Molecular Therapy
Editorial

Adoptive Cell Therapy: ACT-Up or ACT-Out?

This year *Molecular Therapy* celebrates its 20th anniversary. This year I too celebrate an anniversary: 40 years of studying T and B lymphocyte interactions and using those cells in adoptive cell therapies (ACTs). I spent most of the first decade working on T and B cell interactions after immunization; most of the next 20 years transferring T and B cell immunity to immunocompromised patients to prevent infection and treat (virus-associated) malignancy; and the last 15 years trying to combine the virtues of these lymphocytes by expressing B cell receptors (chimeric antigen receptors [CARs]) in T cells to target B lymphocytic and other neoplasms.[1–4]

It quickly became evident that adoptive lymphocyte transfer was indeed feasible and effective in treating cancer and also had the potential to treat autoimmune and inflammatory disorders. Still, it required the dramatic success of CAR-T cells in B cell acute lymphoblastic leukemia (B-ALL) to forcefully capture the imagination of the wider scientific, pharmaceutical, and lay world and propel ACT to its current prominence.[5]

The triumphs of CAR-T cell therapy in hematological malignancies have two flow-on effects. Investigators have become painfully aware that equivalent success using CAR-T cells or other ACTs in solid tumors will be much harder to obtain. Successes against solid tumors will likely require not just identification of better (neo)antigen targets, but also the engineering of cell therapies that are both adoptive and truly adaptive and able to respond to these tumors' evolving antigenic universe and immune-resistance landscape.[6] It has also become apparent that significant investment is needed for the commercial-scale manufacture of ACTs and the clinical support training and infrastructure required to handle these new agents. These elements coupled with the individualized nature of the therapies, the costs of development and licensure, the high failure rate of the process, and the high returns expected by investors have combined to produce eye-wateringly high prices. On top of the cost, bottlenecks in manufacturing and administration have critically limited accessibility. If ACTs ever become the standard of care for common solid tumors, then the inequalities of access that will occur with current practices and prices will inevitably lead to a crisis in healthcare.

Although accessibility may worsen over the short term, if ACTs do indeed live up to their promise of curative therapy with minimal short- or long-term adverse effects, then I have little doubt that solutions will appear.

In the short- to medium-term, the robustness and cost of manufacturing will improve, significantly reducing the cost of goods—an all but inevitable feature of any new technology from pharmaceuticals to integrated circuits. Although there is currently much interest in developing ACTs directed to individualized tumor-specific neoantigens, if we are to have broad applicability at reasonable cost, we will have to transition away from single-patient therapies toward banked (off-the-shelf) products engineered to match a range of diseases. Like many apparently oppositional approaches, the use of individualized neoantigen-specific ACTs and banked cells will likely converge, with the deployment of polyclonal banks directed to a broad range of commoner neoantigens, leaving only a minority of patients who will require truly bespoke products. These efforts will be facilitated by the current focus on preventing rejection of allogeneic cells. Such host-versus-graft effects have been a much more intractable problem for the sustained control of solid tumors than preventing or overcoming graft-versus-host disease caused by alloreactive native T cell receptors on the banked cells. As gene editing becomes more commonplace, solutions should become available.

In addition to these scientific and technical advances, there will also be major changes in health economics. The US Food & Drug Administration (FDA) and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) have already put forward plans for accelerating and facilitating the approval pathway for cell and gene therapies, providing guidance for approvability, and suggesting ways in which smaller studies can provide the data required for a successful license application. These changes should reduce the costs and increase the success rate of developed ACTs, not least by identifying agents that are unlikely to meet the criteria of success so they can be abandoned much earlier in the development process. Moreover, as we collect ever-proliferating 'omics and other data that identify the characteristics of patients, their tumors, and their infused cell products that are associated with successful and unsuccessful outcomes, we will be better at predicting who will respond and who will not. In parallel, this information will facilitate pricing and cost recovery. We are already seeing acceptance, both by biopharma and by payers, of modified reimbursement schemes such as payment for successful outcome or staggered ("reverse annuity") payments for each year of survival. These and other approaches should help ensure that the cost of treatment per quality-of-life-adjusted year comes closer to levels that can be tolerated economically by society as a whole.

Looking beyond the Byzantine complexities of the U.S. healthcare system, many countries with single-payer systems may shift from the pharmaceutical model entirely. Instead, the most expensive ACTs will be treated as another form of destination therapy, like hemopoietic stem cell and solid organ transplantation. ACTs will be prepared regionally and administered by specialist centers all within the healthcare system itself. In fact, we can see the beginnings of this process already as countries like Sweden, Germany, and New Zealand begin to administer their home-grown versions of CD19-CAR-T cells.

In the long term, if ACTs and other immunotherapies do indeed come to supplant the current cancer therapeutic trinity of drugs, radiation, and surgery, then many of their costs will be offset by the reduction in costs attributable to hospital care. Safe and effective ACTs will instead be administered and their effects followed in a

doctor's office, making the vast hospital-industrial complex currently associated with cancer care obsolete. In my own lifetime I have seen advances in medical care lead to closure of isolation hospitals, tuberculosis sanatoriums, and many long-stay institutions for the mentally ill. This shift has not only reduced the costs of caring for those affected but has also freed up tracts of land for housing developments that generated substantial revenues in (pre-Brexit) UK and would likely do the same for any cancer hospitals situated on prime real estate in, for example, Manhattan or Houston.

Overall, despite undoubted short-term obstacles to broader implementation, I am highly optimistic about the mid- to long-term impact of ACTs on the treatment of cancer, autoimmune, and inflammatory disorders. Looking still further into the future, however, it is inevitable that disruptor ACTs will themselves be disrupted by newer technologies. I predict that the convergence of biology, artificial intelligence, and social engineering will ultimately enable us to swallow a single curative pill. I just hope it won't be blue or red and made by Morpheus Pharmaceuticals.[7]

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