[CAR T-Cell Therapy: High Risk, High Reward Part 2](http://blog.fisherbioservices.com/car-t-cell-therapy-high-risk-high-reward-part-2)

**Posted by**[Alexey Bersenev, MD, PhD](http://blog.fisherbioservices.com/author/alexey-bersenev-md-phd)**on Sep 13, 2016 10:00:00 AM**

As discussed in [Part 1 of this blog series](http://blog.fisherbioservices.com/car-t-cell-therapy-high-risk-high-reward-part-1), Chimeric Antigen Receptor (CAR) T-cells are having an incredible impact on the [cell therapy](http://fisherbioservices.com/market-solutions/cell-therapy) industry.  However, despite the many success stories, there are also several items that require consideration if we are to truly harness the potential of this type of therapy.  Let’s begin by exploring some of the unresolved questions and issues surrounding CAR T-cell therapy.

**Toxicity**High efficacy comes with a price of toxicities. Most CAR T-cell therapy procedures in hematological malignancies are associated with so-called Cytokine Release Syndrome (CRS). This complication is specific for [adoptive immunocellular therapies](http://blog.fisherbioservices.com/amazing-samples-tumor-saving-lives). It manifests with septic shock-like symptoms, and could have different degrees of severity which may lead to patient death. A few clinical trials were temporarily suspended by the FDA due to CRS-related deaths in CAR T-cell trials. CRS could be rapid, unpredictable and currently, there is no consensus on prevention and management of CRS.

Other complications associated with CAR T-cell therapy are neurotoxicity (usually reversible aphasia, seizures), immune reaction to murine components of CAR and so-called “on-target off-tumor effects” (destruction of normal cells, shared common antigens with tumor). Until safer clinical protocols with clearer guidance on prevention and management of CAR T-cell therapy-related toxicities are developed, it will not go mainstream and become widely available at any hospital.

**How to dose a dividing drug**One of the remarkable features of CAR T-cells is the ability to multiply in vivo - after infusion and homing to [bone marrow](http://blog.fisherbioservices.com/amazing-samples-bone-marrow). For example, in a seminal case study from UPenn, [published in 2011](http://www.nejm.org/doi/pdf/10.1056/NEJMoa1103849), as low as 1.5 x 105 CAR T-cells, given to chronic lymphocytic leukemia (CLL) patients, expanded more than 1000 times in vivoover time. Because it is a “dividing drug”, determining the correct therapeutic dose becomes an extremely challenging task. Conventional drug-body interaction concepts of pharmacodynamics and pharmacokinetics cannot be easily applied to such a “dynamic/ alive/ persistent drug” as CAR T-cells.

Interestingly, ex vivo expansion of CAR T-cells may not necessarily correlate with in vivoexpansion and potency. Even if standardization of manufacturing and clinical protocols after years of trials may help with figuring out a correct dose for a patient, the interaction of CAR T-cells with a tumor and its environment in each patient cannot be standardized.

Should tumor burden, aggressiveness of disease, comorbidities, history of previous drug treatment and features of CAR product be accounted in dosing of CAR T-cells in the same condition? Until now, nobody knew how to dose CAR T-cells in each particular condition, minimizing risks and maximizing therapeutic benefit. The CAR T-cell therapy-related phenomenon of “living drug” underlines and makes us acknowledge the high complexity of personalized autologous cellular therapy.

**Relapses**The high efficacy data reported from CAR T-cell trials in hematology-oncology is based on short-term outcome measures (i.e. tumor disappearance in one month or 100 days survival). However, if we look at durability of response long-term, the efficacy will be diminished due to relapses. At the one year mark, about 30-35% of b-acute lymphoblastic leukemia (B-ALL) patients will relapse after receiving CAR T-cells. The relapses could be due to antigen (target) escape or due to loss of CAR T-cells. At this point, it is unknown how to avoid post-CAR T-cell relapses, however different approaches have been tested including, better selection of inclusion criteria, CARs for 2 targets, increasing CAR T-cells persistence, and humanized CARs.

**Do we need CAR T-cell persistence in vivo?**It is unknown whether we need CAR T-cells to persist for a very long time (many years or lifelong) or only for a few months. Some [clinical trials](http://www.nejm.org/doi/full/10.1056/NEJMoa1407222#t=article) have demonstrated correlation of durability of response with long-term CAR T-cell persistence.  However, some are not such as the [NIH](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2814%2961403-3.pdf) and [MSKCC](http://stm.sciencemag.org/content/6/224/224ra25.long)). Researchers, who do not favor long-term persistence, are saying that [we need CAR T-cells to stick around for 3-6 months](http://insights.bio/cell-and-gene-therapy-insights/?bio_journals=cell-and-gene-therapy-world) for durable response. One downside of long-term persistence in such hematological malignancy as B-ALL is B-cell aplasia, which is caused by “on-target off-tumor” effects. B-cell aplasia could be a good marker of CAR T-cell persistence. It remains unclear why in some trials CAR T-cell persistence is necessary for durable response, but in some trials it is not.

**Beyond CD19**It is important to acknowledge that all CAR T-cell buzz is based mostly on [the success in CD19-positive malignancies](http://blog.fisherbioservices.com/viral-cell-therapies-fighting-cancer). This is a unique biomarker for all types of immune B-cells. Targeting of malignancies with other biomarkers today is not as successful as CD19. The selection of a good biomarker is a big question for CAR T-cell therapy developers. Unfortunately, surface cell markers, targeted by CAR, are not unique for a tumor and also expressed on normal tissues. At this point we don’t know if targeting other tumor antigens will repeat the success of CD19.

**Beyond liquid tumors**CAR T-cells proved their efficacy in liquid tumors (hematological malignancies), but it remains unclear if and how they will work in solid tumors. Liquid tumors have much lower prevalence in population than solid tumors; therefore the market of CD19-CAR T-cell therapies will be relatively small. Currently, initial results of CAR T-cell therapy clinical trials do not demonstrate a clear benefit in solid tumors including, mesothelioma, brain tumors, breast cancer, and sarcomas. There were less toxicity issues, but signs of efficacy were marginal. Experimental studies demonstrated that solid tumors are much harder to tackle than leukemias due to different structure, mutational signature and plasticity, interaction with immune system and role of tumor microenvironment/ stroma. Efficacy of CAR T-cells in solid tumors is the “one billion dollar question”!

**Manufacturing models and delivery**The field of CAR T-cell therapies is currently highly commercialized with a focus on centralized manufacturing. However, the potential high cost/ high risks from one side and development of new cell processing tools from the other side may shift the translation/ delivery model to point-of-care or decentralized manufacturing. It is unclear at this point how autologous highly personalized (and pricey) CAR T-cell therapy will feel on the competitive market. Many CAR T-cell developers are starting programs for development of “off-the-shelf” CAR T-cell products, generated from “universal” allogeneic donors. It is possible that in the future, allo- CAR T-cell model will stay in industry with centralized manufacturing, but auto- model may shift to “point-of-care” hospital-based decentralized laboratories.

CAR T-cell therapy is a very exciting and innovative approach to treating a variety of different cancers. There are obvious advantages, as discussed in Part 1 of this blog series, but also many challenges that we need to be overcome as an industry for it to be a reliable, effective treatment. This is an exciting time for cell therapy and the future looks very bright!