outline

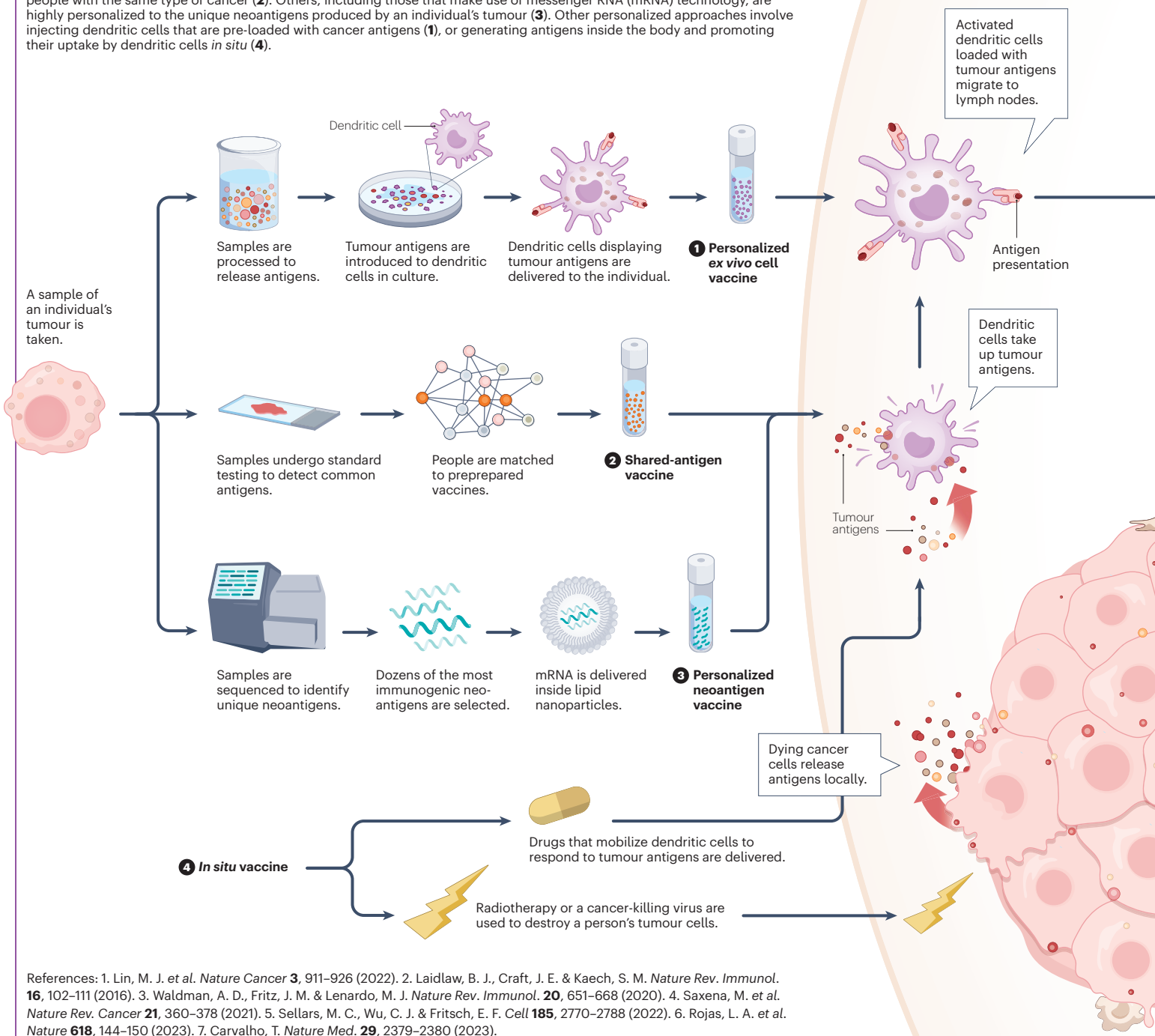
HOW TO BUILD A CANCER VACCINE

After decades of slow progress, therapeutic vaccines that direct the immune system to attack tumours could soon become a fixture of cancer treatment. By **Liam Drew**; *infographic by* **Alisdair Macdonald**

A VARIETY OF APPROACHES

Vaccines are usually used to prevent infectious diseases. A therapeutic cancer vaccine is different. Rather than teaching the immune system to recognize pathogens in advance of an infection, these vaccines use identifying proteins produced by cancer cells, known as antigens, to provoke a powerful immune response to existing tumours.

The first step is to deliver antigens to immune cells called dendritic cells. These present antigens to other immune cells, and stimulate a response. In the past decade, several approaches have emerged[1]. One delivers antigens that are shared by many people with the same type of cancer (**2**). Others, including those that make use of messenger RNA (mRNA) technology, are highly personalized to the unique neoantigens produced by an individual's tumour (**3**). Other personalized approaches involve injecting dendritic cells that are pre-loaded with cancer antigens (**1**), or generating antigens inside the body and promoting their uptake by dendritic cells *in situ* (**4**).



References: 1. Lin, M. J. *et al. Nature Cancer* **3**, 911–926 (2022). 2. Laidlaw, B. J., Craft, J. E. & Kaech, S. M. *Nature Rev. Immunol.* **16**, 102–111 (2016). 3. Waldman, A. D., Fritz, J. M. & Lenardo, M. J. *Nature Rev. Immunol.* **20**, 651–668 (2020). 4. Saxena, M. *et al. Nature Rev. Cancer* **21**, 360–378 (2021). 5. Sellars, M. C., Wu, C. J. & Fritsch, E. F. *Cell* **185**, 2770–2788 (2022). 6. Rojas, L. A. *et al. Nature* **618**, 144–150 (2023). 7. Carvalho, T. *Nature Med.* **29**, 2379–2380 (2023).

