Agonistic CD40 Antibodies and Cancer Therapy

Robert H. Vonderheide and Martin J. Glennie

Abstract

Recent success in cancer immunotherapy has reinvigorated the hypothesis that the immune system can control many if not most cancers, in some cases producing durable responses in a way not seen with many small-molecule drugs. Agonistic CD40 monoclonal antibodies (mAb) offer a new therapeutic option which has the potential to generate anticancer immunity by various mechanisms. CD40 is a TNF receptor superfamily member expressed broadly on antigen-presenting cells (APC) such as dendritic cells, B cells, and monocytes as well as many nonimmune cells and a range of tumors. Agonistic CD40 mAb have been shown to activate APC and promote antitumor T-cell responses and to foster cytotoxic myeloid cells with the potential to control cancer in the absence of T-cell immunity. Thus, agonistic CD40 mAb are fundamentally different from mAb which block negative immune checkpoint such as anti-CTLA-4 or anti-PD-1. Initial clinical trials of agonistic CD40 mAb have shown highly promising results in the absence of disabling toxicity, both in single-agent studies and in combination with chemotherapy; however, numerous questions remain about dose, schedule, route of administration, and formulation. Recent findings about the role played by the IgG isotype and the Fc gamma receptor (FcγR) in mAb cross-linking, together with insights into mechanisms of action, particularly with regard to the role of myeloid cells, are predicted to help design next-generation CD40 agonistic reagents with greater efficacy. Here, we will review the preclinical and clinical data and discuss the major issues facing the field. Clin Cancer Res; 19(5); 1035–43. ©2013 AACR.

Introduction

The last decade has seen unprecedented progress in cancer immunotherapy, with recent approval of 2 cancer immunotherapy drugs: a cell-based vaccine for use in metastatic prostate cancer (sipuleucel-T; ref. 1) and an anti-CTLA-4 monoclonal antibody (mAb) for use in metastatic melanoma (ipilimumab; ref. 2). Recent success with PD-1/PD-L1 blocking mAb (3, 4) underlines the potential of immune control and indicates that many cancer types are immunogenic yet able to annul effective destruction. A major advantage of cancer immunotherapy is the prospect of a durable response, but the difficulty is that only an unidentified proportion of patients (<25%) respond. Immunostimulatory mAb offer an attractive way of boosting anticancer responses and might be used to potentiate existing responses or as adjuvants for cancer vaccines (5). Preclinical models show that both approaches are effective. In such models, one of the most effective reagents is agonistic CD40 mAb, particularly against lymphoid tumors. Like all such immunostimulators, effectiveness is greatest when controlling the more immunogenic tumors. Most of these studies point to CD8 T-cell effectors without the need for CD4 help, suggesting that triggering CD40 with a cross-linking mAb on antigen-presenting cells (APC) can substitute for stimulation normally provided by helper T cells via CD40 ligand (CD40-L). Other potential mechanisms of action have emerged, further driving translational efforts to develop CD40 mAb as a cancer therapy. Clinical activity observed in initial trials with several CD40 agonistic mAb is highly promising. This review will focus on agonistic CD40 mAb, how they work, and what we have learned from clinical trials to date that can help pave the way forward.

Mechanisms of action of agonistic CD40 mAb

CD40 is a TNF receptor superfamily member expressed on APC such as dendritic cells (DC), B cells, and monocytes as well as many nonimmune cells and a wide range of tumors (6–8). Interaction with its trimeric ligand on activated T helper cells results in APC activation, required for the induction of adaptive immunity. Physiologically, signaling via CD40 on APC is thought to represent a major component of T-cell help and mediates, in large part, the capacity of helper T cells to license APC. Ligation of CD40 on DC, for example, induces increased surface expression of costimulatory and MHC molecules, production of proinflammatory cytokines, and enhanced T-cell triggering. CD40 ligation on resting B cells increases antigen-presenting function and proliferation. The consequences of CD40 signaling are multifaceted and depend on...
the type of cell expressing CD40 and the microenvironment in which the CD40 signal is provided (8). Like some other members of the TNF receptor family, CD40 signaling is mediated by adapter molecules rather than by inherent signal transduction activity of the CD40 cytoplasmic tail. Downstream kinases are activated when the receptor-assembled, multicomponent signaling complex translocates from CD40 to the cytosol (9) and a number of well-characterized signal transduction pathways are activated (10, 11).

