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CD30: from basic research to cancer therapy

Hiromi Muta and **Eckhard R. Podack**
Department of Microbiology and Immunology, Leonard Miller School of Medicine, University of Miami, Miami, FL, USA

Eckhard R. Podack: epodack@miami.edu

Abstract

The FDA recently approved an agonistic anti-CD30 drug conjugate, Brentuximab vedotin, for the treatment for CD30-positive lymphomas. The potent clinical activity of Brentuximab vedotin in Hodgkin's lymphoma and anaplastic large-cell lymphoma was greeted with great enthusiasm by oncologists as it provided a new treatment modality for these diseases. In this review, we will describe how we obtained the hybridoma by pursuing a basic research experiment unrelated to CD30. I will also review what we know about the normal biological functions of CD30 that were studied primarily in murine models of disease but also in patients. The picture emerging is that one of the primary functions of CD30 is the control of memory cells providing costimulation and trafficking information or inducing apoptosis in a microenvironment and cytokine milieu-dependent manner.

Keywords

Memory; CCR7; Asthma; Colitis; Mucosal immunity; Th17; Hodgkin; ALCL

Isolation of agonistic anti-CD30 by functional screening

The NK-like YT lymphoma is able to kill Raji cells. The killing mechanism had been reported to be independent of Perforin-1. Our analysis of YT cells revealed that they do contain Perforin-1 and use it for cytotoxicity toward Raji. However, we also considered the possibility that YT may use Perforin-1-independent mechanisms for killing of Raji cells. To address this possibility, we used YT cells as immunogen to generate monoclonal antibodies that were screened in several different assays. First, we screened for potential anti-Perforin-1 antibodies by permeabilizing YT cells and staining with the hybridoma supernatant and a secondary FITC-labeled antibody, followed by fluorescence microscopy. In this way, the δG9 antibody was identified that turned out to be the first antihuman Perforin-1 antibody detecting native Perforin by flow cytometry and immuno-precipitation. The δG9 anti-Perforin-1 antibody has since then become a standard reagent to follow Perforin-1

Correspondence to: Eckhard R. Podack, epodack@miami.edu.

Present Address
H. Muta, Department of Medicine and Bioregulatory Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

expression by flow cytometry in NK cells and CTL [1–6]. In a second screen, we were searching for antibodies that may be able to interfere with killing mechanisms that are independent of Perforin-1 [7]. Our interest was focused on the killing step and the killer molecule, which of course is preceded by recognition and adherence of the killer cell to the target cell. Inhibition of adherence prevents killing; we therefore developed a screening assay for the monoclonal antibodies that could detect killing inhibition without interfering with adherence. In this screen, we looked for antibodies that inhibited killing of Raji by YT cells *only* when YT cells had been preincubated with the hybridoma supernatant for several hours. Antibodies that inhibited killing when added directly to the assay, without preincubation, were excluded from further analysis. This functional screening assay essentially ruled out membrane molecules on YT important for adherence to Raji. Rather, inhibition of cytotoxicity had to be by other mechanisms that had to be defined. One antibody was obtained that exhibited potent inhibition of YT cytotoxicity for Raji after 4-h preincubation at 37 °C. The antibody, labeled C10, recognized a membrane protein on YT cells with an apparent molecular weight of 120kD by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) [7]. In efforts of cloning the molecule, we obtained the partial amino acid sequence of proteolytic fragments. At that same time, a manuscript was published cloning CD30 and predicting the complete sequence by Duerkopp et al. [8]. Our partial amino acid sequence was identical to the newly published CD30 sequence. Our functional screen therefore suggested that we had identified a novel function of CD30, namely down-regulating cytotoxicity by an NK-like lymphoma.

