HHS Public Access

Author manuscript

Cancer Discov. Author manuscript; available in PMC 2021 April 29.

Published in final edited form as:

Cancer Discov. 2021 April ; 11(4): 798–800. doi:10.1158/2159-8290.CD-21-0022.

T cells as the future of cancer Therapy

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Summary:

In the next 10 years, gene-engineered T-cell therapies have the potential to provide broad benefit for the treatment of patients with cancer. Advances in immunology, molecular biology, and bioengineering allow the design of gene-engineered T cells that actively target metastatic lesions, specifically recognize and kill cancer cells, and maintain long-term immunologic memory.

The basic principle of any cancer therapy is to kill cancer cells and spare normal cells. If we were to generate a wish list of properties for a therapy that is aimed at treating any metastatic cancer, we would design it to actively circulate throughout the body, actively accumulate in areas with cancer cells, specifically recognize cancer cells separate from normal cellular counterparts, kill cancer cells, amplify the antitumor response to kill more cancer cells, continue to circulate through the body looking for other cancer cell deposits, and remember the cancer cells and attack them again and again. Chemotherapy agents and small-molecule drugs can achieve some of these features using their pharmacologic properties for distribution throughout the body with repeated administrations, and interact with key cancer cell functions leading to cell death. Antibody therapies and antibody–drug conjugates have a remarkable ability to circulate long-term and specifically recognize surface proteins, and then engage effector processes to kill cancer cells. Cancer immunotherapy with immune-checkpoint blockade takes advantage of the ability of antibodies to target surface proteins on immune cells and release them to attack the cancer, achieving some of the wish list of properties partially through an indirect way of reactivating endogenous immune responses to cancer. All of these therapies fulfill some, but not all, of the wish-list attributes, and have achieved remarkable success in treating and curing several cancer subtypes. For the rest of the patients whose cancers are not treatable with existing cancer therapies, we need a next generation of anticancer agents that fulfill as many as possible of the wish list of attributes of an ideal cancer therapy.

Adoptive cell transfer (ACT) T-cell therapies have the potential to fulfill all of the desired characteristics of the ideal anticancer therapy. A fraction of tumor-infiltrating lymphocytes (TIL) recognize cancer cells specifically due to the MHC presentation of mutational neoantigens or differentially expressed cancer lineage antigens. Upon reinfusion after conditioning chemotherapy, they can amplify *in vivo* by brisk cellular division, specifically recognize cancer cells, exert the remarkable cellular cytotoxicity of antigen-specific

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cytotoxic T lymphocytes, and generate a progeny of long-lived memory T cells specific for the cancer antigens (1). This therapy induced durable responses in patients with melanoma, but the ability to isolate and expand TILs was limited for common epithelial cancers (1). Expressing artificial receptors on T cells using gene transfer approaches allowed the successful development of chimeric antigen receptor (CAR) therapy for leukemias and lymphomas (2). The artificial T-cell surface receptor recognizes hematopoietic lineage antigens expressed by cancer cells, such as CD19 or BCMA, that are also expressed on normal cellular counterparts, as it is feasible for humans to live without B and plasma cells for a period of time (2). However, the use of CAR therapies for other cancer types has been limited by the paucity of truly unique cancer-specific surface proteins. As the specific recognition of T-cell targets is endowed by the T-cell receptor (TCR), the genetic transfer of the TCR from one T cell to another allowed the generation of large armies of TCR transgenic T cells for ACT (1, 3). This approach is limited by the HLA restriction of TCR recognition, but it can target any intracellular protein that is presented as an immunogenic peptide, significantly broadening the potential list of targets over the CAR surface molecule targets. Overall, gene-engineered T-cell cancer therapies have resulted in responses and cures in specific cancers, and these pioneering successes have opened a new field where immunology, molecular biology, bioengineering, and clinical experimentation have a broad space to develop new approaches to treat cancer.

Several technical advances building on the current approaches predict a significant increase in the clinical testing and utility of T-cell therapies in the next 10 years. The commercialization of CD19 CAR therapies for ACT, becoming mainstream treatment products, has triggered the bioengineering and cell therapy manufacturing field to develop improved means to expand and genetically manipulate T cells in closed culture systems (4). It is a new biopharmaceutical industry paradigm where, instead of the generation of large batches of a drug (a chemical molecule or an antibody) to be used in thousands of patients, a small modular culture system makes multiple individualized batches repeatedly (4). The ability to engineer multiple proteins in T cells to avoid recognition upon allogeneic infusion and graft-versus-host reactions has opened the way to the development of allogeneic T-cell therapies that can be used for multiple patients (5). Significantly increasing the number of gene edits on progenitor cells and the expansion of the resulting progeny T-cell therapy can be achieved with culture systems that start from stem cells and generate large numbers of mature T cells that can be redirected to attack cancer cells by gene engineering (6).

The expression of foreign genes by T cells had been a key limiting step, which was addressed with the use of retroviral and lentiviral vectors that insert foreign transgenes into the T-cell genome (1). However, this approach limits the speed in testing T-cell gene edits (both knockout and knock-in), as each time it requires the generation of a new clinical-grade viral vector. An approach based on CRISPR/Cas editing of T cells following a physical method of electroporation promises increased versatility in the testing of knock-in and knockout gene edits in T cells (7). With this technique, clinical-grade manufacture of gene-modified T cells relies on nonviral nucleotide sequences and protein complexes that can be generated in a shorter time and released for clinical use with much lower expense.

