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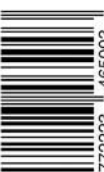
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Cancer Vaccines: Immunotherapy's New Wave

Therapeutic cancer vaccines, a relatively new area of immunotherapy research, stimulate the body's immune system in a more active way than previously-developed immunotherapy drugs to fight tumours. Although researchers face a multitude of challenges, cancer vaccines may hold the key to making immunotherapy treatments a more effective and less expensive way to battle some of the world's most deadly cancers

Last August, doctors at the National Cancer Centre Singapore (NCCS) announced the launch of a US FDA-approved in-human clinical trial for an immune system-based cancer therapy known as a therapeutic cancer vaccine, one of the first such trials of its kind to be conducted in Asia.

For the Phase I trial, NCCS and the Singapore Clinical Research Institute (SCRI) are collaborating with a US-based biotech MicroVAX to test the effectiveness of the cancer vaccine in patients with breast, ovarian, prostate, colon and lung cancer – cancers that are extremely prominent in Western countries as well as East Asia.

The science behind cancer vaccines' proposed therapeutic effect lies in vaccines' ability to trigger the body's immune system to produce antibodies that attack a very specific protein found on the surface of cancer cells, but not found in healthy cells. In the case of MicroVAX's vaccine, the vaccine

targets the protein MUC-1, found in certain types of colon cancer, breast cancer, and others. Once delivered into the body, the vaccine stimulates the immune system to produce antibodies that attach themselves to the MUC-1 protein, enabling the body to attack and kill the tumour cells.

The trial will continue through most of this year, and results will be known after an additional year of patient follow-up, says Dr. Toh Han Chong, NCCS Principal Investigator of the Phase I clinical trial, who is also deputy director at NCCS. The MicroVAX vaccine is first being tested in patients with advanced stage cancer to prove its effectiveness versus conventional cancer therapies like chemotherapy.

"MicroVAX is of the vision that immunotherapy will be key for cancer therapy going forward. We believe that cancer vaccines will play a major role in this vision," Jacob Frank, a spokesperson for MicroVAX, told *Global Health and Travel*.

PHOTO CREDIT: NCCS



THE NATIONAL CANCER CENTRE SINGAPORE (PICTURED) AND THE SINGAPORE CLINICAL RESEARCH INSTITUTE ARE CURRENTLY CONDUCTING CLINICAL TRIALS FOR CANCER VACCINES

Cancer vaccines emerge as a growing segment of immunotherapy research

The pioneer of immunotherapy can be traced back to the 1890s. William Coley, a New York-based surgeon, observed that infections hitting cancer patients were occasionally associated with the remission of the tumour. On these empirical grounds, he started to treat cancer with streptococcal bacteria in order to further investigate the connection. In this way, he managed to stop the progression of the tumour in a few cases.

Immunotherapy emerged as a major research area of oncology in the 1990s, when US scientists discovered that the immune systems in mice could be “engaged” in order to fight cancer cells. Since 2013, when *Science* magazine declared immunotherapy to be its “Breakthrough of the Year”, the development of immunotherapy drugs and funding for new research has skyrocketed. Credit Suisse predicted that two immunotherapy drugs developed by Bristol-Myers Squibb, Yervoy (Ipilimumab) and Opvivo (Nivolumab), both used to treat metastatic melanoma, could generate US\$8.5 billion in annual revenue by 2020, according to *The Wall Street Journal*.

Speaking on immunotherapy as a whole, Dr. Kee Chee Soo, director of National Cancer Centre Singapore, called it “the new wave in cancer treatment” that will lead to sustained improvements in survival for patients who do not respond to conventional cancer therapies.

“There are many forms of immunotherapy, including Keytruda from Merck, that have prolonged patient’s lives,” Dr. Soo told *Global Health and Travel*. “When you look at the survival curves, they are plateauing, suggesting that it’s not just a statistical survival advantage, but an actual survival advantage.”

In the past few years, cancer vaccines have emerged as a hot area for investment, with major drug developers like Johnson & Johnson and Roche signing multimillion-dollar deals with biotech companies to develop cancer vaccines.

A July 2014 report on Sfgate.com, citing industry analysts at Citi, predicted that cancer vaccines and other “emerging immunotherapies” would be US\$35 billion market by 2023. In June of last year, Johnson & Johnson invested US\$55 million in the privately-held biotech Aduro, which is developing a cancer vaccine technology for prostate cancer.