We were cognizant of the fact that CD30 is a unique marker for Hodgkin's lymphoma, anaplastic large-cell lymphoma, and germ cell tumors. Since C10 was an agonistic antibody to CD30 that blocked cytotoxicity proliferation of YT cells and resulted in homotypic aggregation [7], we speculated that the antibody may be of therapeutic use for the treatment for CD30-positive tumors including Hodgkin's lymphoma. We suggested patenting the antibody but the Technology Transfer office of the University declined. Several years after publication, Seattle Genetics called to inquire whether the C10 antibody was available for licensing and for development and testing for therapeutic use in Hodgkin's lymphoma. We agreed enthusiastically, and the antibody was licensed to Seattle Genetics by the Technology Transfer office of University of Miami.

Cluster determinant 30 (CD30) has been recognized since the 1980s by a monoclonal antibody (Ki-1) as an epitope of a membrane protein highly expressed on Reed–Sternberg and Hodgkin's lymphoma cells [9–11] and infrequently on normal blood lymphocytes. In 1992, the protein recognized by Ki-1 was cloned and CD30 recognized as a member of the TNF receptor superfamily (TNFRSF8) [8]. Its cognate ligand is CD30 ligand also known as CD153 or TNF superfamily (TNFSF8).

CD30 (TNFRSF8) function

Upon T cell activation, CD28 and other costimulatory receptors, including CD27, CD30, CD134, CD137, and CD154, are up-regulated. CD30, a 120-kDa type I trans-membrane glycoprotein member of the TNFR family, is expressed on some B cells and on mitogen-stimulated T cells [12, 13]. The peak time for CD30 expression after TCR activation is about

4–5 days in vitro [12]. CD30 expression upon TCR stimulation requires CD28 or IL-4R signaling [14], and CD30 signals augment T cell proliferation at low levels of in vitro TCR stimulation [14, 15]. Similar to other members of the TNFR family, CD30 engagement regulates T cell survival. For example, CD30 signaling regulates peripheral T cell responses, controlling T cell survival and down-regulating cytolytic capacity [12, 16–20]. CD30 also regulates thymocyte survival. Thymic selection appears to be influenced by the level of CD30 expression. In one study, CD30-deficient (CD30 −/−) mice were reported to express a negative selection defect [21], although selection was not affected in another study using a different CD30 −/− mouse strain [22]. Conversely, CD30-overexpressing mice had increased thymocyte apoptosis after TCR engagement [19].

CD30 ligand (CD30L, CD153, TNFSF8) is a 40-kDa type II membrane-associated glycoprotein belonging to the TNF family [13, 15, 23, 24]. CD153 is expressed on activated T cells, primarily CD4 T cells of both Th1 and Th2 phenotype, as well as on a subset of accessory cells [12, 13, 23–25] and B cells ([26–29]. In addition, CD153 can provide signals for B cell growth and differentiation [13, 23].

CD30 in MHC unrestricted cytotoxicity

The natural killer cell line YT2C2 kills B7 (CD80) expressing target cells in an LFA (CD11a/CD18)-dependent fashion. YT2C2 expresses CD28 that is engaging B7 on the target cell. Both B7 and LFA expressions on the target are required for lysis to occur [30]. The new mAb, C10, binds to CD30 on YT cells and induces the inhibition of the cytotoxicity of YT for Raji cells. C10 inhibition of cytotoxicity requires several hours preincubation of YT with C10; the antibody has no effect if added directly to YT cytotoxicity assays. CD30 stimulation by C10 down-regulates CD28 expression on YT by >80 % within 48 h. Because CD28 is required for YT cytotoxicity toward Raji cells and other B7/BB1-bearing targets, it is suggested that the inhibition of cytotoxicity of YT is mediated by control of CD28 expression and/or signaling via CD30 [30]. Accordingly, conjugation of YT with Raji is only slightly affected by CD30-mediated down-regulation of CD28, and Perforin mRNA steady-state levels are not changed at all. C10 treatment of YT cells additionally down-regulates the expression of CD45 and up-regulates IL-2R p55. Moreover, CD30 stimulation by C10 causes homotypic aggregation of YT. Homotypic aggregation is slow, requiring gene transcription, translation, metabolic energy at elevated temperature (37° C), magnesium ions, and an intact cytoskeleton [7, 31]. These studies offered insights into the function of CD30 as a complex regulator of T cells and prompted more comprehensive analysis of CD30 signaling functions.

