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REVIEW

Will T-cell therapy for cancer ever be a standard of care?

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Cellular therapies for cancer are showing increasing efficacy but their introduction as a 'standard of care' for these disorders is hampered by technical, regulatory and financial concerns. This review identifies some of the major problems and suggests potential solutions.

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Cellular Immunotherapy for Cancer has recently received two major boosts. The first was the approval of the first ever cellular therapy in the United States, in which a dendritic cell vaccine, Provenge, was shown to be both safe and effective for the treatment of advanced prostate cancer.[1] The second was more directly related to the subject of this commentary, namely the demonstration in five patients with advanced B-cell malignances of remarkable responses to the infusion of autologous T cells that had been genetically modified to express chimeric antigen receptors (CARs) directed to the tumor-associated antigen CD19.[2] Although by no means the first report of advanced tumors responding to the infusion of tumor-directed T cells,[3–11] the responses were so rapid and dramatic that the force and extent of the resulting positive publicity caught the attention of the wider scientific and lay communities, and broke through the pre-existing barriers of indifference.

These successes could not have come at a better time for cellular immunotherapy in general and T-cell immunotherapy in particular. Despite the many obvious advantages of these targeted therapies compared with the blunt instruments of chemotherapy, radiotherapy and surgery, and their clinical successes over the preceding 20 years,[3–11] it had proved stubbornly difficult to get cell therapies into the clinic as a standard of care. If the future really is to prove different to the past and the true potential of the approach is to be realized, then it is important to understand the nature of the difficulties and the reasons why this time around 'things are different'.

One of the major obstacles to the introduction of cell therapies, including T-cell therapy, as approved drugs is that the developmental pathway does not bear any relationship to the pharmaceutical model. Thus, each product is made separately for each individual treated, rather than being prepared in bulk in a standardized form. This in itself is a challenge to the robust scalability required for late phase clinical studies. Moreover, the standard pharmaceutical business model is to spend a great deal of money in the initial phase of drug development and then recoup this by selling cheap-to-manufacture goods with exceedingly high margins. For cell therapies and other complex biological agents, however, the cost of goods will remain high even after approval and scale-up. Worse, the very complexity of these agents that renders them difficult and expensive to make also means that it is often necessary to perform iterative early phase clinical studies with a single product, making minor modifications to each sub-component of the agent to enhance overall safety and potency, rather than the more conventional linear drug development of phase 1, phase 2, phase 3 and approval that is typical of conventional small molecules. This process with its unknowable duration and unpredictable timelines makes financial structuring of the project difficult for Biotech and major pharmaceutical companies alike. Last but not least, the biological complexities of these products often means that the associated intellectual property is complex and diversely held, leading to lengthy negotiations over cross-licensing and the payment of stacked royalties, complexities that may prove insuperable when multiple investigators, companies and countries are involved. As a consequence, T-cell therapy, like other cell therapies for cancer, has languished within academic medical centers as a boutique therapy of marginal interest to the outside word and with minimal impact on public health.

To change the status of T-cell therapy for cancer and make it broadly applicable, we need to accomplish four tasks. The first is to show that the approach is qualitatively ***better*** than any other available therapies. In other words, these therapies must clearly be shown to ameliorate, and ideally cure, diseases that are otherwise not amenable to conventional treatment. Simply briefly extending life or slowing disease progression by a few weeks will almost always (*pace* Provenge) be insufficient to convince individuals and companies to commit the necessary resources. Moreover, there needs to be at least some evidence of these qualitatively superior activities even in phase 1 (safety) clinical studies, otherwise phase 2 (efficacy) studies will rarely be implemented. An excellent recent example of this requirement for superior results during phase 1 study is the recently reported study of CD19 CAR T cells, which helped dramatize the potency of the approach for a wider public.[2] The combination of these data with other dramatic results for T-cell therapy of cancer[3–11] have formed a cluster of success that has finally helped convince the broader community of the potential value of the approach.

The second task is to make T-cell therapies as ***broad*** as possible, by designing these effector cells in such a way as to allow a single type of cell manipulation (for example, introduction of a chimeric receptor) to be minimally modified (for example, by changing the targeting or the signaling domain) to permit application to as many disorders as possible. Such a building-block approach means that it should not be necessary to completely restart the

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product development clock every time a slightly different patient population is targeted.

It is also necessary to make T-cell therapies ***simpler*** than they currently are, by which I mean easier to scale and more robust to process. In this way, we can avoid a requirement for large teams of highly skilled and experienced research technicians and investigators to implement any study for each individual at every center, and will have the option of rapid transition into larger pivotal or licensing studies.