A report from xconomy.com highlighted that Johnson & Johnson was planning to use a bioengineered strain of *listeria* bacteria, which is ingested by a type of immune system cell called dendritic cells to ‘teach’ T-cells, known as the immune systems’ “fighter” cells, to attack cancer. According to the report, the bacteria might be combined with a prostate cancer vaccine called GVAX, which Aduro acquired in 2013, in order to increase that vaccine’s effectiveness.

In a statement provided to *Global Health and Travel*, Marco Gottardis, vice president and prostate cancer disease area leader for Janssen Research & Development LLC, part of Janssen Pharmaceuticals, Johnson & Johnson’s pharmaceutical arm, said that the company’s *listeria* technology, known commercially as LADD, could be used in tandem with the company’s other immunotherapy products.

“We anticipate that LADD-based prostate cancer immunotherapies could be used in combination with other Janssen products, including ZYTIGA, which has been approved for prostate cancer, as well as ARN509, which is currently in late-stage clinical trials,” Gottardis said.

In 2013, Roche signed a US\$17 million deal with German cancer vaccine manufacturer Immutics to develop IMA942, a cancer vaccine aimed at gastric, prostate and non-small cell lung cancer. Roche also invested US\$10 million with another vaccine maker, US-based Inovio, to develop another type of cancer vaccine known as a synthetic DNA vaccine that would target prostate cancer, but terminated its relationship with Inovio in November 2014, according to a Scrip Intelligence report. Inovio is now planning to move the vaccine into Phase I testing independently in the first half of 2015, the report said.

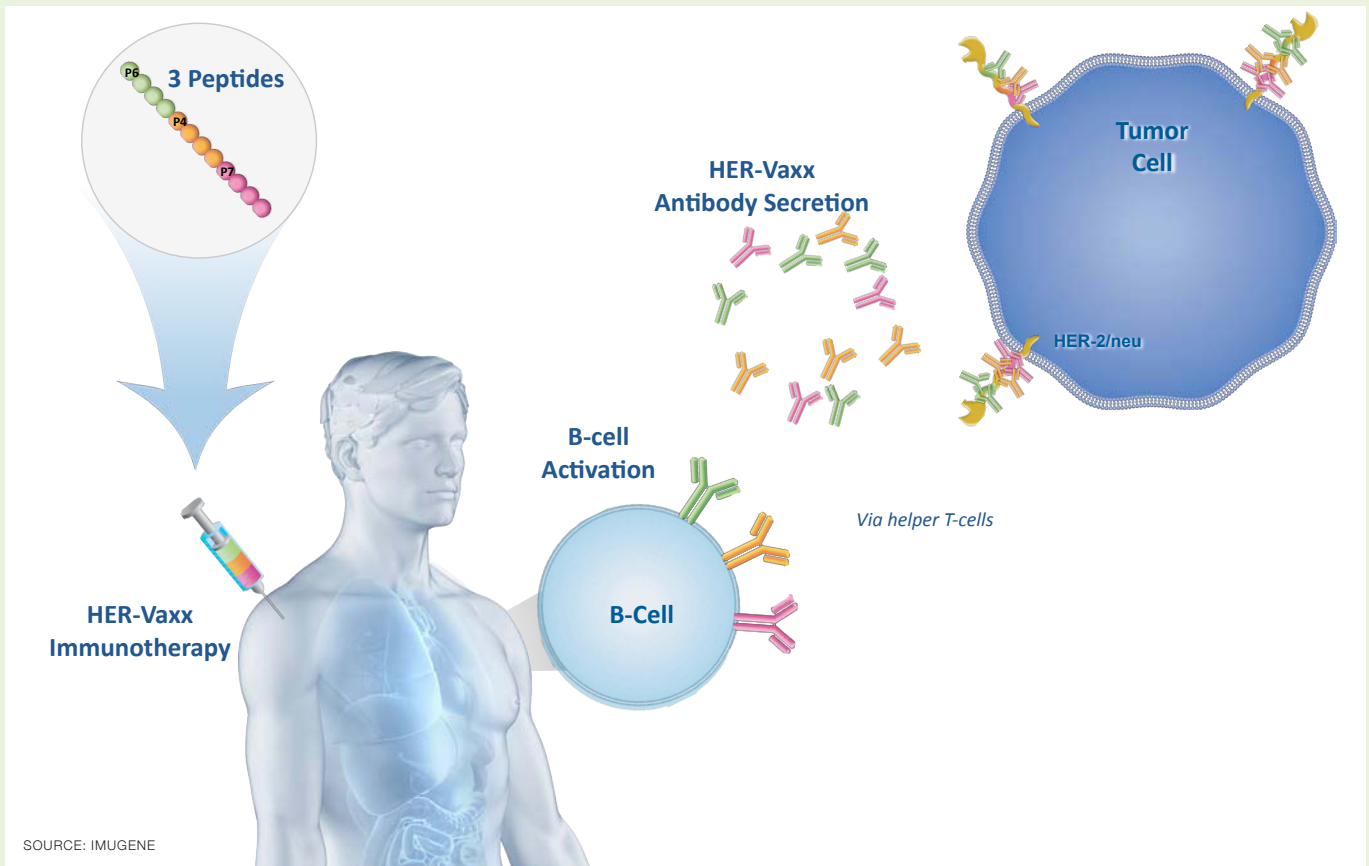
The benefits of a natural antibody response

