

## CAR-T-Cell Therapy for Multiple Myeloma

Faculty Presenter

**Eric Smith, MD**, Director of Clinical Translation, Cellular Therapeutics Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

### Scholars' Summaries

*Authored by **Tanaya Shree, MD, PhD**, Stanford University School of Medicine, Stanford, CA, USA*

Dr. Smith began by describing why CAR T cells might be a good therapeutic strategy in multiple myeloma (MM). We know it is a bone marrow-based disease, like ALL in which CAR T cells have been so successful, and we know that immune-mediated therapies such as lenalidomide and allogeneic stem cell transplants work in myeloma. Though allogeneic stem cell transplant is infrequently used in MM due to the high mortality rates, the patients who do survive do very well, suggesting long-term protective antitumor immunity.

However, there are also challenges to targeting MM with CAR-T cells, primarily regarding the optimal antigen to target. CD19 (the target for which CAR T-cells have been efficacious in ALL) is not typically expressed on MM cells, or expressed at low levels. There is some evidence that CD19 may be expressed on MM stem cells and a study at the University of Pennsylvania using a CD19-targeted CAR in relapsed/refractory myeloma patients did show response in 2 out of 10 patients. Another clinical trial attempted to target the kappa light chain but failed, likely due to the fact that most light chain produced by myeloma cells is secreted, not retained on the surface, and the secreted protein may then block the CAR on the T-cells.

Other possible cell surface targets in MM include CD38, CD138, CD56, and SLAMF7, and all of these are being explored as targets for use in CAR-T cell therapies. However, all of these proteins are expressed on other important cells in the body, which may lead to undesirable side effects. Dr. Smith has instead been pursuing CAR-T cells targeting B Cell Maturation Antigen (BCMA). BCMA is important for plasma cell survival and differentiation. It is not significantly expressed in other normal tissues. Although BMCA also exists in soluble form, it does not seem to affect the function of the CAR.

Dr. Smith's team designed anti-BCMA CAR-T cells with the 41BB costimulatory domain as this results in greater persistence than CD28 domain containing CAR-T cells. He detailed the process for CAR-T cell generation and optimization, including quality controls that assayed for the ability of other types of cells to activate the CAR-T cells, and looking for off-target binding against HEK293 cells transduced with a broad protein library. They had to optimize the copy number of the CAR in the T cells and they ultimately also made a companion immunohistochemical test for BMCA to use during development and clinical testing. Finally, he described an ongoing trial with this BMCA CAR-T cell at Memorial Sloan-Kettering (NCT03070327). Nine patients have been dosed so far and although the efficacy data has not yet been released, they have had at least one remarkable responder.

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*Authored by **Andrew Dunbar, MD**, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

Dr. Smith provides an update on this exciting area of active research and the development of CAR T-cells directed against plasma cells for use in multiple myeloma. He provides rationale for the targeting of CARs directed against B-cell Maturation Antigen (BCMA), a highly specific marker of two plasma/multiple myeloma cells and takes participants through the epitope/antigen discovery process, which identified BCMA as a target. He also provides early clinical trial data of BCMA-directed CAR T-cells currently in development in myeloma clinics at Memorial Sloan Kettering, which shows incredibly promising results. He also briefly describes common toxicities with CAR-T cell therapy, including primarily cytokine release syndrome, and the protocols being developed to help best treat these serious complications.