In preclinical models, rat anti-mouse CD40 mAb show remarkable therapeutic activity in the treatment of CD40+ B-cell lymphomas (refs. 12, 13; with 80%–100% of mice cured and immune to rechallenge in a CD8 T-cell dependent manner) and are also effective in various CD40-negative tumors (14, 15). These mAb are able to clear bulk tumors from mice with near terminal disease (12). To date, 4 CD40 mAb have been investigated in clinical trials: CP-870,893 (Pfizer and VLST; ref. 16), dacetuzumab (Seattle Genetics; ref. 17), Chi Lob 7/4 (University of Southampton, Southampton, UK; ref. 18), and lucatumumab (Novartis; ref. 19; Table 1). These reagents show diverse activities ranging from strong agonism (CP-870,893) to antagonism (lucatumumab; ref. 20). Currently, there is no satisfactory explanation for this heterogeneity, with little evidence for epitope specificity being the determining factor, and some suggestion that isotype and Fc:FcγR may be important, given that F(ab′)2 fragments of CD40 are usually inactive. Indeed, preclinical experiments show that such activity requires that the CD40 mAb has an intact Fc and hence F(ab′)2 could not substitute for IgG, even when given in large doses to compensate for its shorter half-life (21).

Although the primary mechanistic rationale invoked for agonistic CD40 mAb is to activate host APC, especially DC (termed “licensing” of DC), to induce clinically meaningful antitumor T-cell responses in patients, other immune mechanisms that are not necessarily mutually exclusive have been proposed (Fig. 1). These include T-cell–independent but macrophage-dependent triggering of tumor regression (22, 23). CD40-activated macrophages can become tumoricidal, and at least in pancreatic cancer may also facilitate the depletion of tumor stroma, which induces

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NOTE: Only reagents showing agonistic activity are included and thus lucatumumab (Novartis) has not been discussed. Abbreviation: NHL, non–Hodgkin lymphoma.
Importantly, these mechanisms do not require expression of CD40 by the tumor, which has justified inclusion of patients with a broad range of tumors in many of the clinical trials. Insofar as these strategies aim to activate DC, macrophages, or both, the goal is not necessarily for the CD40 mAb to kill the cell it binds to, for example, via complement-mediated cytotoxicity (CMC) or antibody-dependent cellular cytotoxicity (ADCC). Thus, by design, the strong agonistic mAb CP-870,893 is a fully human IgG2 molecule, which does not mediate CMC or ADCC (24). In contrast, other human CD40 mAb used to date have been of the IgG1 isotype and therefore more able to mediate CMC and ADCC against CD40+ tumors, such as nearly all B-cell malignancies, a fraction of melanomas, and between 40% and 75% of carcinomas (Fig. 1). Dacetuzumab, for example, has been primarily tested in patients with B-cell malignancies that nearly uniformly express CD40 (17). Finally, there is some evidence that ligation of CD40 on tumor cells promotes apoptosis and that this can be accomplished without engaging any immune effector pathway. This has been shown for CD40+ B-cell malignancies and certain solid tumors such as CD40+ carcinomas and melanomas (25–29). For low-grade B-cell malignancies (as for normal B cells), CD40 engagement may actually be a strong activation and perhaps growth signal (30), and patients with such tumor types have often, but not always, been excluded from clinical trials of agonistic CD40 mAb. In fact, blocking the potential CD40-CD40L tumor growth signal has been a rationale for developing the CD40 antagonistic mAb lucatumumab in diseases such as chronic lymphocytic leukemia (CLL; ref. 19). Immunologically, direct tumor cytotoxicity accomplished by CD40 agonists is hypothesized to provide a source of tumor antigen that can be processed and presented by APC which are simultaneously activated by the same intervention. This "two-for-one" mechanism postulated for strong CD40 agonists has provided further justification for single-agent clinical trials, even though it seems likely that combining CD40 mAb with strong vaccines or cytokines may be clinically more potent for driving an adaptive antitumor immune response.