CD30 signaling and mRNA expression

Although CD30 has long been recognized as an important marker on many lymphomas of diverse origin and as activation molecule on B cells and T cells, its primary biological function has remained obscure. To define the effects of CD30 signaling, the agonistic C10 antibody to human CD30 was used to trigger CD30 on YT cells and induced gene expression analyzed by gene arrays [32]. A total of 750 gene products were induced and 90 gene products were suppressed > twofold by CD30 signals. Signals emanating from CD30

use both TNFR-associated factor 2-dependent and TNFR-associated factor 2-independent pathways. CD30 signals can inhibit effector cell activity by integrating gene expression changes of several pathways important for cytotoxic NK and T cell effector function. In the large granular lymphoma line YT, CD30 signals down-regulate the expression of mRNA encoding the cytotoxic effector molecules, Fas ligand, Perforin, granzyme B, and abrogate cytotoxicity. Cellula myc (c-myc), a regulator of proliferation and an upstream regulator of Fas ligand expression, is completely suppressed by CD30. Furthermore, CD30 signals strongly induce and up-regulate CCR7, suggesting a role for CD30 signals in the homing of lymphocytes to lymph nodes. The up-regulation of Fas (TNFRSF6), death receptor 3 (TNFRSF25), and TNF-related apoptosis-inducing ligand (TNFSF10) by CD30 suggests an increase in susceptibility to apoptotic signals, whereas up-regulation of TNFR-associated factor 1 and cellular inhibitor of apoptosis 2 protect cells from certain types of apoptosis. The integration of CD30 signals in a lymphoma line suggests that CD30 can down-modulate lymphocyte effector function and proliferation while directing the cells to lymph nodes and increasing their susceptibility to certain apoptotic signals [18]. These studies may provide a molecular mechanism for the recently observed CD30-mediated suppression of CD8 CTL activity in vivo in a diabetes model [17, 33].

Murine CD30 and CD30-L

The studies described above were done with human cells using human CD30 and CD30 antibodies (C10). To obtain further insight into CD30 biology, mouse models and reagents are necessary. We cloned murine CD30 cDNA [12], which predicts a protein of 498 amino acids with homology to the TNF receptor family of proteins characterized by repeated cysteine-rich motifs in the extracellular domain. Murine CD30, although homologous to human CD30, has a 90 amino acid gap in an extracellular region that appears to be duplicated in human CD30. Murine CD30 cDNA was shown to be functional through the production of a soluble murine Ig fusion protein (CD30-Ig) that was active in binding to cells that expressed CD30 ligand. CD30-Ig also served as an immunogen for the production of hamster anti-mouse CD30 mAbs, which recognized both CD30 expressed by murine lymphocytes and CD30 expressed by cells transfected with murine CD30 cDNA. CD30 mRNA is highly expressed in the thymus and in activated spleen cells, but not in other tissues tested. In anti-CD3-activated spleen cells, CD30 ligand is expressed primarily by activated CD4 + T cells, with peak expression at days 1 and 2, whereas CD30 is expressed primarily by CD8 + T cells, with peak expression on days 4 and 5. Stimulation of CD30 by plate-bound anti-CD30 directly signaled for IL-5 but not IFN-gamma production by CD30 + CTL lines. These studies demonstrated that CD30 can direct cytokine secretion and suggest that CD30 signaling may be pivotal in the pattern of cytokine production by T cells.

CD30 is expressed on activated CD4 + T cells in the presence of IL-4. [34]. In the absence of endogenously produced IL-4, however, even Th2 lineage cells lost CD30 expression. Thus, CD30 is not an intrinsic marker of Th2 cells, but is inducible by IL-4. CD30 was also found to be down-regulated by IFN-γ. Committed Th1 effector cells do not express CD30, although differentiating Th1 lineage cells temporarily express CD30. The transient expression of CD30 on differentiating Th1 lineage cells was mainly the result of endogenously produced IL-4 induced by IL-12. Culture of IL-12-primed cells under

conditions that reverse the phenotype (Ag plus IL-4) resulted in two cell populations based upon their ability to express CD30. One population responded to IL-4 upon restimulation and became a CD30-positive, Th0-like cell population, while the other remained CD30-negative and synthesized only IFN-gamma. Thus, CD30 expressed on CD4 + T cells reflected the ability of CD4 + T cells to respond to IL-4. The data indicate that CD30 expression is strongly influenced by the prevailing cytokine environment.

