INVITED COMMENTARY

Targeting of ^{125}I-Labeled B Lymphocyte Stimulator

B lymphocyte stimulator (BLyS), also identified as TALL-1 (TNF and apoptosis ligand-related leukocyte-expressed ligand 1), BAFF (B cell activating factor belonging to the tumor necrosis factor family), THANK (tumor necrosis factor homologue that activates apoptosis, nuclear factor-κB, and c-Jun NH_2-terminal kinase), TNFS20 (tumor necrosis factor superfamily member 20), and zTNF4 (*1–5*), is a cytokine that is important in regulating B cell immunity (*6*). Its importance is readily demonstrated in animal models, where its absence is associated with a severe deficit in mature B cells and its presence in excess causes B cell hyperplasia and autoimmunity (*1–3,6*). BLyS is a type II transmembrane protein expressed as a membrane-bound form on cells of myeloid origin, including macrophages and dendritic cells, that is also released as a soluble protein (*2,7*). The soluble protein is a homotrimer of 56-kDa size that binds to at least 3 different receptors expressed primarily on B cells (transmembrane activator and calcium modulator and cyclophilin ligand interactor, B cell maturation antigen, and BAFF-receptor/BLyS receptor 3) with subnanomolar affinities (*5,8–12*). It does not bind to T cells, monocytes, natural killer cells, granulocytes, or pro- or pre-B cell populations. It does bind to malignant B cells from non-Hodgkin's lymphoma (NHL) patients. Patients with diffuse large cell, mantle cell, and marginal cell NHL have receptor expression similar to normal B cells, whereas lower receptor expression is characteristic of follicular NHL and chronic lymphocytic leukemia.

These characteristics have led the authors of an article in this issue of *The Journal of Nuclear Medicine*, Riccobene et al. (*13*), to hypothesize that BLyS may serve as a targeting molecule for selective delivery of radionuclides to normal and malignant B cells. Riccobene et al. labeled BLyS with ^{125}I and studied its biodistribution after intravenous injection into normal mice, mice bearing mouse BCL-1 B cell tumor in the spleen, and mice bearing subcutaneous murine J558 plasmacytoma tumors, by counting tissues in a γ-counter and by quantitative whole-body autoradiography. Although the in vitro binding of ^{125}I-BLyS to normal B cells, BCL-1 cells, and J558 cells was not reported in this article, Kanakaraj et al. (*14*) performed Scatchard analyses of ^{125}I-BLyS binding to human tonsillar B cells, mouse B cells, Raji human lymphoma cells, and BCL-1 mouse lymphoma cells. The affinity of binding to these cells was 0.1, 0.35, 0.16, and 0.93 nmol/L, respectively; the number of receptors per cell was 2,600, 179, 1,700, and 4,800, respectively. Riccobene et al. found that the half-life of ^{125}I-BLyS in plasma was 2.7 h in normal and tumor-bearing mice. The highest uptake of ^{125}I-BLyS occurred in spleen (maximum concentration [C_{max}] = 35–45 percentage injected dose per gram [%ID/g] at 1–3 h after injection), lymph nodes (C_{max} = 20 %ID/g in normal and J558 tumor-bearing mice and 8–15 %ID/g in BCL-1 tumor-bearing mice), and J558 tumors (C_{max} = 15 %ID/g). The uptake in kidney, liver, bone, small intestine, and muscle was less than or equal to 5 %ID/g. Only a single protein dose (50 μg/kg) was examined in this biodistribution study. More animal studies will be required to determine the dose effect on biodistribution given the large splenic pool of B cells and its predominant site of BLyS localization at this dose.

Illidge et al. (*15*) investigated the binding of ^{125}I-labeled anti–major histocompatibility complex (MHC) class II, anti-CD22, and anti-CD37 monoclonal antibodies to BCL-1 tumor cells and found 40,000–180,000 molecules of the various antibodies bound per cell at saturation. The splenic localization of ^{125}I-labeled anti-MHC and anti-CD22 monoclonal antibodies in the BCL-1–bearing mice was 30 and 15 %ID/g, respectively, with a tissue half-life of 24 h. This finding compares with the considerably shorter splenic half-life of ^{125}I-BLyS (40 and 8 %ID/g at 6 and 24 h, respectively, after injection). The area under the curve of the concentration of radiolabeled antibody versus BLyS will determine the relative radiation absorbed doses in tumor and blood (bone marrow). These studies suggest that radionuclide doses delivered by BLyS will require large administered radionuclide doses. The radiosensitivity of B cell lymphomas has contributed to successful treatment with radiolabeled monoclonal antibodies that bind to human leukocyte antigen DR10 (*16,17*), CD20 (*18–24*), and CD22 (*25,26*) antigens, and promising results have been reported with pretargeting radioimmunotherapy (*27–29*). An important concern with radiolabeled BLyS is whether a sufficient radiation absorbed dose will be deposited in tumor at the maximum tolerated dose. This dose will be influenced by the level of receptor expression, whether the receptor undergoes endocytosis or modulation after cytokine binding, and the retention time of the radiolabeled cytokine in tumor.

