Cancer

Vaccine boosts T cells that target pancreatic tumours

Amanda L. Huff & Neeha Zaidi

Efforts to tackle pancreatic cancer by harnessing immune cells have had limited success. A clinical trial reports promising results from testing a personalized approach to boosting immune responses to such tumours. **See p.144**

The development of a type of immunotherapy that uses drugs known as immune-checkpoint inhibitors (ICIs) has revolutionized cancer treatment. ICIs act by helping to unleash a person's immune system against mutated versions of proteins (termed neoantigens) that are expressed solely by cancer cells. Peptide segments of neoantigens are likely to be viewed as foreign by the immune system, and can activate immune cells called T cells (specifically, those known as CD8 T cells), which are capable of killing cancer cells. Pancreatic cancers generally don't respond to ICIs. This is thought to be partly because these tumours express lower levels of neoantigens than do other types of tumour, and thus are less likely to activate a strong immune response from antitumour T cells.

Rojas *et al.*[1] challenge this idea on page 144, and describe an approach in which neoantigen-specific T cells can be activated — by a vaccine that encodes neoantigens specific to the individual. Their study builds on previous work showing that individuals who are long-term survivors of pancreatic cancer have high-quality neoantigens that can stimulate antitumour T cells[2,3].

Rojas and colleagues designed messenger RNA vaccines (Fig. 1) corresponding to neoantigens for 16 people with pancreatic cancer whose tumours had been surgically removed. Individuals who undergo such surgery generally have up to an 80% chance of disease recurrence[4].

The mRNA vaccines encoded a maximum of 20 neoantigens per patient, identified by sequencing DNA and RNA from the patients' surgically removed tumours. Vaccines were given intravenously around nine weeks after surgery, with plans to speed up the time for vaccine generation and administration in the next stage of the study (a phase II clinical trial). This rapid time to treatment underscores the benefit of mRNA-based cancer vaccines, particularly for highly aggressive tumours.

T cells that recognized specific neoantigens corresponding to the mRNA-encoded peptides were detected in the blood after vaccination in half of the people in the trial — these individuals were termed immune responders. Of these responders, half had T-cell responses to more than one neoantigen (a polytopic response), whereas the other half generated a response to a single neoantigen (a monotopic response). Remarkably, in all immune responders, there was no evidence of cancer recurrence at a median follow-up time of 18 months after surgery, compared with a median time to recurrence of 13.4 months in non-responders. These data are exceedingly promising, and will provide the framework for a planned further clinical trial.

All patients also received a single dose of an ICI called atezolizumab before being given the mRNA vaccine. Atezolizumab targets the protein PD-L1 found on tumour cells, and acts by reinvigorating pre-existing tumour-reactive T cells that have entered a dysfunctional, 'exhausted' state because of interactions between PD-L1 and the immunosuppressive receptor PD-1. The authors analysed patient blood samples after ICI treatment, and identified T-cell lineages that had proliferated (expanded) — a sign of T-cell activation in response to neoantigen recognition. The authors identified these lineages by sequencing DNA corresponding to part of the T cell involved in immune responses (the T-cell-receptor β-chain). The T cells that proliferated with atezolizumab treatment were different from those that proliferated after mRNA vaccination, providing evidence that the vaccine had activated neoantigen-specific T cells.

Four weeks after the final mRNA vaccination, patients received chemotherapy, which can sometimes suppress immune cells, but the authors found that the vaccine-boosted T cells were not suppressed. This highlights the fact that sequential combination treatment strategies are feasible for people with pancreatic cancer.

Perhaps the most compelling part of the data set is evidence of the accumulation

From the archive

A conference examines foods of the future, and a book unscrambles some cryptography mysteries.

50 years ago

At the special meeting of the Federation of European Biochemistry Societies (FEBS) in Dublin ... one of the most interesting contributions was the description ... of a physiological mechanism for producing a polyunsaturated lamb chop ... Professor A. Spicer ... may well have raised the price of beef ... with his well founded prediction "no beef by 2000". The trouble was that cattle are extraordinarily inefficient converters of crop products into protein. Whereas the cow puts on only 1 pound of protein a day, pound for pound growing soya beans put on 100 pounds a day, yeasts put on 100,000 pounds a day and bacteria put on 10^{14} pounds a day.

From *Nature* 1 June 1973

100 years ago

Cryptography. By André Langie — As there is no manual of cryptography in English, this book ... will be welcomed by all who wish to make a serious study of the subject, either for practical purposes or as an intellectual exercise. The author deals with his subject under three heads. Under the first he gives a brief history of the methods of conveying information secretly, beginning with the Greeks, Egyptians, and Romans; under the second he gives examples of cryptographical writings of which he himself has found the solution ... and under the third he gives lists and tables of frequency of single letters, bigrams, and other combinations in English and other languages. This section will naturally be one of the most frequently consulted in the book, as a knowledge of the relative frequency of occurrence of the different letters and combinations is essential in all decipherment. The translator adds a supplementary chapter dealing with methods of conveying information secretly, such as the use of sympathetic inks ... the marking of cards by cardsharpers, ... and describes the Playfair cipher, a substitution system extensively used for military purposes.