The field of therapeutic cancer vaccines is relatively new and distinct from earlier-generation immunotherapies like monoclonal antibodies, an immunotherapy drug type that relies on laboratory-produced antibodies that bind to cancer cell proteins, thus enabling the immune system to target the cancer. The list of FDA-approved monoclonal antibody therapies includes Yervoy as well as Herceptin, a monoclonal antibody-based drug manufactured by Roche used to treat HER-2 positive breast cancer.

A main difference between cancer vaccines and monoclonal antibodies is that cancer vaccines act as an “active” stimulator of the immune system as opposed to a “passive” stimulator, says Dr. Anna Ferrari, professor of oncology at New York University’s Langone Medical Center.

“In contrast to monoclonal antibodies, cancer vaccines are ‘active’ immunotherapy treatments because through various means (live or dead cells, viral vectors, DNA fragments or peptides) they train the host’s immune system to recognise tumour cells by one or more specific antigens and mount an innate, long lasting response against them,” Dr. Ferrari says.

Monoclonal antibodies, in contrast, are a ‘passive’ immunotherapy treatment because they rely on an artificially-produced antibody to generate the immune system response,



SOURCE: IMUGENE

CANCER CELLS TYPICALLY EVADE THE IMMUNE SYSTEM BY TRICKING THE BODY'S IMMUNE DEFENCE INTO NOT ATTACKING THEM. HER-VAXX, A CANCER VACCINE CURRENTLY BEING DEVELOPED BY AUSTRALIA-BASED IMUGENE, STIMULATES THE BODY'S B-CELLS TO PRODUCE ANTIBODIES THAT CAN CONNECT TO TUMOUR CELLS THAT EXPRESS THE PROTEIN HER-2, FOUND IN SOME BREAST AND GASTRIC CANCERS. ONCE ANTIBODIES CAN CONNECT TO CANCER CELLS, THE IMMUNE SYSTEM CAN DESTROY THEM

instead of stimulating the body's immune system to produce its own antibodies that can target proteins found on cancer cells. "Therefore, [passive immunotherapies] require repeated administration to sustain efficacy," she says.

These benefits are being touted by cancer vaccine manufacturers such as Australia-based Imugene, which is developing a cancer vaccine that targets the tumour antigen known as HER-2, found in some breast and gastric cancers. The vaccine would compete with Roche's Herceptin, a monoclonal antibody drug also directed at HER-2.

Charles Walker, CEO of Imugene says that his company's vaccine, HER-Vaxx, which is set to begin Phase II clinical trials, could eliminate a number of problems with monoclonal antibody treatment. These include the problem of the body developing resistance to the drug, which can limit the number of doses the patient can receive; and secondly, reducing the chance of side effects such as congestive heart failure.

"Herceptin is an artificial antibody, and its job is limited in what it does," Walker says. "The human system making its own antibodies is always going to be better than an antibody made in a factory."

Because they require lab-produced antibodies adapted from other animals like mice, monoclonal antibody drugs are also very expensive – Herceptin, for example, can cost up to

US\$70,000 per year, Walker says. However, the research behind Herceptin – which identified the HER-2 protein – has enabled companies like Imugene to try to build an improved treatment that would also be more cost effective.

"When HER-Vaxx works, it has the chance of delivering a number of benefits to patients, including better survival outcomes, decreased side effects and lower cost," Walker says. "While improving side effects and cost of therapy is attractive, our real aspiration is that we can get a patient's own immune system to work many times better than Herceptin, and deliver improved outcomes for patients."

Cancer vaccine developers struggle to overcome the 'valley of death'

Despite the millions being invested in cancer vaccines, only one therapeutic vaccine – Provenge, a cancer vaccine for prostate cancer manufactured by Dendreon, has thus far managed to grab FDA approval. Even so, Provenge has not performed well in the market due to its steep price tag and limited ability to prolong survival. Patients treated with Provenge are expected to live an average of four months more compared to those who did not undergo the treatment. Additionally, it comes at the hefty cost of US\$93,000 per treatment, according to American Cancer Society figures.