A key issue on the use of ACT T-cell therapies continues to be the specific recognition of cancer cells. TCRs to mutational neoantigens are the ultimate specific recognition of cancer, as $CD8^+$ T cells can differentially recognize single-nucleotide mutations that change one amino acid in a sequence of nine presented by an HLA on the surface of cancer cells. The infusion of isolated TCR-specific T cells has achieved clinical responses when bulk T cells did not (8). Isolation of T cells based on their recognition of a mutational neoantigen presented by one of the six HLA class I alleles of each patient enables the cloning of the alpha and beta chains of neoantigen-specific TCRs (9). These TCRs can then be used to generate a personalized ACT TCR transgenic T-cell therapy specific for the private cancer mutations of any patient.

As most, if not all, surface molecules on cancer cells are not really cancer-specific, the use of CAR therapies has been limited by the potential of on-target recognition of normal cells leading to serious toxicities. The potential to use a combination of chimeric and switch receptors that allow differential recognition of a positive input signal on cancer cells and a negative input signal to not attack normal cells, or two positive signals that are specific for cancer cells (a way to increase the probability to result in a cancer-specific combinatorial target), is significantly broadening the universe of surface targets for CAR therapies (10–12). Another approach being tested in the clinic is the use of bispecific CARs. Such CARs have two positive inputs, which can be designed as “or” or “and” inputs (12). The first bispecific CARs are able to respond to either of their two targets, thereby avoiding antigen-escape variants that lose one of the two targets, a feature that has been detected in CARs to CD19 and BCMA (12). Furthermore, it is now possible to engineer CARs to not only recognize proteins on the surface of a target cell, but to respond to a soluble antigen (13), and it is also possible to generate orthogonal receptors that recognize an artificial protein (14). These features allow gene-engineered T cells to derive a positive proliferative signal in response to secreted proteins by cancer cells, or to engineer the T cells to respond to orthogonal cytokines that would only induce T-cell proliferation to the genetically engineered antitumor T cells. It can be envisioned that the ability to specifically signal to gene-engineered cancer-specific T cells will allow us to avoid the need for lymphodepleting conditioning chemotherapy as the adoptively transferred T cells with the artificial receptor are the only ones to proliferate upon providing the orthogonal cytokine ligand (15).

Other current limitations of ACT therapies will be overcome with the gene engineering of new functions on T cells or blocking certain genes. For example, it can be easily envisioned that the complication of cytokine release syndrome with current CAR therapies will be modulated by inserting tunable gene switches that decrease cytokine release by the engineered T cells. Similarly, T-cell programs that limit their *in vivo* functionality, such as the development of T-cell exhaustion or limited tissue penetration of T cells, will be overcome by specific knockout of gene programs leading to exhaustion or knock-in of genes that provide gain of functions to T cells that maintain their antitumor activity long term despite repeated TCR engagement, and by expressing genes that facilitate T-cell circulation and homing to tumors. Finally, current issues with artificial TCRs such as tonic signaling with CARs, or the lack of costimulation with TCR engineering, are being improved with advances in protein engineering and synthetic biology. All of these approaches predict that T cells will be programmable to induce continued antitumor activity with limited toxicities.

In conclusion, the field of ACT therapy for cancer has demonstrated proof-of-principle evidence that it can become a broadly applicable therapy to treat patients. The pioneering experiences with TIL, CAR, and TCR transgenic ACT therapies are in the process of becoming standard-of-care therapies for selected cancers. The basic principle of T cells recognizing specific sequences presented by cancer cells and then exerting their cytotoxic power, together with the ability to expand *in vivo* upon antigen encounter, actively circulate through the body, and maintain long-term memory, predicts that this mode of therapy will find broader uses in the future. The research in this field is providing solutions to key technical challenges that had limited the applicability of gene-modified T-cell therapies for common cancers, which will result in improved gene-engineered T-cell ACT therapies being developed in the clinic.

Acknowledgments

A. Ribas is supported by NIH grants R35 CA197633, P01 CA244118, and P30 CA016042, The Parker Institute for Cancer Immunotherapy, and The Ressler Family Fund.

Author's Disclosures

A. Ribas has received honoraria from consulting with Amgen, Bristol-Myers Squibb, Chugai, Genentech, Merck, Novartis, Roche and Sanofi; is or has been a member of the scientific advisory board and holds stock in Advaxis, Apricity, Arcus Biosciences, Compugen, CytomX, Five Prime, ImaginAb, Highlight, Isoplexis, Kite-Gilead, Lutris Pharma, Merus, RAPT, PACT Pharma, Rgenix and Tango Therapeutics; and has received research funding from Agilent and from Bristol-Myers Squibb through Stand Up to Cancer (SU2C). A.R. has received licensing revenue from a patent application covering the use of non-viral gene editing of T cells that was licensed by The Regents of the University of California to Arsenal Bio (South San Francisco, CA).

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