Role of FcR cross-linking with CD40 mAb

Recent studies have highlighted the importance of FcR for cross-linking agonistic CD40 mAb, offering the opportunity of Fc region engineering for "fine tuning" the relative level of agonistic activity. This work is important because it helps explain why F(ab')2 of CD40 mAb, unlike the parental IgG, were not agonistic and how a bivalent mAb when hyper-cross-linked by FcR can mimic the molecular changes and transmembrane signaling that follows...
CD40:CD40L interaction in the immunologic synapse of an APC and a T helper cell. Fc receptors are coded by a multigene complex with a number of members (FcγRI, -II, and -III in human and FcγR-I, -II, -III, and -IV in mice), each containing a range of allelic variants with differing functions, cell distribution, and affinities for IgG isotypes. Most of the FcγR are able to trigger cellular activation as a result of signaling via an immunoreceptor tyrosine-based activation motif (ITAM). In addition, there is one family member, FcγRIIb (the homologous receptor in mice is sometimes called FcγRII), which is widely distributed on hematologic and nonhematologic tissues, that contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain and is inhibitory to cellular responses. Activatory and inhibitory FcγR often work in concert such that the balance of their engagement on effector cells, that is, the activatory:inhibitory ratio (A:I), regulates cellular responses and immunologic outcome.

Most clinical mAb used to date have been of the human IgG1 isotype, selected because they bind with a high A:I ratio to a wide range of FcγR and are active in ADCC (Fig. 2). IgG2 by contrast is relatively inactive in recruitment of FcγR-expressing effectors as it only binds to one FcγR with appreciable efficiency, the H131 allelic variant of FcγRIIa. Three of the clinical CD40 mAb used to date are IgG1 (dacetuzumab, Chi Lob 7/4, and lucatumumab), and hence should mediate CMC and ADCC, whereas the fourth (CP-870,893) is IgG2; however, it is now apparent that the IgG2 Pfizer reagent is far more agonistic (see below).

Considerable insight about the impact of isotype in the function of CD40 mAb comes from the studies of White and colleagues (31) and Li and Ravetch (32). Both groups found that the inhibitory receptor FcγRIIB was critical in controlling the agonistic activity of CD40 mAb. Despite all having the same V-region sequences, rat IgG2a and mouse IgG1 CD40 mAb which bind relatively strongly to FcγRIIB were far more agonistic than equivalent mouse IgG2a reagents. These results are surprising because just as most human therapeutic mAb have used IgG1 (because of its stronger binding to the activatory FcγR, high A:I ratio, and potent cytotoxic activity) in mice, IgG2a shows similar functionality and would be a first choice when making a therapeutic (33). However, human IgG1 and mouse IgG2a mAb are only most appropriate when cytotoxic activity is required yet are clearly not the most potent CD40 mAb agonists. White and colleagues (31) have gone on to show that the FcγRIIB is only required for cross-linking, as the ITIM-containing cytoplasmic tail of the molecule can be deleted, at least in vitro, and it still provides cross-linking function to agonistic CD40 mAb. Furthermore, when individual FcγR, activatory and inhibitory, were over expressed on feeder cells, then they were all able to provide the necessary cross-linking of CD40 mAb (mouse IgG1 or IgG2a) to promote B-cell activation and proliferation. Thus, it appears that the importance of FcγRIIB reflects availability of FcγRIIB in vivo rather than a special function, such as signaling or affinity.

An alternative suggestion for the relatively lower potency of mouse IgG2a (mlgG2a) CD40 mAb is the cytotoxic activity toward CD40+ APC via CMC or ADCC when the activatory FcγR is engaged. While this would be a logical explanation, there is no evidence to support this. We have found that in mice, in vivo administration of mlgG2a CD40 mAb does not significantly delete CD40-expressing B cells or DC (23, 31), and a mixture of mlgG1 and mlgG2a CD40 mAb did not reduce the agonistic activity of the mlgG1 (32). Furthermore, deleting natural killer (NK) cells or using mice deficient in FcγRIIB, both maneuvers known to reduce the cytotoxic activity of mlgG2a, did not increase the agonistic activity of mlgG2a CD40 mAb. These observations reinforce the view that there is nothing inherently amiss or
cytotoxic with mlgG2a mAb; rather, activatory FcγR are not available and/or not at the right location to provide cross-linking to the IgG2a CD40 mAb on DC, macrophages, or B cells.

