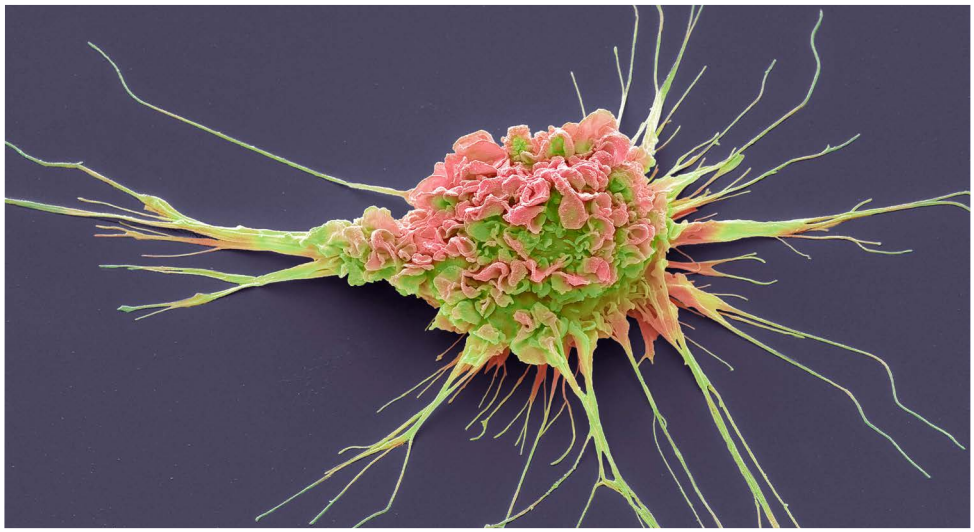
MILESTONE 17

A dendritic cell cancer vaccine



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In 1909 Paul Ehrlich postulated that the immune system may defend the host against neoplastic cells and hinder the development of cancers. This concept has been widely recognized ever since, and eventually led to the development of novel cancer treatments in more recent years that revolutionized cancer care.

While the vast majority of cancer drugs target cancer cells directly, immunotherapies set off the body's own immune response against tumours. A complex network of cells and soluble factors can thus be mobilized as preventive and therapeutic cancer vaccines, monoclonal antibodies that reactivate an immune response, or immune cell-based therapies.

A common feature of cancer vaccines is the presentation of tumour-specific antigens (generated for instance by somatic mutations or oncogenic viruses) to immune cells to elicit an immune response against these cancer epitopes. Arguably the greatest success of cancer vaccines has been the development of vaccines against 'high-risk' strains of the human papillomavirus (HPV) for prevention of HPV-related cervical and other cancers (MILESTONE 14).

Dendritic cells, discovered in 1973 by the late Ralph Steinman, are the major antigen-presenting cells in the body, which, once activated, present antigens to $CD4^+$ and $CD8^+$ T cells and induce protective T cell responses. If a cancer-specific antigen is presented, this can result in an anti-tumour response. As T cell responses are indeed crucial for eliciting an immune response against cancers, dendritic cells have for a long time been suggested as potential cell-based vaccines. Crucial to the development of dendritic cells as vaccines, in the 1990s researchers developed the concept of loading, or 'pulsing', dendritic cells ex vivo with tumour-specific antigens.

The multi-centre phase III IMPACT trial reported in 2010, and two supporting phase III trials reported in 2006, showed a benefit to median survival, as well as induction of a T cell response, in patients with metastatic hormone-refractory prostate cancer who were treated with the dendritic cell-based vaccine sipuleucel-T (trade name Provenge), even though the time to disease progression was not altered. On this basis, in 2010, sipuleucel-T became the first approved dendritic cell cancer vaccine, for the treatment of late-stage prostate cancer.

Sipuleucel-T is a personalized treatment. Dendritic cell precursors are extracted from each patient and pulsed with a fusion protein of prostate acid phosphatase (PAP; an antigen present on most prostate cancer cells) and the cytokine GM-CSF, which helps antigen-presenting cells to mature. The pulsed dendritic cells are then reinfused into the patient over several cycles.

> "Sipuleucel-T became in 2010 the first approved dendritic cell cancer vaccine"

Although sipuleucel-T has not been very widely adopted (and is no longer available in the European Union), it was recently announced that the combination of hormonal therapeutics with sipuleucel-T extended the survival of patients with metastatic castration-resistant prostate cancer. Other clinical trials combining sipuleucel-T with radiation, hormonal, targeted or other immunotherapies are ongoing. So far sipuleucel-T remains the only vaccine-based immunotherapy approved for prostate cancer, and is also the only approved cell-based vaccine in the USA.

Overall clinical responses to dendritic cell vaccines have been disappointing, but with increasing knowledge, newer and more sophisticated strategies are being investigated to improve the efficacy of dendritic cell-based vaccines. Improved methods to generate more mature and 'effective' dendritic cells using ex vivo protocols, alternative combinations of antigens, optimized loading of dendritic cells and transfection of dendritic cells with RNA or DNA are among the strategies under investigation. The exploration of dendritic cell subsets and of other agents beyond GM-CSF that may mobilize dendritic cells in vivo, such as FLT3L, are also being pursued.

One important consideration is that tumour-associated immunosuppression can hamper the efficacy of the vaccines. In more recent years, T cell therapies — and in particular antibody-based immunotherapies that disarm inhibitory immune cell interactions (so called immune checkpoint inhibitors) — have proved very successful for some patients across a wide range of cancer types. Vaccines designed to boost these treatments are now in combination trials and may yield even more effective immunotherapies.

Barbara Marte,
Nature

ORIGINAL ARTICLES Small, E. J. et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J. Clin. Oncol.* **24**, 3089–3094 (2006) | Kantoff, P. W. et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N. Engl. J. Med.* **363**, 411–422 (2010)

FURTHER READING Saxena, M. & Bhardwaj, N. Re-emergence of dendritic cell vaccines for cancer treatment. *Trends Cancer* **4**, 119–137 (2018) | Chen, D. S. & Mellman, I. Elements of cancer immunity and the cancer-immune set point. *Nature* **541**, 321–330 (2017)