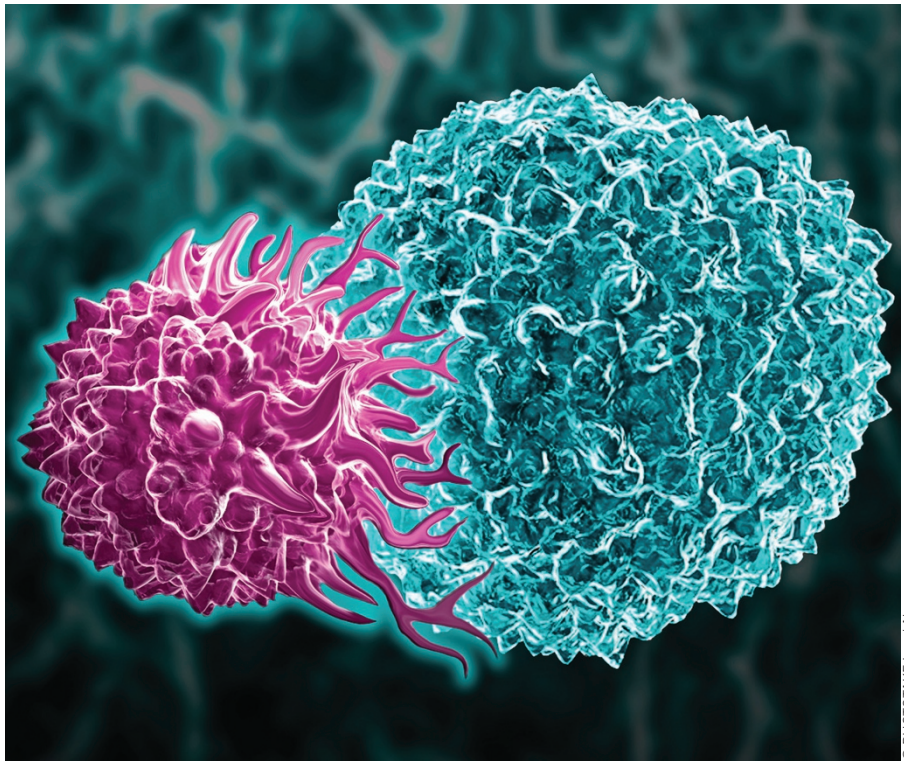
CAR-T cell therapy seeks strategies to harness cytokine storm

A grading scheme to predict toxicity to chimeric antigen receptor T (CAR-T) cell therapies published on May 29 is a bold attempt to manage one of the most promising immunotherapy approaches to fight cancer. Crystal Mackall, chief of pediatric oncology at the National Cancer Institute, and colleagues from multiple institutions came up with the scheme (*Blood* doi:10.1182/blood-2014-05-5527292014, 2014) after clinical trials by investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York were put on temporary hold in March due to several infusion-related patient deaths. "[The clinical hold] made it clear that if we don't get a handle on this toxicity, even this very potent therapy could self-destruct," Mackall says. Earlier this year, the MSKCC group and other New York–based cancer centers also defined a staging system designed to prevent or limit the toxicities that may develop with these therapies (*Sci. Transl. Med.* **6**, 224ra25, 2014).

The deaths should have come as no surprise to anyone following the field of immunotherapy, since in 2006, the (now defunct) British company TeGenero, nearly killed six healthy volunteers in a phase 1 study of an anti-CD28 monoclonal antibody, TGN1412, being tested for use in B-cell tumors and autoimmune disorders. What CAR-T cells and TGN1412 have in common is that they both lead to T-cell expansion *in vivo*, which can in turn lead to the release of toxic levels of cytokines, referred to variously as cytokine storms or cytokine release syndrome (CRS). Infusion reactions are common with antibody therapeutics, with symptoms ranging from mild nausea and fever, to life-threatening multiple organ failure, as seen with TGN1412 and more recently with some CAR-T cell therapies.



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A T cell engaging a tumor cell. Cancer treatments using CAR-T therapies lead to T cell expansion *in vivo*, which, unless carefully dosed, can release toxic levels of cytokines.

After agreeing with the US Food and Drug Administration to tweak the protocol, the MSKCC trials resumed in April. The dose of the therapy is being reduced in patients with large tumor burdens, as tumor burden seems to correlate with the severity of CRS. Patients with pre-existing conditions, such as cardiac problems, would not be eligible for the trial, and the length of time between induction chemotherapy and the application of CAR-T cells will be cut in half. Treatment can be done with nonspecific corticosteroids with or without Actemra (tocilizumab), an anti-IL-6R antibody, approved in several autoimmune indications.

But the emphasis at the moment is on patient parameters rather than the therapy itself. Mackall and colleagues recently published system factors in patient characteristics—tumor burden, age, co-morbidities—and prescribes when to give supportive care and when to treat aggressively.

> "What no one knows is whether cytokine release syndrome is essential for maximum effect."

What no one knows is whether CRS is essential for maximal effect. Mackall believes some CRS toxicity is needed. "I'm used to being an oncologist, you don't have any pain, you don't have any gain," she says. This notion has kept physicians from using immunosuppression prophylactically, for fear of subverting the therapy. Clearly, much more needs to be learned about the biology. "What will be critical about the more therapy-specific issues are variables like the degree of T-cell expansion *in vivo*," says Mark Frohlich, executive vice president at Seattle-based Juno Therapeutics, which is taking MSKCC's CAR-T cell therapy into commercialization.

In addition to CRS, off-tumor toxicity could derail CAR-T cell therapy. So far, the clinical work has focused on cells targeting CD-19, a B cell–specific antigen, and although it depletes normal B cells as well as B cell–derived cancers, this off-tumor toxicity can be managed with the application of intravenous immunoglobulin to fight infections. However, other antigens that may cause a cell therapy to cross-react with normal antigens on other tissues, may not be so easily managed. Several deaths have been reported in patients receiving engineered T-cell receptor cell therapy, a modality related to CAR-T cell therapy. An affinity-enhanced TCR for melanoma-associated antigen 3 (MAGE-A3) under development for melanoma and myeloma caused cardiogenic shock and death in the first two patients to receive it, because the antibody recognized an unrelated peptide on striated muscle.

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