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The T-body approach combining antibody specificity with T cell activity for adoptive vaccination of cancer

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Abstract

The "T-body" approach is based on engineered T cells expressing chimeric antibody receptor (CAR) that endows them with antibody-type specificity to any pre-defined target antigen. We have designed the modular CAR construct so that the modified, redirected T cells will undergo activation and perform their effector or regulatory function upon encountering their target. Accordingly, the CAR's composition includes extracellular recognition domain made of a single chain variable fragment (scFv) of an antibody linked to intracellular domains of various stimulatory and co-stimulatory molecules that dictate the function of the transduced cells. For antitumor reactivity we constructed CARs made of scFv specific to human Her2/neu, CEA and CD24 (a cancer stem cell marker of certain adenocarcinomas such as pancreatic and colorectal ones).

To optimize the antitumor effect in therapeutic settings we have treated either immunodeficient mice bearing human cancer xenografts or transgenic mice that spontaneously develop tumors expressing TAA. T-bodies effectively rejected primary as well as disseminated tumors. Multiple systemic administrations of T-bodies were required for complete elimination of xenografts and autologous murine tumors. Of note, single intratumoral injection was sufficient to eliminate breast, prostate cancer bone metastases as well as colorectal and pancreatic cancers. Moreover, under certain conditions, we have established a time-window which allows allogeneic T-bodies to serve as universal donors.

Recently, our pioneering studies in murine models have been reproduced and applied in pilot trials to end-stage cancer patients. Dramatic complete responses have been already reported in neuroglioma, chronic lymphocyte leukemia, and acute child and adult B cell lymphoma patients. These trials have also reported on several treatment-related severe yet manageable side effects (mostly associated with acute 'cytokine-storm' and 'tumor lysis' syndrome, both outcomes of the vigorous antitumor responses of the T-bodies that could eliminate a huge tumor mass within the first few weeks treatment. The dynamics of the T-body antitumor effect reflect both their built-in ability to specifically recognize the tumor, propagate and reject it and further differentiate into memory cells that keep the tumor on-check

Biography

Zelig Eshhar has completed his PhD at the Weizmann Institute and post doctoral Studies from Harvard University Medical School. He spent sabbatical years of research at DNAX Institute of Molecular Biology and Stanford University and at the National Cancer Institute at the NIH. He served as the Chairman of the Department of Immunology at the Weizmann Institute and holds the position of Chairman of research in Immunology Tel Aviv Sourasky Medical Center and guest professor at the Faculty of Medicine of Tel Aviv University. Professor Ehhar has published more the 210 research articles.