This work clearly has considerable implications when designing human reagents. First, it is important to note that unfortunately the mouse IgG1/IgG2a differences which allow the activatory and inhibitory FcγR to be differentially engaged do not exist in humans (Fig. 2). In particular, there is no human equivalent to the mouse IgG1 (and rat IgG2a) with its preferential binding to FcγRIIB. An alternative is to engineer human IgG1 to increase its tendency to bind to FcγRIIB. Early results show this can be highly successful with S267E and S267E/L328F Fc region substitutions increasing affinity by 30- and 430-fold, respectively, with a corresponding improvement in their ability to activate B cells via CD40 in vitro (White, personal communication) and to increase the in vivo immunostimulatory and therapeutic activity in human FcγRIIB transgenic mice (32, 34).

Clinical development of agonist CD40 mAb

The effort over the last 10 years to develop CD40 agonists as a new class of drug for cancer treatment has been extensive (20). These approaches primarily include agonistic CD40 mAb but also include recombinant CD40L and CD40L gene therapy—all of which have been tested in patients, each with promising initial results (20). Many other formulations to accomplish CD40-mediated immune activation are in preclinical testing (35, 36). In the first clinical trial of CD40 agonists, recombinant human CD40L showed clinical activity and led to long-term complete remission in a patient with advanced squamous cell cancer of the head and neck (37). Similarly, CP-870,893 has shown clinical efficacy in a number of settings of patients with advanced cancer. The initial trial, testing a single intravenous infusion of CP-870,893, resulted in 4 partial responses of 29 patients with advanced cancer, with all responses at the maximum tolerated dose (MTD) of 0.2 mg/kg (16). One of these patients received 9 subsequent doses of CP-870,893 over the next year and a half (roughly one infusion every 8 weeks) and remains in complete remission more than 5 years later. Peripheral B-cell depletion and activation is a prominent pharmacodynamic effect of CP-870,893 (16). However, a trial of weekly CP-870,893 was conducted in 27 patients with advanced cancer, and no objective clinical responses were observed, with some evidence suggesting that the dosing interval of 1 week was too short although further study is needed (38).

Because of a potential synergy between chemotherapy (to release tumor antigen) and CD40 agonists (to activate APC), CP-870,893 has been tested in combination with carboplatin and paclitaxel (every 3 weeks in a trial of patients with advanced cancer; ref. 39) and gemcitabine (every 4 weeks in a trial of patients with metastatic pancreatic carcinoma; ref. 23). Objective tumor regressions were observed in about 20% of patients in each study. In pancreatic cancer, these findings were seen as significant because the response rate of standard-of-care gemcitabine alone is 5% or less. A trial of gemcitabine with CP-870,893 for patients with resectable pancreatic cancer recently opened at the University of Pennsylvania (Philadelphia, PA), as has a trial of CP-870,893 in combination with anti-CTLA-4 blocking mAb tremelimumab for patients with metastatic melanoma. A trial of CP-870,893 with cisplatin and pemetrexed for patients with advanced mesothelioma was recently completed at the University of Western Australia based on a previously published murine model (40). Importantly, whether or not CP-870,893 mAb infusion is associated with the induction of cellular tumor-specific immunity in patients, as predicated by preclinical models, remains to be fully explored, although it is noteworthy that 2 patients with melanoma receiving CP-870,893 with chemotherapy developed widespread vitiligo (39), a T-cell–dependent autoimmune phenomenon.

Dacetuzumab, a weaker CD40 agonist than CP-870,893, has shown single-agent activity when given intravenously every week, especially in patients with diffuse large B-cell lymphoma (DLBCL; ref. 41). Stable disease but not tumor regression was observed with dacetuzumab in multiple myeloma (42) and CLL (43). Preclinical data suggest synergy of dacetuzumab and other agents such as the CD20 mAb rituximab, leading to combination clinical trials (44). In a phase Iib study of dacetuzumab in combination with rituximab and gemcitabine in patients with relapsed or refractory DLBCLs, complete response rate was 20% and partial response rate was 27% (45). However, a randomized, double-blind phase Iib clinical trial of dacetuzumab versus placebo in combination with rituximab plus ifosfamide, carboplatin, and etoposide chemotherapy for patients with relapsed or refractory DLBCL was terminated early because it was decided that the study was unlikely to meet its primary endpoint of superior complete response rate in the dacetuzumab arm. In further analysis, however, dacetuzumab investigators recently presented data showing a trend toward increased survival in the dacetuzumab arm. Presence at baseline of a 15-gene signature of the tumor from patients with DLBCL treated with dacetuzumab predicts clinical response with an 80% overall accuracy, suggesting the prospect of patient selection to aid in the development of dacetuzumab (46). This signature includes genes directly regulated by CD40 stimulation, part of the CD40 pathway network, or a component of the germline center B-cell–like or activated B-cell–like classifier (46). Currently, there are no registered trials of dacetuzumab.

