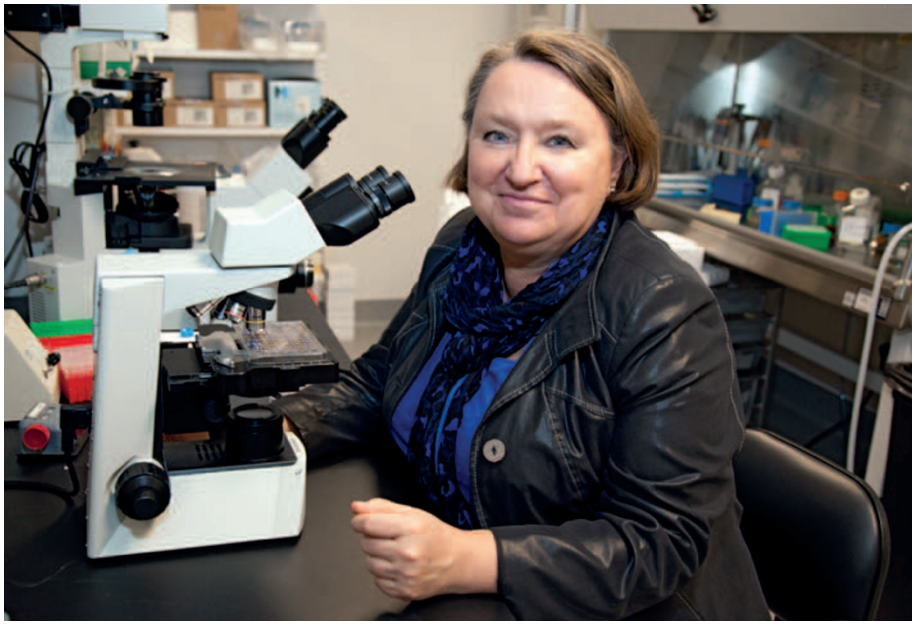

BAYLOR RESEARCH INSTITUTE, DALLAS, TEXAS

Q&A Karolina Palucka
Evidence presenter

Immunologist Karolina Palucka, at Baylor Institute for Immunology Research in Dallas, Texas, helped treat Nobel prizewinner Ralph Steinman's pancreatic cancer with dendritic cells — the cells he co-discovered. Here she explains the use of dendritic cells in cancer immunotherapy.

What are dendritic cells, and how do they work with T cells to create a cancer vaccine?
Immunity results from a complex interplay between the adaptive immune system (which is antigen-specific) and the innate immune system (which isn't). B cells and T cells of the adaptive immune system use receptors that recognize antigens, or their derived peptides, in a highly specific manner. Dendritic cells (DCs) provide an essential link between the innate and adaptive immune responses.

The generation of anticancer immunity depends on DCs presenting cancer antigens to T cells. But cancers can create an environment that inhibits T cells. The aim of DC vaccination is to boost cancer-specific effector T cells that can not only fight existing cancer but also induce immunological memory to control the recurrence of cancer.

What approach did you and Ralph Steinman take to treat his pancreatic cancer?
It was a cell-based therapy. In this approach, you take DC-precursor cells from the blood of a cancer patient, differentiate and activate them in culture, load them with tumour antigens, and then inject the cells back into the patient. The hope is that these DCs will activate tumour-specific T cells. The tumour antigens can either be shared antigens, which are expressed by many cancers, or patient-specific antigens. With Ralph, it was patient-specific: together with colleagues from other institutes, we studied cells from his tumour to work out which antigenic sequences to go after.

What was the outcome?
Ralph received eight injections of this vaccine over the course of eight months, in combination with a chemotherapeutic drug called gemcitabine. After each injection, we saw an expansion of T cells specific to the vaccine antigens in his blood, so it was clear that the DC treatment boosted the immune response against the cancer. Although we can't say for sure that this treatment was responsible, Ralph survived for 4.5 years after his diagnosis — something that only around 5% of patients with this disease achieve.

How are you following up on this approach?
We wanted to see if this could help other patients with pancreatic cancer. We've developed a full clinical trial that we're hoping will start in early 2014, in which we'll try this approach in a larger number of patients with the same diagnosis.

Will this trial be as personalized?
No. To make it more feasible we're combining two approaches. We're using a shared tumour antigen called mesothelin. But there are shortcomings to shared antigens. Not all patients will express them, and some shared antigens are also expressed by healthy cells. That's why, in patients from whom we can get tumour samples, we're going to try to identify patient-specific mutations and go after these in the boosting phase of the trial. I think a combined approach like this represents a more realistic view of what we can do in the clinic, and will be the way things are going to go.

What roles do you see emerging for DC vaccines?
The cancer immunotherapy field has made tremendous progress, thanks to the development of antibodies against immune-suppressing molecules, such as PD-1 and CTLA-4, that are expressed by cancer cells. We're seeing promising results of clinical trials with these antibodies, but they still don't work for all patients.

One reason could be that if there isn't a pre-existing immune response against the cancer, blocking these molecules may not be enough. This is one area in which DC vaccines, because of their ability to prime immune responses, could make a big difference. So far, however, we have seen a discrepancy between the immunogenicity of DC vaccines and their clinical efficacy — for example, some patients who get an immune boost in response to the vaccine nevertheless show no tumour regression. I think we can diminish this discrepancy by combining DC vaccines with immunomodulatory antibodies.

Another potentially big area is using DCs for preventive vaccination of people with cancer mutations, such as *BRCA1,* to prevent progression from premalignant to malignant disease.

How can we develop better DC vaccines?
The various types of DCs interact differently with the immune system. So one exciting area is exploring how subsets of DCs contribute to human immunity, and how they each respond to inhibitory factors. We also need to enhance platforms where academia and pharmaceutical companies can collaborate to test therapies at an early stage of their development and do more mechanistic studies, so we can better understand what the vaccines are doing.

I have been in this field for 17 years and this is the best time for our research. We have made tremendous progress and there is a lot of optimism. ■

INTERVIEW BY MARIAN TURNER