Although a few months increase in life expectancy could mean a lot from patients' standpoint, the real challenge is how to build on the progress made possible by Provenge in order to provide cancer patients with better outcomes.

"Provenge is excellent in that it shows immunotherapy can work," Charles Walker of Imugene says. "While there have been commercial limitations for the drug, it's still proven the concept."

Another difficulty for developers is proving that cancer vaccines can be effective in a large sample of patients. One notable failure was major pharmaceutical Merck's announcement in September 2014 that it would discontinue its late-stage vaccine Stimuvax, directed at non-small cell lung cancer, after it "flunked" a Phase III trial in Japan, biotech blog Fiercevaccines.com reported. Earlier that year, GlaxoSmithKline's Phase III trial for its non-small cell lung cancer vaccine MAGE-A3 suffered a similar fate.

According to Angus Dalgleish, professor of oncology at St. George's University of London, some previous cancer vaccine trials which held promise in the early stages eventually fell through due to a variety of factors, including poor patient selection and inappropriate administration of the vaccine.

One potential explanation for this is an inconsistency among the centres involved in the trials. In a 2011 paper published in the journal *Vaccine*, Professor Dalgleish wrote that some researchers testing cancer vaccines used intradermal injection, which is in between the upper and lower layers of the skin, while others administered the vaccine subcutaneously, in the fat layer underneath the skin.

Other researchers disagree. Dr. Toh Han Chong of NCCS says he doubts that the way the vaccine is administered is a key driver for the outcome of cancer vaccine trials.

"While there is some scientific evidence that intradermal injection may be better than the subcutaneous route for cancer vaccines, there is no concrete evidence that it confers a real advantage; this is certainly not the reason why therapeutic cancer vaccines fail in late-stage clinical trials," Dr. Toh says.

In his paper for *Vaccine*, Professor Dalgleish also notes that the patients' overall motivation to fight cancer, especially their attention to a healthy diet and exercise, can differ among multiple testing centres, thus affecting trial outcomes.



DR. TOH HAN CHONG, DEPUTY DIRECTOR AT NCCS, IS THE PRINCIPAL INVESTIGATOR FOR THE PHASE I CLINICAL TRIAL OF THE CANCER VACCINE DEVELOPED BY US BIOTECH MICROVAX LLC

"Having visited several centres recruited for the randomised studies I was struck by the difference in general health and self-motivation of patients recruited compared to those in the principal centre," he wrote.

Professor Dalgleish has been integrating the experience he made by analysing previous failures in cancer vaccine trials into the development of another cancer vaccine known as IMM-101 for pancreatic cancer, which actually he prefers not to call a "vaccine." Thus far, the vaccine, which is in Phase II trials, has been tested in 110 patients, and has proved to offer an average increase in survival that adds up to about three months with no toxicity, Dalgleish says.

"The IMM-101 project started off life as a vaccine, we now wish to call it an injectable immune modulator, as cancer vaccines have been given a bad name by big pharmaceuticals, who have trialled many cancer vaccines which have all failed as they are single antigen based. IMM-101 is a multi-antigen product which is why it works," he says.

Wary of the numerous failures in the cancer vaccine field, drug developers are trying to learn from each others' mistakes. Pharmaceutical giant Pfizer is currently in preclinical testing of a therapeutic cancer vaccine for prostate cancer that the company says may have a better chance of success than some of its predecessors, because it addresses a fundamental problem with earlier vaccines — the fact that those vaccines were too focused on specific antigens found on cancer cells.

"By and large, most of the common antigen approaches as a vaccine immunotherapy have had limited success," Dr. John Lin, vice president of experimental medicine and cancer immunotherapy for Pfizer, told *Global Health and Travel* while attending The Economist magazine's "War on Cancer: Enemy of the State" conference in Hong Kong on Mar. 20. "Some tumour cells may express a high level of that particular antigen, and yet other tumour cells may have very little expression. When you try to elicit an immune response to that particular antigen, maybe some tumour cells will be eliminated, but some tumour cells in the same tumour may not be eliminated."

"One of the big considerations when it comes to our own cancer vaccine program is that we don't believe a single antigen is sufficient. We want to make it less restrictive, in the sense that we include more than one antigen," Dr. Lin says.

Another possible explanation for the high rate of failures in late-stage cancer vaccine trials is the employment of an inappropriate framework to analyse potential outcomes.