Finally, T-cell therapies must be shown to be ***safe***. There is currently a low societal tolerance for severe adverse effects from genetically modified cells. Indeed, such intolerance may be well justified since, cell therapy, unlike most small molecule drugs, may produce unwanted consequences that persist and indeed progressively worsen over time, with graft versus host disease (GvHD) being the classical example of this phenomenon.[12]

Fortunately, the past decade has seen major progress in all four tasks, such that T-cell therapies really have now become better, more broadly applicable, safer and simpler.

T CELLS MAY BE BETTER THAN CONVENTIONAL THERAPIES

Because of the complexity of manufacturing T cells, most subjects who receive these agents as therapy for cancer have advanced resistant disease and so are essentially end-stage patients. With conventional small molecule drugs, these patients would enter phase 1 studies that were not designed with therapeutic intent, but rather to establish safety of, and tolerance to, the agent; any beneficial effects on tumor growth would be seen as icing on the cake and would not be deemed necessary for proceeding to the initial therapeutic phase of drug development, termed phase 2. Fortunately, T-cell therapies for cancer have often had a better track record, even when they are given to patients in advanced disease,[13] and most investigators plan their studies in the hope of seeing evidence of disease response even in a small phase 1 study. Indeed if such benefit is not seen, investigators are often discouraged from proceeding or unable to obtain additional grant or other funding and do not continue further. Although this early exit has probably led to some therapeutic approaches being abandoned prematurely, for all the reasons stated earlier, T-cell therapies for cancer will likely only ever be competitive if dramatic benefits are obtained; these should therefore be observed even in early phase studies and even in patients with advanced disease. Fortunately, there are now publications from many investigators showing impressive activity for T-cell immunotherapy, demonstrating remarkable tumor responses and complete remissions in over 60% of patients with advanced Epstein Barr Virus (EBV)-positive lymphomas[7] and in over 25% of patients with advanced nasopharyngeal cancer using EBV-directed T cells.[10,11] Similar results are also well established for patients with advanced melanoma using tumor-infiltrating leukocytes or T cells redirected to tumor-associated antigens by introduction of a transgenic T-cell receptor (TCR).[4,14] Pediatric malignancies too are beginning to benefit from T-cell therapeutics, with promising data reported for neuroblastoma using T cells directed against the tumor-associated antigen GD2.[15]

There is no doubt that we are only at the beginning of exploiting the full potency of these agents. We already know that benefits can be enhanced if patients are first depleted of endogenous lymphocytes by drugs and/or radiation, likely because the homeostatic mechanisms responsible for restoring lymphopoiesis after lymphodepletion also favor the expansion of the introduced tumor-directed T cells. It is also probable that the combination of T-cell immunotherapy with checkpoint inhibitor antibodies such as CTLA4 or PD1 will further boost the activity and persistence of tumor-directed T cells and thereby enhance their activity.[16]

In addition to enhancing expansion and survival by using lymphodepletion and checkpoint antibodies, the T cells themselves may be engineered to enhance their survival in the generally hostile tumor microenvironment. For example, the so-called second- and third-generation CARs have been created that improve on the original CARs by incorporating one or more endodomains from co-stimulatory receptors (such as CD28 or 41BB) that provide signals to maintain and enhance T-cell survival, proliferation and function once the antigen-specific signal is received through the native or chimeric receptor.[17,18] In addition to engineering T cells to receive superior stimulation upon tumor cell engagement, it is also possible to introduce countermeasures to tumor immune evasion strategies, thereby allowing anti-tumor T cells to continue to flourish even in an otherwise hostile tumor environment. To this end, T cells have already been engineered to express a dominant-negative TGFβ receptor (DNRII), which inhibits the cells' response to this immune-inhibitory cytokine that is widely produced by tumor cells and their environment.[19] Forced expression of the DNRII in EBV-specific T cells has been safe, and in early phase clinical trials is showing promise for enhancing their *in vivo* survival and anti-tumor activity in patients with therapy-resistant EBV+ lymphoma. Other investigators are developing chimeric receptors in which the binding of a tumor-derived inhibitory cytokine such as IL4 induces instead a pro-inflammatory response in the T cells. These and other engineered countermeasures should enable tumor-directed T cells to have a broader role in the treatment of human disease.