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The level of radiolabeled BLyS localization in J558 plasmacytoma tumors relative to spleen and lymph node was modest, with a ratio of less than 0.7, possibly because of the low level of BLyS receptor expression in tumor, the short plasma half-life of BLyS, or the low dose of BLyS administered. Furthermore, dehalogenation occurred with high levels of radioiodine present in the thyroid, stomach, and salivary glands, presumably as a consequence of internalization of the ^{125}I-BLyS-receptor complex in B cells. Previous studies have shown that ^{125}I-labeled anti-CD22 antibody underwent modulation from the surface of BCL-1 tumor cells in vivo, whereas the anti-MHC class II antibody did not undergo modulation (*15*). Radioiodinated monoclonal antibodies targeting antigens that are not modulated from the surface of tumor cells have been found to be more therapeutically effective than those that are modulated (*15*,*30*–*32*). However, radiometal-labeled antibodies show a longer tumor retention time if the antibodies are internalized (*33*). Labeling of BLyS with radiometals has not yet been reported but could enhance radioactive persistence at tumor sites. Although ^{125}I-BLyS had a low uptake in kidney, it is unknown what the kidney uptake and toxicity would be if BLyS were labeled with a radiometal such as ^{90}Y. Another concern is the extent to which unlabeled BLyS produced in tumor and lymphoid tissues would compete with radiolabeled BLyS for binding to tumor cells, thus lowering the radiation absorbed dose delivered to tumor. It remains to be determined whether radiolabeled BLyS will have greater therapeutic efficacy than conventional or pretargeted radioimmunotherapy both in preclinical animal models and in clinical trials. An additional concern based on the studies with radiolabeled peptides and antibody fragments is the high radionuclide doses required to achieve efficacy (*34*–*36*). Nevertheless, this article presents the first results on the biodistribution of this B cell–specific molecule and offers a novel direction for further studies of radioimmunotherapy of B cell malignancies in mice and humans. The results of this initial study are interesting and provocative, but more animal and human data with maximum tolerated dose information, toxicity, and therapy outcomes are needed.

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Erratum *(continued from page 330)*

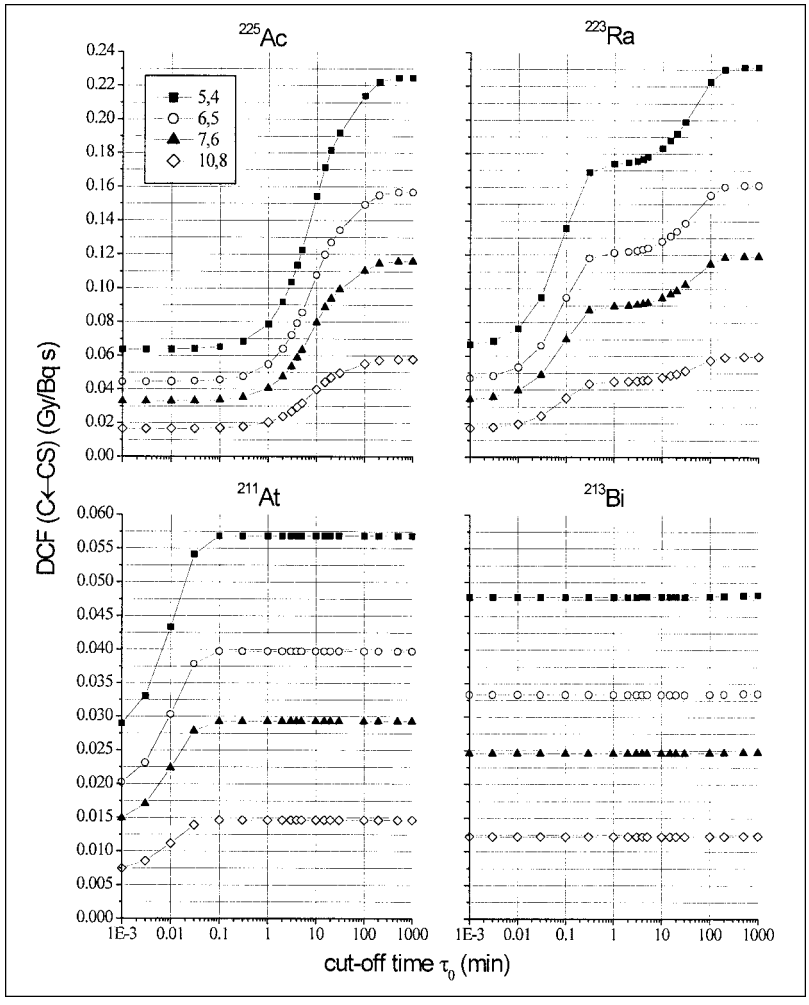

FIGURE 2. DCF values vs. τ_0 for (C ← CS) where CS represents cell surface. Plots for several different cellular dimensions are shown and denoted by (R_C, R_N), representing radius of cell and of nucleus, respectively.