CD37: the comeback kid

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In this issue of Blood, Heider et al describe the preclinical development of a novel Fc-engineered monoclonal antibody targeting the B-cell antigen CD37, an antigen that may have very different properties than CD20.1

In 1997, the first monoclonal antibody for treatment of cancer, rituximab, was approved by the US Food and Drug Administration to treat low-grade lymphoma. It was quickly adopted by clinicians to treat nearly all forms of CD20-positive B-cell malignancies. This use was supported by numerous clinical trials demonstrating its efficacy, including a clear survival advantage when rituximab was combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with diffuse large-cell lymphoma.2 Since rituximab’s approval, numerous other monoclonal antibodies have been studied, including anti-CD19, anti-CD20, anti-CD22, anti-CD23, anti-CD80 and anti–HLA-DR antibodies (see figure). These antibodies have provided a few small successes to date. Alemtuzumab has been approved for the treatment of chronic lymphocytic leukemia (CLL). The radioimmunoconjugates131I tositumomab and 90Y-ibrutumomab tiuxetan have been approved for the treatment of low-grade lymphoma, and ofatumumab was recently approved for refractory CLL. So far none of these antibodies have achieved the widespread use that rituximab enjoys.

Here, Heider and colleagues describe the preclinical development of a novel monoclonal antibody targeting CD37, mAb 37.1.1 The target of this antibody, CD37, is not novel, but it has been forgotten by most for many years. CD 37 is a tetraspanin. It is expressed on mature B cells and very minimally expressed on T cells, monocytes, and macrophages. There is a high level of expression of CD37 across all subtypes of B-cell non-Hodgkin lymphoma. It is also expressed in CLL, hairy cell leukemia, and lymphoplasmacytic lymphoma.3,4 It was used in the late 1980s and early 1990s as the target for radioimmunotherapy. However, interest in CD37 as a target for radioimmunotherapy waned with the development of anti-CD20 antibodies, which were hypothesized to have better targeting and biodistribution.5,6

An important question is the relative importance of CD37 as a target compared with CD20. While there are some minor differences, the 2 antigens are expressed on a similar spectrum of malignancies, and trying to develop an anti-CD37 antibody based on these differences alone would be difficult. Recently there has been a revival in interest in targeting CD37. TRU-16 is a small modular immunopharmaceutical (SMIP) that also targets CD37. It is composed of a single-chain antibody variable region specific for CD37 linked to an immunoglobulin constant domain. It is also being developed for CLL and other B-cell malignancies. Professional illustration by Paulette Dennis.
In addition to targeting a relatively under-studied antigen, mAb 37.1 is of interest because the Fc portion of the antibody has been engineered to increase affinity for Fc-γ RIIA. There are a variety of ways one might improve the efficacy of an antibody for a particular antigen. Modifying the Fc portion to elicit superior antibody-dependent cellular cytotoxicity is one approach that has seen some early success. For instance, GA-101 is an Fc-engineered type II IgG-1 antibody targeting CD20. It has both superior direct cytotoxicity as well as immune effector cell–mediated cytotoxicity in comparison to rituximab. GA-101 accomplishes this modification through glycoengineering, a process in which the carbohydrate component of the Fc portion of the antibody is altered to enhance affinity for Fc-γ RIIA. In the case of mAb 37.1, the improved affinity is accomplished by a point mutation rather than glycoengineering.

Ultimately, whether this antibody will succeed where numerous others have failed is hard to say. However, the combination of a relatively novel target that likely induces apoptosis through pathways different from approved agents combined with improvements in antibody function through Fc engineering is attractive. The clinical developmental pathway for this B-cell antibody or any other therapy for lymphoma is challenging. It is a crowded field with both approved and investigational agents. The next generation of antibodies will have to be substantially better than what is available today to make it through FDA approval. The development of mAb 37.1 into a clinically useful therapy for patients with B-cell malignancies is clearly many years away. Its story is one that will be followed with great interest by laboratory and clinical investigators alike.

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REFERENCES

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Comment on Mailankody et al, page 4086

“Sowing dragon’s teeth?” Myeloma and AML

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In this issue of Blood, Mailankody et al demonstrate that patients with multiple myeloma (MM) or monoclonal gammopathy of uncertain significance (MGUS) have an increased incidence of developing acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). 1

Greek mythology describes the separate legends of Cadmus and Jason who, in the face of challenges, sowed dragons’ teeth that grew into warriors. These initially uncontrollable and destructive warriors were eventually subjugated by Cadmus and by Jason in the respective legends. These stories have led to the phrase “sowing dragons’ teeth,” which has been changed over time to mean that one’s actions can result in unintended consequences.

Chemical agents have been associated with risk of cancer, often AML/MDS. 2 Andersen and Videbak 3 and Kyle et al 4 in 1970 reported the first associations between melphalan use and the development of AML in 4 MM patients described in each study. However, Kyle et al described 1 case of AML presenting with monoclonal gammopathy without clinical features of MM and in the absence of prior therapy. This case might have been MGUS. Indeed, other cases of monoclonal plasma cell disorders presenting simultaneously with AML in the absence of prior therapy have been described. 3 Simultaneous or near simultaneous presentation of MM/MGUS and AML in the same patient were thought initially to be coincidental. In retrospect, it was reasonable to postulate that mutagenic chemotherapy such as melphalan would result in the development of second cancers such as AML/MDS. However, the Seligmann group might be considered prescient when they proposed that a common etiologic agent could be responsible for some cases of concomitant AML and MM/MGUS. 5 This was based on clinical observation and preclinical research. 6,7 The latter, by Warner et al, demonstrated the induction of an AML cell line (the Walter and Eliza Hall Institute [WEHI] series) in mice by intraperitoneal injection of mineral oil and testosterone that normally would cause MM and plasmacytomas. 6

The Mailankody et al paper is exciting because it demonstrates the value of a formal national tumor registry system for tracking all cancers and “premalignant” cases, including MM, AML, MGUS, and MDS diagnoses, and the power of an epidemiologic study that will guide future research in mechanisms of carcinogenesis. Their study confirms the strong association between MM and the development of AML/MDS. As a retrospective cohort study, it is limited by lack of information regarding patient treatment and timeline assumptions regarding the type of therapy. However, because of the introduction of therapy concomitantly over time in Sweden, timeline estimates might be made regarding the use of low-dose melphalan chemotherapy, high-dose melphalan chemotherapy with autologous hematopoietic cell transplantation (HCT), and immunomodulatory drug (IMiD) use. These registry data demonstrate that the increased risk (11.51-fold) of AML/MDS in MM patients has remained relatively constant over time, regardless of changes in MM therapy.

A novel finding by Mailankody et al is the 8.01-fold increased risk of AML/MDS in
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