Chimeric antigen receptors redirect T cells to surface antigens. Discovery and validation of appro-
appropriate target antigens expands the possible indications for chimeric-antigen receptor (CAR) T cells. CS1
is expressed at high levels by multiple myeloma cells, but also to some extent on other lymphocytes.
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In this issue of Clinical Cancer Research, Chu and colleagues (1) explore the potential of targeting the CS1 glyco-
protein antigen with chimeric-antigen receptor (CAR)–transduced T cells, with the goal of developing a clinical
T-cell therapy to treat multiple myeloma.

The early and impressive success of CAR-transduced T cells targeting the CD19 antigen in B-cell malignancies
has spurred a great deal of interest in broadening this type of technology to other malignancies. Briefly, CARs are engi-
neered proteins that fuse the antigen-binding domains of antibodies to T-cell signaling molecules such as CD3ζ, with
or without additional signaling domains derived from costimulatory molecules such as CD27, CD28, or 4-1BB (2).
The technology to molecularly engineer the constructs is readily available, and producing retroviral vectors and
transducing T cells with the construct of interest is rapid and reliable. Obtaining or generating an antibody sequence on
which to base the antigen-binding moiety can take time, but the greatest challenge in developing a new CAR remains
finding a suitable antigen to target.

CS1 is a glycoprotein expressed on the cell surface of nearly all myeloma cells. However, it is also expressed at
lower levels on the majority of lymphocytes, including natural killer (NK) cells and subsets of T cells and B cells,
but not hematopoietic stem cells (3). Although testing is under way to determine the exact number of molecules that
a CAR T cell can respond to (4), clinically, CAR T cells are known to detect and target cells expressing even low levels of
cognate antigen: CD19-directed T cells cause B-cell aplasia, carbonic-anhydrase IX-directed T cells targeted bile duct
epithelium and caused cholangitic liver toxicity (5), and Her2/neu-directed T cells caused rapid death due to low-
level expression of Her2 on the pulmonary vascular endo-

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cytotoxicity directed to fraternal CS1-bearing NK cells, as demonstrated both in vitro and in vivo (8, 9). In the findings described in this article, CS1-directed T cells did not seem to degranulate in the absence of myeloma target cells, although there was increased expression of the activation marker CD69, suggesting some low-level recognition of fraternal CS1-bearing T cells. Significant fratricide could impair CAR T-cell expansion, and therefore reduce the feasibility of manufacturing the target cell dose. Moreover, immune deficiencies could occur in vivo if a specific subset of T cells, such as CMV-specific T cells, were subject to CS1-directed elimination. Although some of these safety questions could be addressed in the preclinical setting, the ultimate determination of safety and efficacy can only occur in clinical trials. In this article, the authors report on their transduction of T cells; the same group previously transduced the same type of CAR into NK cells (10). Recent studies have shown that NK and T cells can exert cytotoxic activity with remarkably different contact dynamics (11). Therefore, it would be interesting to evaluate the two CAR cell types side by side in vitro, and even perhaps in vivo in a competitive repopulation trial design.

Finally, the CS1-directed antibody elotuzumab is safe, and although it has almost no single-agent activity, it does improve response rates when administered in combination with agents commonly used in the treatment of myeloma. Elotuzumab in combination with the immunomodulatory drug lenalidomide and low-dose dexamethasone yielded an 82% objective response rate (12); elotuzumab in combination with the proteasome inhibitor bortezomib yielded a 48% objective response rate (13). The mechanism of these drugs is thought to be synergistic with the postulated mechanisms of elotuzumab. Although investigators often use lymphodepleting drugs with CAR T cells, it would be interesting to integrate this new platform more closely with standard myeloma therapies.

Given the knowledge that antibody targeting of CS1 is safe, and that CS1-directed CAR T cells effectively eliminate myeloma in vitro and in xenogeneic mouse models, CS1-CAR T cells have significant potential to change the landscape of myeloma treatment.

Disclosure of Potential Conflicts of Interest
C.H. June has ownership interest in a patent in the field of CAR T cells. No potential conflicts of interest were disclosed by the other author.

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