THE T-CELL PLATFORM MAY BE BROADLY APPLICABLE

While each T-cell product is distinct and usually intended for a single recipient (but see '*T-cell Manufacture can be made* ***Simpler***' below), many of the biological and pre-clinical studies needed to develop and justify the approach can be applied to T-cell therapies of multiple different tumors and tumor targets in which investigators simply modify the cancer-directed receptor sequence while retaining the same technologies to produce optimized gene transfer and expression. Thus, the past decade has seen major, and widely applicable, improvements both in the vectors used to transfer the genes of interest (for example, using lentiviral vectors)[20,21] and in optimizing the expression of the transgenes they encode, for example by introducing appropriate spacer elements to enhance CAR expression or by manipulating the expression of native α and β TCRs to limit cross-pairing of introduced transgenic TCR.[3,22,23] Such technologies are applicable for essentially all planned uses of T cells for cancer therapy. Similarly, the development of countermeasures to tumor immune evasion strategies can be widely introduced into therapies targeting a multiplicity of different cancers since there is considerable conservation of evasion techniques between tumors.

T-CELL MANUFACTURE CAN BE MADE SIMPLER

At some time or another almost every investigator who has written a grant application to use a T-cell therapeutic will have received a hostile review that dismisses the entire concept as of limited impact, since the approach is simply too complex to become standard of practice. It would be wrong to suggest that such reviewers are 'either fools or knaves' but they nonetheless demonstrate ignorance of modern civilization. Every manufactured item we see or touch is the product of a multiplicity of processes of staggering complexity, whether the object is a pencil or an iPad. The broader introduction of T-cell therapies has been limited not by their excessive complexity but rather by the lack of robust, scalable manufacturing processes. Until recently, T-cell manufacturing has been highly labor intensive, requiring sustained input from highly skilled operators who have to assess and manipulate the growing T cells over a considerable length of time, with a significant failure rate. This lack of scalability and robustness is not a reflection of any unique disadvantage of T cells

but a consequence of the lack of resources that have been devoted to developing industrialized (that is, scalable and robust) processes. In other words, T cells have not been widely used because manufacturing is not robust and scalable, and manufacturing has never become robust and scalable because T cells are not widely used. We are now finally escaping from this Catch 22.

Sufficiently impressive results have now been obtained by a sufficient number of investigators to justify the investment in manufacturing process development required to ready T cells for large-scale clinical trial and registration. For example, in our own laboratory we have helped to develop disposable gas permeable rapid expansion devices (G-Rex Wilson Wolf Manufacturing, Minneapolis, MN, USA) which are scalable from 10 cm^2 to at least 600 cm^2 and will grow tumor-directed T cells in large numbers with minimum investigator interference.[24,25] It is no exaggeration to say that these and other 'load, lock and leave' devices are revolutionizing the scalability and robustness of T-cell manufacture and will undoubtedly be widely implemented in later phase studies.

Paradoxically, these improved expansion devices for individual therapies may become less universally required than had previously been thought, since off-the-shelf T cells made in bulk from third party donors may be able to substitute for individualized cell therapies. For example, a recent multi-center study manufactured and stored anti-viral T cells directed to cytomegalovirus, EBV and adenovirus in advance and gave them to partially HLA matched hemopoietic stem cell transplant recipient when they suffered from a disease caused by one or more of these viruses. The investigators showed that these partially HLA-matched stored T cells controlled or eradicated infection in $>70\%$ of patients after stem cell transplantation even when the T cells were matched at, and had anti-viral activity through, just a single HLA locus.[26] If this approach can be extended beyond virus-specific T cells to be used for cancer-specific T cells, then the production and maintenance of large banks of stored off the shelf T cells could be used for patients across the world.

SAFETY

While T cells can be highly effective treatments for cancer with an excellent safety profile in many applications,[27] it has become abundantly clear that these effector cells may also have substantial toxicity. The adverse effects of T cells have been appreciated for many years, becoming clearly evident since the introduction of donor lymphocyte infusions (that is, donor T-cell infusions) for the treatment of leukemic relapse in recipients of allogeneic stem cell transplants. These patients may benefit from the anti-leukemic activity of the T cells but also have a high risk of developing severe or fatal GvHD. More recently, T cells expressing either CARs or transgenic native $\alpha\beta$ receptors directed to cancer-associated antigens have produced severe and even fatal adverse effects.[28–32] These effects may be due to cytokine storms induced by interaction of the effector T cell with its target, to extensive tissue destruction by the effector cells (tumor lysis syndromes), or to on-target but off-organ toxicities when the tumor-associated antigen is also expressed by normal tissues at a sufficient level to be targeted by the infused T cells.

