A number of concerns remain for translating this work to humans. First, we do not know whether the molar concentration of CD3 is similarly limiting for the expression of transgenic human TCRs. If CD3 is indeed limiting, then the enhanced expression and functionality we achieve by cotransfection of CD3 and TCRs may be accompanied by enhanced toxicity. Thus, enhanced expression may increase the risk of mispairing of endogenous and transgenic TCRs, and increase the risk of unwanted gain of function. It is, however, encouraging that the autoreactivity observed with such gain-of-function mispairing has yet to be observed in clinical trials, and indeed was absent in Ahmadi et al’s murine studies. Even without gain-of-function mispairing, however, T cells with transgenic TCRs may produce on-target antigen but off-target organ toxicities, such as the damage to melanin-expressing cells in the inner ear and the retina observed using MART1-specific TCRs and the severe colitis observed in recipients of T cells expressing transgenic CEA-specific TCRs. These toxicities may become more frequent and more severe if we simply increase overall TCR expression.

The above concerns notwithstanding, there will undoubtedly be much interest in exploring whether CD3-mediated “easing” of TCR expression really will benefit human T-cell therapies of cancer.

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Comment on Al-harbi et al, page 3579

Targeting Bcl-2 in CLL: cui bono?

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Antagonizing function of Bcl-2 is an attractive goal in chronic lymphocytic leukemia (CLL) and other lymphoid malignancies. In this issue of Blood, Al-harbi et al describe a way to combine mRNA expression data from several Bcl-2 family members into a tool that predicts in vitro sensitivity of CLL cells to ABT-737, a small molecule Bcl-2 antagonist. The Bcl-2 family of proteins that controls the mitochondrial pathway of apoptosis is made up of both pro- and antiapoptotic members. Antiapoptotic Bcl-2 is expressed at high levels in many lymphoid leukemias, perhaps nowhere more consistently than in CLL. Targeting Bcl-2 in CLL is therefore of great interest. Current efforts focus on small molecule...
inhibitors of Bcl-2. ABT-737 is the mechanistically best validated of these. An orally available analog, ABT-263, or navitoclax, is in clinical trial in several cancers, including CLL. Despite the promise of this target, clinical response has not been homogeneous. What determines response to navitoclax in CLL remains obscure.

Predictive biomarkers have been receiving renewed attention in our era of targeted therapies. Many of these therapies act best only in subsets of cancers that are not predicted using traditional groupings according to histology and anatomic location. However, it is becoming clear that molecular analysis may supersede histopathologic diagnosis in importance for personalizing treatment as targeted therapy. In some cases, drug-sensitive subsets can be defined by genetic means, as is the case with epidermal growth factor receptor (EGFR) mutant lung cancers and EGFR inhibitors. However, in all too many cases, the prospective identification of patients who will best benefit from a targeted therapy is not yet feasible.

Al-harbi et al attempt to solve this problem for treatment of CLL with Bcl-2 antagonists. Taking a supervised approach of biomarker discovery, they first test whether message levels for several individual Bcl-2 family proteins known to be expressed in CLL predict in vitro CLL response to ABT-737. They find that neither any single message level nor any simple linear combination of message levels provides significant predictive power. Confronted with similar findings, we had developed a functional assay, BH3 profiling, that can predict response to ABT-737 in vitro. However, Al-harbi et al, informed by the obvious mechanistic importance of Bcl-2 governing response to a Bcl-2 antagonist, and the demonstrated roles of Mcl-1 and BFL-1 in resistance to ABT-737, ask whether combining these factors would be a useful predictor. They hypothesize that higher Bcl-2 and lower Mcl-1 and Bfl-1 will correlate with better response, and so construct a predictor that is an arithmetic combination of message levels of the form (Mcl-1 + Bfl-1)/Bcl-2. They find that this indeed has the power to predict response of CLL cells in vitro. Moreover, they find that they can extend the use of this predictor to other cancer cell lines, including leukemia and small cell lung cancer. Finally, they demonstrate the robustness of this predictor by modulating levels of Mcl-1 and Bfl-1 and finding that sensitivity changes in ways predicted by their predictor.

It is worth noting some important limitations of this study. One limitation is that there are no data supporting the ability of this predictor to determine response to therapy in vivo. Such a test seems worth performing, given the robust performance in vitro. In addition, the predictor might be informative about mechanistic versus pharmacologic causes of resistance to navitoclax in vivo. An additional quibble is that all of the data concern RNA message levels, rather than protein levels, which have been found to be predictive of response previously. Because message and protein levels do not always correlate, one might question how much useful mechanistic insight a purely message-based predictor might provide. Such a criticism is, however, of no consequence if the predictor actually performs well when tested in the clinic. Finally, while the authors go beyond CLL in testing their predictor, it is still not clear how well it would perform in other cancers. For instance, there are plenty of cancers in which Bcl-XL, another target of navitoclax and ABT-737, is apparently expressed at much higher levels than Bcl-2, and it seems likely that this predictor would break down in those cases.

Informed by mechanism, Al-harbi et al develop and test a predictor based on a creative arithmetic manipulation of message levels of mechanistically relevant genes. The success of navitoclax, and indeed, most targeted therapies, will likely be closely linked to the innovation of biomarkers that can direct these exciting therapies where they will do the most good.
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