From *Nature* 2 June 1923

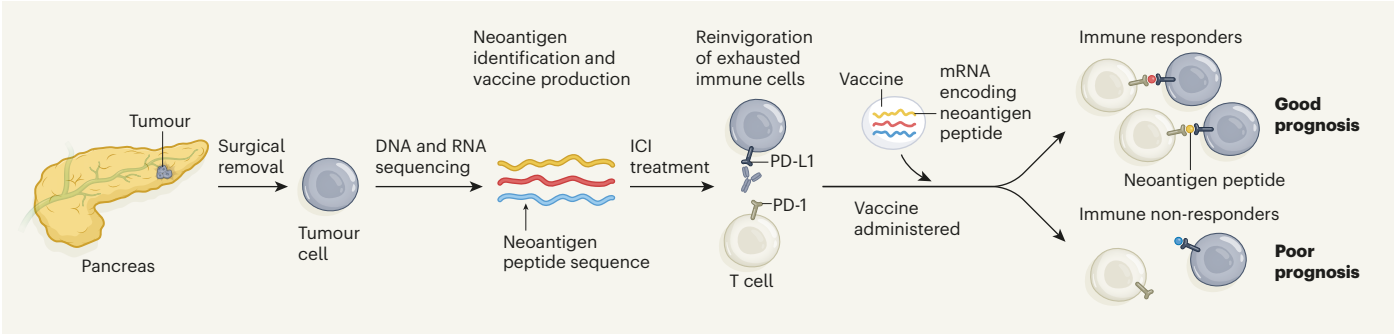

Figure 1 | A treatment for pancreatic cancer. Rojas *et al.*[1] report a clinical trial that tested a personalized approach to treating pancreatic tumours. Patients had their pancreatic cancer removed by surgery. A specimen of cells from each individual's tumour was then used for DNA and RNA sequencing to identify sequences encoding peptide segments of mutant versions of proteins (neoantigens) specifically associated with cancer cells. The authors used this neoantigen information to design and produce personalized vaccines that contained messenger RNA corresponding to chosen neoantigens. The patients received an immune-checkpoint inhibitor (ICI). This ICI was an antibody that targets the protein PD-L1 on tumour cells. By blocking interactions between PD-L1 and its immunosuppressive receptor, PD-1, on immune cells called T cells, ICI treatment boosts T cells in a dysfunctional state called exhaustion. After vaccination, half of the individuals mounted a high-magnitude T-cell response to at least one vaccine neoantigen. Those who mounted an immune response were less likely to have disease recurrence, possibly owing to the presence of new, vaccine-induced, neoantigen-specific T cells capable of eliminating spreading tumour cells. Patients who did have disease recurrence might have shown small and/or low-quality neoantigen-specific T-cell responses.

of immune cells in a liver region with signs of unusual changes (called a lesion) in one responder after vaccination. Although there was no evidence of cancer in this lesion, all vaccine-induced T-cell lineages were found in the aggregate of immune cells. Interestingly, a mutant version of the gene *TP53* was detected in the lesion and matched the *TP53* mutation in the patient's pancreatic tumour, raising the possibility that some cancer cells had migrated to this site. The liver lesion subsequently disappeared, suggesting that the vaccine can help to eliminate tumour cells that have spread to distant sites (micrometastases).

Rojas and colleagues tracked T-cell lineages using two blood-based tests (ELISpot and a T-cell-receptor sequencing approach). These favour the detection of high-magnitude T-cell responses (those with strong signs of T-cell activation), but might not capture lower-magnitude responses. About 11% of the vaccinated neoantigens clearly evoked a high-magnitude T-cell response. In 4 of the 16 individuals, just one neoantigen drove an immune response. Therefore, although one high-quality neoantigen might be enough to trigger T-cell-mediated tumour killing, it will be important to understand why immune responses were not detected in response to the other neoantigens in the vaccine. Furthermore, for neoantigens that evoked lower-magnitude T-cell responses, it might be possible to boost the response, for example by giving further doses of ICI that might also prevent T-cell exhaustion.

Equally crucial will be investigation into why half of the individuals did not respond to vaccination, given similarities in clinical features between responders and non-responders. Hallmarks of baseline immunological function, such as the response to another mRNA vaccine (one targeting the coronavirus SARS-CoV-2) and the accumulation (density) of CD8 T cells in the initial pancreatic tumour, were similar in the two groups.

By contrast, the authors found a difference between the groups in that the tumours of immunological responders had less mutational diversity than those of non-responders. This lower diversity might reflect the consequences of an earlier immune-system response to the tumour, suggesting that the immune system is better able to recognize the tumours of immunological responders. Comparing the quality of each neoantigen in terms of its predicted ability to drive a T-cell response, using data for responders, revealed that the predicted higher-quality neoantigens drove a stronger antigen-specific T-cell response, as previously reported[2,3].

Unlike some personalized vaccine studies[5,6], the investigation by Rojas and colleagues showed predominant activation of neoantigen-specific CD8 T cells, which are considered to be key players in enabling direct killing of tumour cells. Interestingly, the authors did not find another type of neoantigen-specific T cell – CD4 helper T cells – even though the neoantigens included in the vaccine were selected and prioritized to activate both T-cell types (although tests designed to detect low-magnitude T-cell responses might capture vaccine-induced CD4 T cell responses). CD4 T cells are known to be key partners in aiding CD8 T-cell function and longevity in controlling tumour growth[7,8].

This raises the question of how mRNA vaccines can be generated to promote optimal activation of both types of T cell, including optimizing for persistence of immune cells, reduced exhaustion and the development of immunological memory. Prioritizing selection for CD4-specific neoantigens remains a challenge, and techniques to improve their identification might, in turn, lead the way to high-quality responses by CD4 T cells[9–11]. Furthermore, some aspects of the mRNA vaccine itself, such as the design of the mRNA and the composition of the lipid nanoparticles that encase the vaccine, might provide further opportunities to optimize T-cell-specific responses[12].

Rojas *et al.* have established the feasibility of using mRNA-based neoantigen vaccines for pancreatic cancer, a disease that has previously been considered too aggressive for personalized therapeutics. The data also highlight the potency of pancreatic cancer neoantigens, giving hope that they might lead to the development of new treatment options for this refractory cancer.

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