The third agonistic CD40 mAb, Chi Lob 7/4, again less agonistic than CP-870,893, is undergoing initial clinical testing. Infusion of this chimeric IgG1 mAb has been well-tolerated up to 160 mg per intravenous weekly dose times 4 in patients with advanced histologically proven CD40-expressing solid tumors or DLBCL (18). Eleven of the first 21 patients have had stable disease as best response (no complete or partial responses). Enrollment and dose escalation are continuing.

Interestingly, the MTD of a single infusion of CP-870,893 is estimated at 0.2 mg/kg, but single doses of at least 12
mg/kg dacetuzumab and Chi Lob 7/4 of at least 160 mg total have been tolerated in patients, highlighting the differences in each of these 3 mAb.

**Words of caution and toxicity**

The development of agonistic CD40 mAb as a novel cancer therapy has not been universally endorsed. Concerns cited include the prospect of triggering cytokine release syndromes (47), autoimmune reactions (47), thromboembolic syndromes (because CD40 is expressed by platelets and endothelial cells), hyper immune stimulation leading to activation-induced cell death or tolerance (48, 49), and tumor angiogenesis possibly on the basis of CD40-dependent activation of tumor endothelial cells (50). It is hypothesized that these effects may cause untoward toxicity or the promotion of tumor growth (51), but most of these concerns have not been realized in a clinically significant way. For the strongest agonist tested, CP-870,893, the most common side effect is cytokine release syndrome, manifesting as chills, fever, rigors, and other symptoms soon after infusion, but this has largely been grade II or less, transient, and easily managed in the outpatient setting (16, 38, 39). Several cases of thromboembolic events have been observed with CP-870,893, but this has been confounded by the advanced state of the patients with cancer treated in these trials for whom thromboembolism is a well-recognized comorbidity related to the cancer burden. Autoimmune reactions have not been observed, including no cases of colitis, dermatitis, hypophysitis, or thyroiditis (in distinction, e.g., to the U.S. Food and Drug Administration–approved mAb ipilimumab). Noninfectious inflammatory eye disorders have been observed with dacetuzumab but not CP-870,893 (41). Agonist CD40 mAb have also triggered mild elevations in liver enzymes and decreases in circulating platelet numbers, but importantly, liver necrosis, hemolysis, and disseminated intravascular coagulation have not been reported in patients. With regard to hyper immune stimulation, weekly infusion of CP-870,893 led to a marked diminution in circulating T-cell numbers (38)—potentially consistent with activation induced cell death—but these effects have not been observed when CP-870,893 is dosed every 3 or more weeks. Overall, toxicity has not been a major issue with CD40 agonists in the clinic. It remains to be proven, of course, that immune activation can be optimally and reliably achieved in vivo in patients treated at the current doses, schedules, and routes of administration. Local administration of CD40 mAb, rather than systemic, is one alternative approach that merits further testing (52).