CD30 expression is restricted to activated T cells and regulated by CD28 signal transduction [14]. Blockade of CD28 interactions or depletion of IL-4 inhibited the induction of CD30, suggesting that both CD28 and IL-4 play important roles in the induction of CD30 expression on wild-type cells. IL-4-deficient T cells stimulated with anti-CD3 and anti-CD28 also expressed CD30. Induction of CD30 in the absence of IL-4 was not due to the IL-4-related cytokine IL-13. CD30 can act as a signal transducing receptor that enhances the proliferation of T cells responding to CD3 cross-linking. Once expressed on the cell surface, CD30 can serve as a positive regulator of mature T cell function.

Unlike CD28, ligation of CD30 on normal effector T cells induces IL-13 production in the absence of concurrent TCR engagement [35]. TCR-independent CD30-mediated IL-13 release correlated with the activation of c-Jun N-terminal kinase, p38 mitogen-activated protein kinase (MAPK), and NF-κB, and was completely inhibited by the expression of a TNFR-associated factor 2 (TRAF2)-dominant-negative transgene, but not by that of an I-kappa B-alpha-dominant-negative transgene. The results suggest that TCR-independent CD30-mediated production of IL-13 is triggered by the association of CD30 with TRAF family members and subsequent activation of p38 MAPK. Inasmuch as IL-13 can promote airway inflammation and cancer progression, production of IL-13 in a TCR-independent manner has important pathological implications in vivo.

Indeed, in CD30-deficient (CD30(−/−) mice, lung inflammation is significantly diminished in the ovalbumin (OVA) model of allergic lung inflammation [36–38]. In CD30(−/−) mice, the recruitment of eosinophils into the airways after OVA-aerosol challenge of OVA-primed mice was significantly diminished when compared with wild-type (w.t.) mice. IL-13 levels were also significantly reduced while levels of IFN-γ, IL-4, IL-5, and IgE in bronchoalveolar lavage fluid, lung tissue, and serum were comparable to w.t. mice. Exogenous IL-13 reconstituted airway recruitment of leukocytes in OVA-challenged CD3O(−/−) mice. Adoptive transfer of in vitro OVA-re-stimulated spleen cells from CD30(−/−) mice to naive w.t. mice failed to induce eosinophilic pulmonary inflammation in contrast to transfer of primed cells from w.t. mice. These results indicate that CD30 is a regulator of Th2 responses in the effector memory phase and a regulator of IL-13 production in memory cells in the lung.

In vivo and in vitro studies in CD30-L knockout mice

The multiple signaling functions of CD30 are triggered by its cognate ligand CD30-ligand (CD153). Rather than studying CD30-deficient cells that may have skewed signaling pathways due to the absence of CD30, we decided to generate CD30-L-deficient mice and study their biology. In the absence of CD30-L, CD30 is not triggered and the observed

altered immune function is attributable to CD30 function in vivo. Hiromi Muta created the mice in our laboratory and studied them over the next decade in collaboration with Ioshikai's group in several disease models summarized below.

