its mechanism of action be similar to antagonistic anti-CD137 ligand antibodies (Figure 1). However, the activities of sCD137 may not be restricted to the neutralization of CD137 ligand but it may also be able to insert into existing CD137 trimers and disrupt their signaling capacity. Similar mechanisms are known for soluble CD95 and soluble TNF receptors (105, 106). Due to the bidirectional signaling capacity of the CD137 receptor/ligand system sCD137 could also be a CD137 ligand agonist and exert similar activities as described above for agonistic anti-CD137 ligand antibodies.

That soluble CD137 will be used therapeutically is unlikely though, since large scale production and regulatory issues would favor anti-CD137 ligand antibodies. Also, the half-life of sCD137 is unknown and is likely shorter than that of an antibody. The advantage of sCD137 could be less danger of immunogenicity.

6. OUTLOOK / CONCLUSION

The CD137 receptor/ligand system exerts many different activities. This is partly due to its bidirectional signaling capacity, and the expression of CD137 and CD137 ligand on many types of cells, immune and non-immune cells. Several opportunities to interfere therapeutically result from this range of activities. However, a downside is many potential side effects.

The most advanced CD137-based drugs are agonistic anti-CD137 antibodies. They are potent inducers of anti-tumor immune responses, however, on the other hand also inhibit autoimmune reactions. It is this dual function, which could raise major concerns for therapeutic applications until further mechanistic insights are obtained.'

A solution may be combining CD137 agonists with other drugs. OX40 agonists would be a good choice. Firstly, because OX40 is one of the most selectively expressed proteins in the immune system. It is found only on activated $CD4^+$ T cells, and its only activity is T cell costimulation (107). Therefore, OX40 agonists may bring specificity and more predictability to a therapy using CD137 agonists. Secondly, this combination has already been demonstrated to powerfully induce immune responses (92-94). The reason for this synergism may be that long-term $CD8^+$ T cell responses need $CD4^+$ T cell help. Since CD137 is predominately expressed on $CD8^+$ T cells, and OX40 selectively on $CD4^+$ T cells targeting both molecules results in a potent and lasting T cell response.

Among the other potential applications, antagonistic anti-CD137 ligand antibodies may be useful for therapy of autoimmune disease. But since many conventional drugs are already available and many biologicals for treatment of autoimmune disease are in various stages of development there is less need for new drugs than for an anti-cancer therapy. For all other potential reagents discussed here more data need to be generated in order to be able to assess their therapeutic potential.

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Abbreviations: aa: amino acids, AICD: activation-induced cell death, α-GalCer: α-galactosylceramide, AHR: airway hyper-responsiveness, AML: acute myeloic leukemia, APC: antigen presenting cells, CIA: collagen induced arthritis, CLL: chronic lymphocytic leukemia, DC: dendritic cell, EAT: experimental autoimmune thyroiditis, EAU: experimental autoimmune uveoretinitis, FDC: follicular dendritic cell, GVHD: graft versus host disease, HSK: herpetic stromal keratitis, HSV: herpes simplex virus, Idd: insulin-dependent diabetes, IDO: indoleamine 2, 3-dioxygenase, IFN: interferon, ILA: induced by lymphocyte activation, LCMV: lymphocytic choriomeningitis virus, lpr: lymphoproliferation, 1-MT: 1-methyltryptophan, NHL: Non-Hodgkin lymphoma, NK natural killer, NOD: non-obese diabetic, RA: rheumatoid arthritis. SLE: systemic lupus erythematosus, sCD137: soluble CD137, TCR: T cell receptor, Th: helper T cell, TNF: tumor necrosis factor, TNFRSF: TNF receptor super family, Treg: regulatory T cells.

Key Words: CD137, 4-1BB, Antibody, Immunotherapy, Cancer, Tumor, Autoimmune Disease, OX40, Review

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