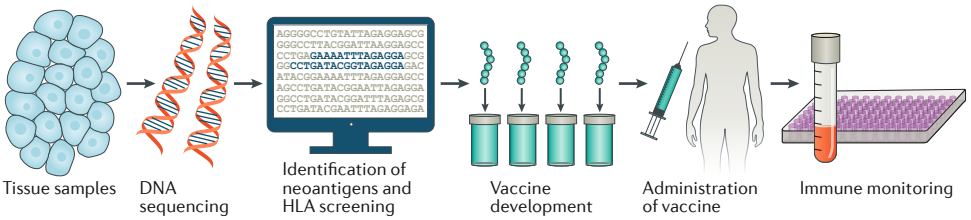

Credit: Springer Nature Limited (Waldman et al. https://doi.org/10.1038/s41577-020-0306-5)

MILESTONE 21

Individualized neoantigen vaccines

The immune system is recognized mostly by its role in protecting from infectious pathogens, but a perhaps less obvious function of immune cells is in surveying the body to find and eliminate transformed cells (i.e. cancer). Because of the inbuilt capacity of the adaptive immune system to recognize foreign proteins, adaptive immune cells can recognize mutated tumours displaying so-called neoantigens, which are former self-proteins with changes in their peptide sequence no longer recognized as endogenous. So, if one can artificially trigger immune responses to pathogens through immunizations, why not vaccinate against tumours?

Cancer vaccines have indeed been developed, and the strategies employed are varied and mimic the approaches used for developing vaccines against infectious pathogens. From formulations based on tumour cell extracts, to strategies based on dendritic cells loaded with tumour antigens (MILESTONE 17), to administration of the purified mutated tumour antigens themselves, featuring multiple delivery systems and adjuvants, preclinical research of a wide range of formulations has been met with varying levels of success in animal models.

But a significant limitation of developing a cancer vaccine versus developing a vaccine to a bacterium, for example, is that while bacteria are totally foreign entities, completely made of non-human proteins, tumour cells retain most of the endogenous proteins and are thus mostly tolerated by the immune system. The challenge is then to identify neoantigens — originally self-proteins that, through the acquisition of mutations, generate new molecular epitopes recognized as foreign by the immune system — for each patient.

Following several reports in mouse cancer models of mounting anti-neoantigen immune responses through vaccination, a small phase I trial in 2015 described enhancement of neoantigen-specific immunity in three patients with advanced melanoma who were immunized with dendritic cells loaded with a mixture of melanoma neoantigens. Although the trial was not designed to assess patient outcomes, it showed a way to effectively boost the immune system towards tumour-specific antigens. It is worth noting that melanoma is especially amenable to a neoantigen vaccine approach owing to its heavy mutation burden, which facilitates neoantigen identification and makes the tumour inherently more susceptible to an antigen-specific immune response.

About 2 years after this landmark paper, two reports published in *Nature* took the strategy further, describing the vaccination of patients with advanced malignant melanoma with neo-epitopes. In one of the studies, Catherine Wu and colleagues devised a vaccine consisting of peptides 13–20 amino acids long containing predicted personal tumour neoantigens for administration to patients who had prior surgical tumour resection; in four of the six patients immunized, no disease recurrence was observed at 25 months after vaccination. In the other study, Ugur Sahin and colleagues followed a different vaccine formulation, in that they used an RNA-based poly-neo-epitope suspension instead of synthesized peptides; also in this study, vaccinated patients developed T cell responses against multiple vaccine neo-epitopes with a reduction in the rate of metastatic events.

These first studies are important because they show a possible approach for boosting antitumour immunity that is safe and potentially effective. Perhaps more importantly, it can be expected that cancer vaccines complement other immunotherapy modalities well — particularly immune checkpoint blockade, as the two approaches follow orthogonal immune mechanisms. Indeed, the two studies suggest a benefit from combining either vaccine formulation with immune checkpoint inhibition.

> “A main challenge in taking cancer vaccines mainstream will be optimizing the complex manufacturing pipeline”

A main challenge in taking cancer vaccines mainstream will be optimizing the complex manufacturing pipeline. Neo-epitope prediction and identification are based on next-generation sequencing data that require processing by a range of bioinformatics tools, such as those for the prediction of neo-epitope binding to human leukocyte antigen molecules that determine antigen presentation. Current manufacturing protocols that enable individualized vaccine production under good manufacturing practices still take several months, and are costly.

Other difficulties are biological in nature: many tumour types (such as neuroblastoma, pancreatic cancer and prostate cancer) have a low mutational burden, which hinders the identification of neoantigens. To optimize doses and combinations with alternative therapy modalities to maximize efficiency, patient and tumour heterogeneity will need to be taken into account. In this regard, patient stratification and integration of response predictors may be necessary.

In the context of all the efforts to create off-the-shelf therapies, the challenge of designing a vaccine for each individual patient may seem herculean. But because it is based on the exquisite specificity inherent to the adaptive immune system, cancer vaccines offer a level of targeting that is still out of reach of most other cancer therapies in the clinic today.

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