To study CD30-L in Th1 cell responses, the fate of Ag-specific CD4(+) T cells was investigated in CD30L-defi-cient (CD30L(−/−)) mice after Mycobacterium bovis bacillus Calmette–Guerin (BCG) infection. The number of bacteria was significantly higher in organs of CD30L(−/−) mice than in wild-type (WT) mice 4 weeks post-infection. The numbers of purified protein derivative- or Ag85B-specific-IFN-γ-producing-CD4(+) T cells in spleen, lung, or peritoneal exudate cells were significantly fewer in CD30L(−/−) mice than in WT mice. During the infection, CD30L was expressed mainly by CD44(+)CD3(+) CD4(+) T cells but not by CD3(+)CD8(+) T cells, B cells, dendritic cells, or macrophages. Costimulation with agonistic anti-CD30 mAb or coculturing with CD30L-trans-fected P815 cells restored IFN-γ production by CD4(+) T cells from BCG-infected CD30L(−/−) mice. Coculturing with CD30L(+/+)CD4(+) T cells from BCG-infected WT mice also restored the number of IFN-gamma(+)CD30L (−/−)CD4(+) T cells. When transferred into the CD30L (+/+) mice, Ag-specific donor CD30L(−/−) CD4(+) T cells capable of producing IFN-γ were restored to the compared level seen in CD30L(+/+) CD4(+) T cells on day 10 after BCG infection. When naive CD30L(+/+) T cells were transferred into CD30L(−/−) mice, IFN-γ-producing CD4(+) Th1 cells of donor origin were generated normally following BCG infection, and IFN-γ-producing CD30L(−/−)CD4(+) Th1 cells of host origin were partly restored. These results suggest that CD30L/CD30 signaling executed by CD30(+) T-CD30L(+) T cell interaction partly play a critical role in augmentation of Th1 response capable of producing IFN-gamma against BCG infection. [39].

CD30 also plays a role in Th17 induction. CD44(low)CD62(hi)CD4(+) T cells from CD30L(−/−) or CD30(−/−) mice exhibited impaired differentiation into Th17 cells but an increased ability to produce IL-2 after in vitro culture under Th17-polarizing conditions. Neutralization with IL-2 by anti-IL-2 mAb partly restored the ability of Th17 differentiation in CD30L(−/−) or CD30(−/−) T cells. Stimulation via CD30L by immobilized anti-CD30L mAb suppressed IL-2 production by CD30(−/−)CD4(+) T cells, indicating that reverse signaling to CD30L is responsible for the down-regulation of IL-2 production [24]. In vivo Th17 differentiation of CD30L(−/−)CD4(+)CD45RB(high) T cells was also impaired after transfer into SCID mice, whereas CD30L (+/+)CD4(+)CD45RB(high) T cells differentiated normally into Th17 cells in CD30L(−/−) SCID mice. The data suggest that CD30L/CD30 signaling executed by the T–T cell interaction plays a critical role in Th17 cell differentiation, at least partly via down-regulation of IL-2 production. [40].

Interleukin-17A (IL-17A)-producing γδ T cells are known to be activated following Mycobacterium bovis bacillus Calmette–Guerin (BCG) infection. Vγ1(−) Vγ4(−) γδ T cells preferentially expressing Vγ6/Vδ1 genes were identified as the major source of IL-17A in the peritoneal cavity during the early stage of BCG infection. The number of IL-17A-producing Vγ1(−) Vγ4(−) γδ T cells bearing Vγ6 increased in peritoneal exudate cells (PEC) of wild-type (WT) mice but not in those of CD30 knockout (KO) mice in response to BCG infection. Consistently, CD30 ligand (CD30L) or CD30 expression, predominantly by Vγ1(−) Vγ4(−) γδ T cells, was rapidly up-regulated after BCG infection.

Inhibition of CD30L/ CD30 signaling by in vivo administration of a soluble CD30 and immunoglobulin fusion protein (CD30-Ig) severely impaired activation of IL-17A-producing Vγ1(−) Vγ4(−) γδ T cells in WT mice, while stimulating CD30L/ CD30 signaling by in vivo administration of agonistic anti-CD30 monoclonal antibody (MAb) restored IL-17A production by Vγ1(−) Vγ4(−) γδ T cells in CD30L KO mice after BCG infection [41].

CD30L/CD30 signaling plays an important role in the maintenance and activation of IL-17A-producing γδ T cells bearing Vγ6 in mucosal tissues of mice [42].

