[**Bridging the Gap with Chimeric Antigen Receptors**](http://www.pctcaladrius.com/pct-pulse/bridging-the-gap-with-chimeric-antigen-receptors)

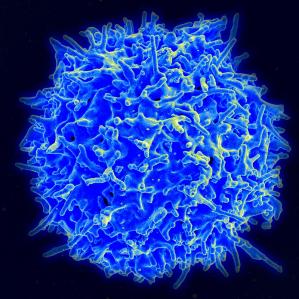
Aug 4, 2015 7:30:00 AM / by **[Cenk Sumen, Manager, Technology & Business](http://www.pctcaladrius.com/pct-pulse/author/cenk-sumen-manager-technology-business-development-pct)**

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Cell therapies armed with crafted weaponry in the form of CARs (Chimeric antigen receptors) and engineered TCRs (T cell receptors) have taken immuno-oncology to a new frontier. These therapies use specifically designed, gene-modified cells (usually T cells derived from the patient’s own blood) not only to attack the cancer cells directly, but also leverage multiple host cells and pathways to develop a durable response that can keep the cancer at bay for many years, perhaps even an entire lifetime.

As we consider that memory T cells can be very long-lived (potentially several decades), and that CAR T cells can react with bystander cells expressing the target of choice, it becomes more compelling to consider how to control aberrant T cell responses should the need arise to keep these cells in check, perhaps immediately upon infusion, but also several years after the initial treatment. Beyond the obvious approaches of “kill switches” and suicide genes such as TK (HSV-1 thymidine kinase, triggered by the antiviral drug ganciclovir), one approach is to introduce an intermediary soluble molecule between the T cell and the tumor cell to act as a molecular “bridge.”

This concept is far from new, and the field of bispecific antibodies has shown promising results in pre-clinical and clinical models, with Regeneron, MacroGenics, and Amgen (BiTE immunotherapies) among the leaders. The introduction of a bridging molecule (typically a humanized antibody) between the T cell and the tumor cell holds several advantages:

1)      The bridging molecule is titratable, whereas the T cell therapies are not as straightforward to dose (since the final drug product can replicate in vivo to varying extent)

2)      The on-target, off-tumor side effects can be more precisely ameliorated, at least in principle

3)      T cells can be “turned off” by removing the bridging molecule, and without tonic TCR or CAR signaling, are not expected to last for too long in vivo

What would be potential drawbacks to this approach? As with any biologic, reaching the appropriate concentrations in the desired anatomical location (say, in the sections of a solid tumor most vulnerable to immune attack) remains a key challenge. Next up is a simple question of timing—should the T cells be immediately pre-coated with the bridging molecule prior to infusion, or should the bridging molecule be administered once the T cells have been permitted to “settle in” (perhaps taking advantage of a lymphodepleted host environment) and home to secondary lymphoid organs (or the tumor itself, in the case of solid tumors)? What are ideal structures on the surface of the T cell to target, apart from Fc receptors and highly expressed molecules such as CD45? One might even envisage multiple bridging molecules administered sequentially; the first one to bind activating molecules on the T cells, and the second to bind inhibitory molecules to turn the response down once the desired clinical effect has been achieved.

Several academic and industry groups are now in the race to find optimal bispecific-T cell therapy combinations, which would allow greater control over the duration and extent of the anti-tumor response. This approach, while being more complicated than a straightforward CAR directly targeting a tumor surface antigen, holds considerable promise for future combination therapy, and promises to keep dealmakers busy, working to assemble the right partnerships to enable this approach.