Thus, T-cell therapies will never reach their widest applicability unless we can control the incidence and severity of the adverse events that they may cause, particularly since these adverse effects may worsen rather than improve over time. As a consequence, there has been increasing interest in developing suicide or safety gene systems which will allow an 'exit strategy' from a cellular therapy should severe adverse events occur. The first and most widely used suicide gene is the HSV (herpes simplex virus)-derived thymidine kinase gene. Incorporation of this gene in adoptively transferred T cells after allogeneic stem cell transplantation has allowed beneficial effects from the cells to immune reconstitution (reducing virus disease and perhaps relapse) while allowing significant GvHD to be abrogated by administration of nucleoside analogs such as ganciclovir, which are phosphorylated by the HSV-Tk and block DNA synthesis.[33] The overall safety and efficacy of this approach is now being established in a pivotal multi-center phase 3 clinical trial.

Despite the undoubted value of the HSV-TK-ganciclovir suicide system, the approach has limitations that may limit the ultimate range of applications. Because cell toxicity is produced by inhibiting DNA synthesis, actively dividing cells are the most susceptible. This selectivity may be beneficial, for example by sparing non-alloreactive (that is, non-dividing) T cells when treatment is given to terminate GvHD, but under other circumstances, and for other cell types, the discrimination may be less helpful. For example, the system cannot readily eliminate post-mitotic cell populations, and since the mode of action means it may be days or even weeks before benefit is obtained, the more acute toxicities that have been associated with tumor-directed T-cell therapies may not be responsive. As an alternative therefore, investigators have developed the inducible Caspase-9 system that relies on dimerization of a semi-synthetic inducible Caspase-9 molecule using an otherwise bioinert small molecule, leading in turn to cleavage and activation of endogenous caspase 3 and the rapid onset of apoptosis.[34] Since this approach works within minutes of administration of the dimerizing agent and may be effective irrespective of whether the target cell population is dividing or post-mitotic,[35] it can be combined with the CAR or TCR expressing T cells if they cause rapid toxicity and allow investigators to more effectively gauge the risks and benefits of their therapy by controlling adverse effects as they occur. This in turn will allow the more rapid and more widespread introduction of these approaches.

HOW DO WE ENSURE FULL IMPLEMENTATION?

All of the above advances will not by themselves ensure full implementation of T-cell therapies as a standard of care. We also need effective mechanisms by which these therapies can be initially explored in small-scale clinical studies. Because of their lack of similarity to conventional pharmaceuticals, many of these initial studies will continue to be executed by academic investigators and then (ideally) seamlessly selected for commercial development. Such a process requires a cadre of clinical research investigators with access to an infrastructure that is adequate to follow the good manufacturing practices required to prepare and distribute the cellular and vector products. This infrastructure must also ensure that even early phase studies are performed to meet good clinical practice standards, a requirement made more difficult by the unusually complex regulatory requirements surrounding gene modified (T)-cell therapies.[21] The magnitude of the manufacturing and clinical support required means that individual investigators in the field cannot be expected to develop the necessary infrastructure. Fortunately, in the United States the NIH (National Institutes of Health) uses a variety of mechanisms to support the manufacturing of vectors and of cells for small-scale clinical trials and the impact of these infrastructure support programs on investigator initiated trials of T-cell therapies has been substantial. The European Union and Japan have developed alternative approaches that are also government sponsored but there is no doubt that their further enhancement would accelerate progress in this area.

In terms of good clinical practice, there is at least some hope that the approval and reporting process for gene modified cell therapies may be simplified—for example, by removing from the remit of the NIH Recombinant DNA Advisory Committee the responsibility for individual protocol review. Such a change would remove at least one layer of extra review and may encourage more

commercial investment in the field by harmonizing regulatory procedures with those applied to conventional therapeutic agents.

CONCLUSION

The efficacy of T-cell therapy for the treatment of multiple different cancers is now undisputed; the potency and range of benefit will undoubtedly increase over the next few years. While pharmaceutical companies still need to be persuaded that these agents are truly commercially viable, successful efforts by investigators to increase the activity of tumor-directed T cells, broaden their reach, increase their scalability and ensure their safety should all see an explosion of interest over the next 5 years, until T cells are indeed a standard of care for cancer, matching or even surpassing the importance of monoclonal antibody immunotherapy.

CONFLICT OF INTEREST

The author is a scientific advisory board member of Jennerex and of BluebirdBio. The Author's spouse is a scientific advisory board member for CellMedica. Some of the approaches described in this article are licensed by CAGT investigators to commercial entities (CellMedica, Bellicum).

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