CD30 in CD4(+) T cell-mediated graft versus host disease

Although human alloreactive T cells preferentially reside within the CD30(+) T cell subset, implicating CD30 as a regulator of T cell immune responses, the role of CD30/ CD153 in regulating graft-vs-host disease (GVHD) has not been reported. To analyze the effect of CD30/CD153 interaction on GVHD induction, a neutralizing anti-CD153 mAb was used in combination with CD30(−/−) donor mice and newly generated CD153(−/−) recipient mice [43]. The data indicate that the CD30/CD153 pathway is a potent regulator of CD4(+), but not CD8(+), T cell-mediated GVHD. Although blocking CD30/CD153 interactions in vivo did not affect alloreactive CD4(+) T cell proliferation or apoptosis, a substantial reduction in donor CD4(+) T cell migration into the gastrointestinal tract was readily observed with lesser effects in other GVHD target organs. Blockade of the CD30/CD153 pathway represents a new approach for preventing CD4(+) T cell-mediated GVHD.

CD30 in CD8 memory cells

>Memory CD8 + T cells can be divided into two subsets, central memory (T(CM)) and effector memory (T(EM)) CD8 + T cells. CD30 signaling is involved in differentiation of long-lived CD8 + T(CM) cells following Listeria monocytogenes infection. Although CD8 + T(EM) cells transiently accumulated in non-lymphoid tissues of CD30 ligand-deficient (CD153 −/−) mice after infection, long-lived memory CD8 + T(CM) cells were poorly generated in these mice. CCR7 mRNA expression was down-regulated in CD8 + T cells of the spleen of CD153 −/− mice in vivo, and the expression was up-regulated in CD8 + T(EM) cells by anti-CD30 mAb cross-linking in vitro. These results suggest that CD30/ CD30 ligand signaling plays an important role in the generation of long-lived memory CD8 + T cells at least partly by triggering the expression of high endothelial venule (HEV) homing receptors for T(CM) cells [44].

CD30 in colitis in animal models and man

The level of soluble (s)CD30 was assessed in serum of patients with ulcerative colitis (UC) and Crohn's disease (CD) and in healthy individuals. In addition, a model of enteritis induced by anti-CD3 monoclonal antibody injection was studied in wild-type mice and in CD30L knockout mice. Increased sCD30 was observed in UC and CD patients, and the level was correlated with disease activity in both conditions. In the murine model of enteritis, histological intestinal damage was significantly reduced in CD30L knockout mice and levels of Th1 and Th17 cytokine were decreased. Moreover, blocking of CD30L/CD30 signals by

CD30 immunoglobulin (CD30-Ig) resulted in reduced inflammation. Increased sCD30 expression correlating with disease activity suggested that CD30L/CD30 signals play an important role in the pathogenesis of UC and CD. CD30L/CD30 pathway acts as an accelerator of enteritis in a murine disease model. CD30-Ig may be a therapeutic tool to block [45].

Serum levels of soluble CD30 levels increased in inflammatory bowel diseases patients (IBD), suggesting that CD30L/CD30 signaling is involved in the pathogenesis of IBD [46]. The role of CD30L in oxazolone (OXA)- and trinitrobenzene sulfonic acid (TNBS)-induced colitis was studied in CD30L knockout (KO) mice [47]. Colitis was induced by OXA or TNBS in CD30LKO mice with BALB/c or C57BL/6 background, respectively, and diverse clinical signs of the disease were evaluated. CD30LKO mice were susceptible to OXA-induced colitis but resistant to TNBS-induced acute colitis. The levels of T helper cell 2-type cytokines such as IL-4 and IL-13 in lamina propria T cells were significantly higher, but the levels of interferon gamma were lower in OXA- or TNBS-treated CD30LKO mice than in wild-type mice. In vivo administration of agonistic anti-CD30 mAb ameliorated OXA-induced colitis but aggravated TNBS-induced colitis in CD30LKO mice. The results suggest that CD30L/CD30 signaling is involved in the development of both OXA- and TNBS-induced colitis and that the modulation of CD30L/CD30 signaling by mAb could be a novel biological therapy for IBD.