According to Charles Walker of Imugene, in past years researchers used the parameters for chemotherapy effectiveness as the basis to evaluate cancer vaccines. For example, if the tumour was seen to enlarge after the administration of the vaccine, the trial could have been deemed unsuccessful and consequently stopped. This paradigm is useful in determining the efficacy of chemotherapy, which is supposed to decrease or at least stabilise the size of the tumour, but it can be misleading when it comes to evaluating the effectiveness of immunotherapy.



PHOTO CREDIT: PFIZER



“Even with the best immunotherapy that is currently available, it will probably not be sufficient by itself. Eventually, if you want patients to benefit the most, you will need some sort of combination. Hopefully we can move away from the traditional radiation and chemotherapy into less toxic and more specific therapy like targeted therapies and immunotherapy”

- Dr. John Lin, vice president of experimental medicine and cancer immunotherapy for Pfizer

Professor Ferrari of NYU says that even though the tumour’s size can increase immediately following immunotherapy treatment, the patient’s survival may improve.

“The immune anti-tumour response does not cause tumour shrinkage as observed with cytotoxic chemotherapy but leads to significant delay in progression and longer overall survival with minimal toxicity or compromise in quality of life,” she says.

Could a breakthrough in cancer vaccine research be on the horizon?

Given the daunting challenges in developing a cost-effective cancer vaccine that can significantly prolong life in a wide range of patients, researchers realise that alternative logic may be necessary to break through barriers that the cancer vaccine field is currently facing.

Dr. Brendon Coventry, an associate professor of surgery at the University of Adelaide and Martin Ashdown, a research fellow at the University of Melbourne, may have found one of the keys to increasing effectiveness of a broad range of immunotherapies.

The pair of researchers focused on Interleukin-2 (IL-2), a hormone that stimulates immune system cells to grow faster and it is usually employed as a treatment for kidney cancer and metastatic melanoma, and tried to make sense of its apparently random seven percent rate in leading patients towards total remission.

They discovered that IL-2 is able to activate an immune response only if the immune cells have a specific receptor detecting IL-2. Unfortunately, these receptors are present on immune cells just for a determined slot of time ranging from eight to 12 hours before fading away. And this period varies from patient to patient as each individual has a distinctive immunological cycle.

“If we could accurately target the therapeutic window at the correct time-point in each patient’s immune cycle, this would make responses to therapy much more predictable and would lead to a real possibility of treatment success that is much closer to 100 percent,” Dr. Coventry and Ashdown wrote in the June 2014 cover story of *Australasian Science Magazine*.

This led the researchers to claim that they could have unravelled a sort of “Rosetta Stone” for cancer. The one of a kind piece of rock was discovered in 1799 and made the understanding of hieroglyphics possible for the first time by providing the same inscriptions in three different languages: hieroglyphics, demotic and Greek. Interleukin-2 is believed to offer similar information to decipher the proper time to deliver

immunotherapies and make them successful.

The two researchers have examined serial blood samples to figure out how to identify patients’ immunological cycle and they have eventually personalised each therapy to match it with the right slot of time. “These examples indicate that the techniques we propose are both achievable and effective, but require improvement, testing and wider acceptance,” they wrote in *Australasian Science*.

In an interview with *Global Health and Travel*, Dr. Coventry says that this theory also applies to cancer vaccine administration. “The immune system is in a process most of the time of either turning off and turning on to keep it relatively constant, but not absolutely constant,” he said. “And therefore, ‘when’ the vaccine is given in this particular cycle that’s going on in the patient, it will be particularly important as to whether a response against the cancer gets generated or not.”

“The ‘therapeutic window’ for enhancing the immune response lies somewhere around each ‘trough’ in the patient’s individual immune cycle,” Dr. Coventry says. “This window is available to any agent that can stimulate the immune system, including exogenously administered IL-2 and vaccines.”

Although immunotherapies, including cancer vaccines, have been receiving a huge chunk of the attention and investment in the oncology world as of late, Dr. John Lin of Pfizer says that his company is not discounting the development of other next-generation treatments, such as targeted cancer therapies, that would eventually take their place alongside chemotherapy and radiotherapy as benchmark treatments. Another important thing to remember is that developing combination treatments, as opposed to standalone treatments, will probably have the best chance at improving patient outcomes, he says.

“Eventually, if you want patients to benefit the most, you will need some sort of combination. Hopefully we can move away from the traditional radiation and chemotherapy into less toxic and more specific therapy like targeted therapies and immunotherapy,” Dr. Lin says.

“Even with the best immunotherapy that is currently available, it will probably not be sufficient by itself,” he says. [GHT](#)

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