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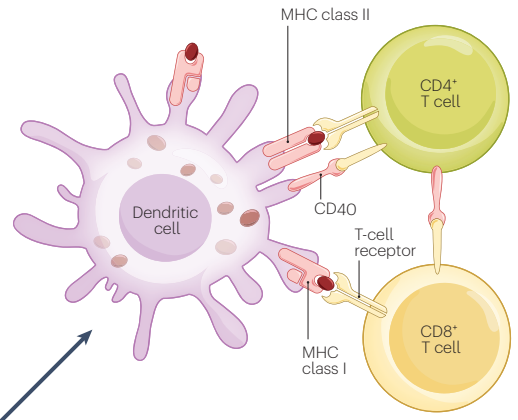
MOUNTING A RESPONSE

Unlike preventive vaccines, which focus mainly on activating antibody-producing B cells, a therapeutic cancer vaccine must generate a strong T-cell response. Dendritic cells loaded with tumour antigens bind and activate $CD8^+$ cytotoxic T cells, which can then mount an attack on the tumour[2].



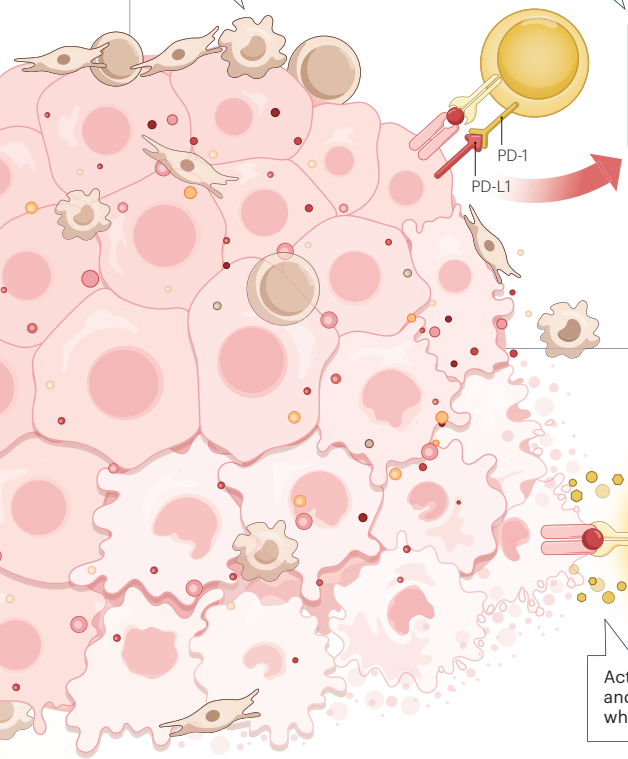
For maximal effect, dendritic cells also stimulate $CD4^+$ 'helper' T cells, which aid in the activation of $CD8^+$ T cells and cell memory.

OVERCOMING DEFENCES

T cells have the capacity to destroy even large tumours, but cancer cells can acquire ways of evading immune attacks. These barriers probably account for the failure of many early therapeutic cancer vaccine trials[4], and must be overcome for the therapies to achieve their potential.

Immunosuppressive cells
Regulatory T cells, macrophages, fibroblasts and other cells in the tumour's microenvironment can inhibit an immune response[5].

Intrinsic resistance
Cancer cells can reduce antigen expression to hide from immune cells, and often express molecules — such as the checkpoint protein PD-L1 — that inhibit tumour-attacking T cells.



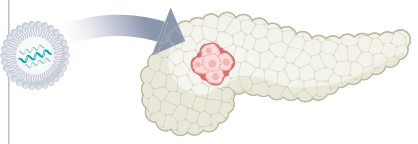
Combining cancer vaccines with checkpoint inhibitors that prevent PD-L1 binding to PD-1 could improve efficacy.

Activated T cells bind to cancer cells and release granzymes and perforin[3], which triggers death of cancer cells.

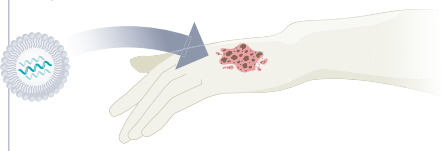
PROMISING RESULTS

Numerous therapeutic cancer vaccines, on the basis of a variety of approaches, are showing encouraging results in trials.

Pancreatic cancer
In a phase I trial of a personalized mRNA vaccine, half of the participants developed T cells targeted to cancer neoantigens[6]. Recurrence-free survival in this group was longer compared with those who did not respond.



Melanoma
A phase II trial of a personalized mRNA vaccine showed a 44% decrease in the risk of post-surgical recurrence or death[7]. A phase III trial is under way, with final results expected in 2029.



Lymphoma
A phase I/II trial of an *in situ* vaccine that combined radiotherapy with signalling molecules that mobilize and activate dendritic cells showed evidence of tumour regression in 8 of 11 people who were treated[1].

OBSTACLES AHEAD

The future development and the clinical uptake of therapeutic cancer vaccines will be shaped by several factors.

Unwieldy trials
Testing multiple combinations of agents makes clinical trials more complex. Another complicating factor is timing when to give a vaccine relative to other interventions, such as surgery.

Immunity monitoring
Tracking acquired immunity is important for assessing vaccine efficacy. For cancer vaccines, new T-cell monitoring techniques are needed.

Scalability
Personalized cancer vaccines could pose logistical challenges. Streamlining production will be essential to keep costs down and availability high.