As mentioned above, CD30 ligand/CD30 signaling executed by T–T cell interaction plays a critical role in Th17 cell differentiation, in part via down-regulation of IL-2 production. This observation was followed up by studying the role of CD30L in the development of colitis experimentally induced by dextran sulfate sodium (DSS), in which IL-17A is involved in the pathogenesis [48]. CD30L(−/−) mice were resistant to both acute colitis induced by the administration of 3 to approximately 5 % DSS and to chronic colitis induced by the administration of 1.5 % DSS on days 0–5, 10–15, and 20–25 as assessed by weight loss, survival rate, and histopathology. The levels of IFN-gamma, IL-17A, and IL-10 were significantly lower but the IL-2 level higher in lamina propria T lymphocytes of CD30L(−/−) mice than those in lamina propria T lymphocytes of wild-type mice after DSS administration. Soluble murine CD30-Ig fusion protein, which was capable of inhibiting Th17 cell differentiation in vitro, ameliorated both types of DSS-induced colitis in wild-type mice. Modulation of CD30L/ CD30 signaling by soluble CD30 could be a novel biological therapy for inflammatory diseases associated with Th17 responses.

Summary of immunological CD30 functions and contribution to disease

CD30 is expressed by naïve T cells upon TCR triggering only following CD28 or IL-4 receptor costimulation. In contrast, CD30 expression on memory rapid cells does not require CD28 signaling. CD30 signaling on memory cells can lead to a transition from effector to central memory cells and together with Ox40 signaling to enhanced survival [49–52]. This function of CD30 is important primarily for the survival of CD4 memory cells that require continued antigen stimulation for the preservation of memory function and survival [53]. Beneficial roles of CD30 through supporting memory cell traffic and survival in vivo include control of infections with Listeria and Mycobacteria. On the other hand, survival of

memory cells supported by CD30/CD30-L is also responsible for supporting autoaggressive disease including inflammatory bowel disease, allergic lung inflammation, and allergic rhinitis [54]. The function of CD30 in IL-17 production by TCR-γδ cells suggests additional functions in the control of infections in skin and mucosa. TCR-γδ cells are effector cells at the interface of innate and adaptive immunity and respond rapidly to bacterial infection. Il-17 triggered by CD30 participates in recruiting polymorphonuclear granulocytes important for anti-bacterial activity. CD30 in addition may contribute to life and death decisions by TCR-γδ T cells.

CD30 in the clinical arena

Several excellent reviews of the clinical activity C10/anti-CD30/Brentuximab vedotin have recently been published [53, 55–59]. The C10 antibody was licensed to Seattle Genetics where it was chimerized with the human IgG1 heavy chain and the κ-light chain and named SGN-30. Initial data in SCID mice xenografted with Hodgkin lym-phoma cells and treated with SGN-30 showed anti-tumor activity in vivo [56]. In addition, the antibody sensitized Hodgkin lymphoma cells to chemotherapeutic agents in vitro [60]. In phase 1 and 2 studies, weekly administration of SGN-30 was safe and showed modest activity in patient with ALCL and Hodgkin's lymphoma [57, 59].

The humanized C10 antibody was also coupled to monomethyl-auristatin E, named SGN-35. It exhibited potent and specific cytotoxicity against CD30-positive cells in vitro and in vivo [61, 62]. In a phase 1 study, SGN-35 now named Brentuximab vedotin induced durable objective responses and caused tumor regression in most patients with Hodgkin's lymphoma and ALCL patients [63]. These data were confirmed in a phase 2 study [58] and resulted in accelerated approval of Brentuximab vedotin by the FDA for treatment for patients with relapsed Hodgkin lymphoma and relapsed systemic anaplastic large-cell lymphoma (sALCL). Deng et al. [53, 59] commented that results like these and from many other upcoming clinical trials, in which Brentuximab vedotin is being investigated in the frontline setting, promise to profoundly change how we manage the CD30-positive lymphoproliferative malignancies.

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