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An empiric victory

Provenge already looks like the product of a bygone era.

The approval of Provenge is remarkable. It represents a triumph of esotericism over the scientific method; a victory for doggedness over diligence; a success for clinical and manufacturing brawn over molecular precision. As the first approved cellular vaccine against cancer, it vindicates the persistence of those who have labored for decades to obtain clinical validation of the approach. More specifically, the product proves that the T-cell arm of the adaptive response can be harnessed to fight advanced cancers. These are good things. But there are also reasons why Provenge is likely to achieve only limited commercial success.

The Provenge story starts with studies at the Stanford University School of Medicine published in 1997 (*J. Immunol.* **159**, 3113–3117) that showed that a cytotoxic T-lymphocyte (CTL) response to prostatic acid phosphatase (PAP) antigen could result in the destruction of PAP-bearing tissues. In other words, eliciting T-cell immunity, and not solely an antibody response, might be effective as a cancer immunotherapy. But as tumors are so adept at cloaking themselves from immune surveillance, the question was how to elicit an appropriate cellular response to the tumor antigen of interest.

Dendreon's solution was to induce cellular immunity *ex vivo* by removing and semipurifying (by centrifugation) patients' antigen-presenting cells (APCs), or dendritic cells, and exposing them to tumor antigen supercharged with an immunomodulator. The specific trick, in essence, is to present dendritic cells with a growth-promoting cytokine (granulocyte-macrophage colony stimulating factor) hooked up to an antigen that is enriched in prostate cancer (PAP).

Thus, from a scientific perspective, Provenge provides evidence of the clinical relevance of anti-tumor T cell–mediated immunity. And it shows that if you can prime APCs correctly and infuse sufficient numbers of them back into the circulation, life-prolonging immune defenses can be invoked. Provenge validates the immunologists' original vision by adding over 4 months (on average) to the lives of very sick patients.

Unfortunately, between the immunological vision and the clinical validation lay a drug developers' nightmare. Provenge stuttered and stumbled through the regulatory pipe. Yes, it was relatively quickly shown to be safe enough (phase 1 studies were reported first in 2000). But the dose escalation and efficacy work took another decade.

This is partly because, when it comes to human cell products, there are no relevant animal studies to guide dose-ranging, product formulation and administration protocols. Humans are the animal model and this, necessarily, slows down development. Furthermore, the autologous nature of the product means that the sources of cells are highly variable. Each patient presents an individual challenge, varying in age, disease severity, prior treatment, tumor microenvironment and immune status. In addition, despite 'enrichment' using the marker CD52, the Provenge preparation remains a complex mixture of lymphocyte and myeloid cell types and their macromolecular products.

Thus, every Provenge treatment is slightly different from the next. It is personalized medicine in its worst sense. Little more is known now about what constitutes an effective cellular compote in Provenge than was known at the beginning of the century. Similarly, little is known about what differentiates patients who have positive clinical responses to Provenge from those who don't. And any knowledge that has been acquired is likely to be of limited use to developers of other cancer vaccines.

Another problem from the drug developer's standpoint is that Provenge is less a product and more a service—and a logistically awkward, multistep, difficult-to-control service at that. Dendreon raised over $600 million in 2009, much of which will fund a production facility for Provenge. Unsurprisingly, the cost of a Provenge treatment is >$90,000 per patient. Any of the slew of other autologous cancer vaccine candidates making their way through the clinic (*Nat. Biotechnol.* **27**, 129–139, 2009) is likely to face a similarly adventurous route to market: difficult regulatory birthing and awkward, expensive, undrug-like products. Label expansion is likely to be equally as painful as the biologic license application process.

As a fourth-line treatment (after surgery, radiation and chemotherapy) in advanced prostate cancer, Provenge's path to commercial nirvana also looks less than straightforward, beset by manufacturing and scale-up issues. While there remains an absence of other treatment options, it has a chance of market success. But it looks very vulnerable to competition from more tractable and patient-friendly immunotherapies, such as the next generation of off-the-shelf cancer vaccines or antibodies that direct prostate cancer antigens to dendritic cells.

As with other new drug modalities, market registration of the first cancer T-cell vaccine product will enable clinicians to start to systematically gather patient data to better characterize the immunotherapy itself as well as the immune responses it elicits in patients. This can only boost a field that has struggled to translate findings gleaned from animal models into human subjects.

With rapid recent progress in our understanding of tumor immunology, emphasis should now shift to assessing the quality and composition of the types of dendritic cells involved in eliciting CD4 and CD8 T cells with the highest avidity for tumor antigens. At the same time, it will be important to understand those cell types that thwart vaccine strategies through promoting the expansion of regulatory T cells or the recruitment of immature myeloid suppressive cells to tumors from the bone marrow. To date, most cancer vaccines in the clinic have focused on factors that promote expansion of CTLs rather limiting immune suppression in the tumor microenvironment. Several immunosuppressive targets are now starting to be explored, including CTL antigen 4 (CTLA-4), TPD-I receptor (CD279) and PD-I (glucocorticoid-induced tumor necrosis factor receptor–related protein ligand).

The market authorization of Provenge marks the end of the beginning for cellular immunotherapy in cancer. The field can now move ahead, with a proof of concept in hand. But if Provenge signifies anything for cancer vaccines, it is that the path forward lies less in empiricism and more in scientific rigor.