**Future challenges**

To improve the clinical effectiveness of agonistic CD40 mAb, several major challenges remain to be addressed including: testing of appropriate therapeutic combinations; determining optimal dose, schedule, and route of administration; and identifying appropriate patient populations. It is also critical that we improve our understanding of the mechanism of action of different CD40 mAb and understand which of the many mechanisms is the most appropriate for a given situation or disease (Fig. 1). Such understanding will allow the design of more appropriate and more potent CD40 agonists for different diseases. For example, Chi Lob 7/4, being a modest agonist of the IgG1 isotype, is able to delete B cells and this is likely to be important in B-cell malignancies such as DLBCL; however, in these same patients, DC are not being depleted and are available for cross-priming tumor antigens to generate useful CD8 responses (Johnson and Williams, personal communication). Nevertheless, these same IgG1 reagents may not be sufficiently agonistic to promote DC activation and allow cross-priming of antigen for the generation of robust T-cell responses. In this situation, CD40 mAb efficacy may be improved by Fc region engineering to increase binding to FcγRIIb to promote agonistic activity, assuming that FcγRIIb in humans behaves in a similar manner to that in mice. The likely cost of such manipulations is a reduced FcγR binding A:I ratio and hence reduced cytotoxic activity which would reduce the direct killing of the tumors at the cost of improved T-cell immunity. The schematic in Fig. 3 shows this change in function as mouse mAb move from binding mainly to the activatory FcγRs (cytotoxic) to the inhibitory FcγRIIb (agonistic).

At the other extreme and for reasons which are still not understood, CP-870,893 is highly agonistic and might be an ideal candidate to generate T-cell responses against a co-administered vaccine (20). This level of agonism might not be ideal for systemic use, as MTD is reached at 0.2 mg/kg, possibly before saturation of CD40 receptors on tissue-resident DC or macrophages is achieved. Local administration might overcome this. Perhaps an alternative reagent for systemic use would display an agonistic activity somewhere similar to ipilimumab but still surpass MTD at 0.2 mg/kg.

**Figure 3.** Schematic showing that, at least in mice, strong binding of mAb to the activatory FcγR (IgG2a) will favor cytotoxic activity via recruitment of cellular effectors, such as NK and macrophages. In contrast, mAb which bind more strongly to the inhibitory FcγRI, FcγRIIb (IgG1) will be stronger agonists ideal for cross-linking TNFR molecules and promoting Ab and T-cell responses. Ongoing work is underway to show whether similar properties can be exploited with human mAb.
between that of dacetuzumab/Chi Lob 7/4 and CP-870,893, and which could be used at appreciable doses with an improved likelihood of fully engaging macrophages and DC in the tissues. Whether the Fc region of a human IgG can be "tweaked" by protein engineering to achieve such characteristics is not yet clear. Such a reagent likely needs a reduced A:1 ratio to allow Fc:FcγRIIIb cross-linking without target killing. Hence, it would display reduced B-cell killing but could be used at increased doses to promote both myeloid and T-cell effectors within solid tumors and their draining lymph nodes.

Conclusions

In our view, agonistic CD40 mAb represent a promising strategy for novel cancer therapeutics. Preclinical investigations with CD40 agonists have been robust and highlight multiple mechanisms of action including activation of APC that drives antitumor T cells, activation of macrophages that are tumoricidal, and induction of apoptosis in CD40+ tumor cells such as lymphoma or certain solid tumors. Initial clinical trials of agonistic CD40 mAb have shown clinical activity in the absence of disabling toxicity. Some clinical responses have been dramatic and very durable, but response rates remain 20% or less. It seems likely that at least for solid tumors, agonistic CD40 mAb will be most effectively used in combination with other modalities such as chemotherapy, radiation, or vaccines; however, single-agent therapy for B-cell lymphoma remains an important possibility. Phase II clinical trials with the strongest agonistic CD40 mAb (CP-870,893 and Chi Lob 7/4) with or without chemotherapy have not been conducted but are needed.

It is important to emphasize that agonistic CD40 mAb as immunostimulatory agents strikingly differ in their proposed mechanism of action compared with mAb that accomplish immune activation by blocking negative checkpoint molecules such as CTLA-4 or PD-1. Indeed, the prospect of combining agonistic CD40 mAb with anti-CTLA-4 or anti-PD-1 mAb is enticing and represents a real immunologic opportunity to “step on the gas” while “cutting the brakes.” As noted in this issue of Clinical Cancer Research, combinations of novel immunotherapy—especially immunomodulatory mAb—is an important goal (53–57).

In summary, with such a wealth of potential mechanisms of action and the ability to fine-tune mAb structure and function to suit particular requirements, the next decade is likely to see rapid advances with agonistic CD40 mAb.

Disclosure of Potential Conflict of Interest

R.H. Vonderheide has commercial research support from Pfizer. No potential conflicts of interest were disclosed by the other author.

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Conception and design: R.H. Vonderheide, M.J. Glennie
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.H. Vonderheide, M.J. Glennie
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