A vaccine for cancer

Professor Pravin Kaumaya of Ohio State University outlines his initial success in finding a cancer vaccine, and his optimism that a subsequent reduction in cancer rates in the near future is a realistic prospect.

Could you outline the methods, and motivation, behind your objective of developing a broadly applicable vaccine to target HER-2 (overexpressed in up to 30 per cent of breast cancers), and VEGF, which becomes increasingly expressed as a result of HER-2 overexpression?

This work started some two decades ago when I was at Northwestern University, after it became clear to me that designing peptide vaccines was rather more complicated than thought at that time. The very first hurdle was how to design peptide sequences that would mimic the corresponding three-dimensional structure of the native sequence. The second obstacle was how to generate an immune response in an outbred population like man. In the early nineties, I devised strategies to address both problems. We proposed and addressed these obstacles by the use of ‘promiscuous’ T-cell epitope as chimeric immunogens with appropriate engineered B-cell epitopes, which can result in highly efficacious antibodies and generation of immunologic memory that can delay, prevent and/or eradicate tumour growth and metastasis. In 1993, I was convinced that we could harness the immune system to fight cancer in the same way as infectious agents are destroyed. We mapped the entire surface of HER-2/neu and narrowed down a potential combination vaccine candidate consisting of two HER-2 epitopes. Recently the idea that to effectively immunise against cancer will require a combination therapeutic strategy has led me to VEGF, which is responsible for the process of angiogenesis: a necessary prerequisite for tumour growth. The overexpression of HER-2/neu results in upregulation of VEGF, making the choice of VEGF an excellent one.

Can you describe how you arrived at and formulated the vaccine that entered the clinical trial?

The entire HER-2 oncogene was mapped to four biologically relevant epitopes, and our results were published in Cancer Research in 2000. Given that the immune response to any given oncogene/protein resides in distinct regions, we decided to combine different epitopes in studies that were completed in 2002. Since optimising a multi-component cancer vaccine requires agents to be tested both individually and in combination with each other, numerous iterations were needed to learn how to obtain an ideal immune response. In our preclinical and extensive studies spanning a decade, we finally identified the two regions of HER-2 that could potentially be a vaccine candidate.

Can you explain why has this vaccine proved effective, relative to its forerunners?

Most ‘active immunotherapy’ vaccines target the cellular immune responses, i.e. T-cell responses. Ours target a specific humoral response to an important biological B-cell epitope, eliciting high affinity antibodies that also require non specific T-cell activation.

Your study is the first to show that a combination B-cell epitope vaccine can elicit antibodies that disrupt two different HER-2 signalling pathways. Do you consider this your greatest success to date?

I do not think this is our greatest success to date, although it is quite significant. Our approach is novel, but needs to be further exploited in ways that will treat and cure cancer using innovative clinical trial designs. Although the present vaccine represents an excellent candidate for Phase II trial and we are pursuing these avenues, we must continue to persevere in developing newer strategies to optimise clinical efficacy and superior benefit for cancer patients.

You and your colleagues have been able to produce a second-generation version of the vaccine, with a trial scheduled for September 2010. What are your thoughts ahead of the trial, and what have you gleaned from the results of the first-generation vaccine?

We are excited that with this second generation vaccine, we might improve on our previous clinical results in producing cancer-killing antibodies in cancer patients with higher efficacy. Based on our previous experience, we will start the new trial at a dose near the optimum biological dose, and identify the best dose to be used in a phase II trial.

How important do you consider global collaboration in cancer research?

In this age of economic global inter-independence, I think that any exchange of ideas and collaboration within the U.S., and around the world, is paramount in achieving the desired objectives of delivering innovative cures to patients. We have collaborated with scientists in many different countries as such expertise warrants.

Finally, is there anything else you wish to mention regarding your recent clinical trials and vaccine developments?

We are looking forward to the results of the new clinical trial and whether the second generation combination vaccine will be better than our previous trial. This would obviously impact on future strategies such as combination strategies with angiogenic inhibitors and low-dose chemotherapy. There are still major challenges that impede the development of future cancer vaccines. We must identify promising new immune agents, and bring them together to construct cancer vaccines with greater therapeutic potential than ever before. We should endeavour to make these next generation vaccine treatments immediately available to clinical trial participants, years before they might otherwise become commercially obtainable. So the way we perform clinical trials must change dramatically from present practices. If proper toxicity studies are performed at an early stage, we should be allowed to test our vaccine in less compromised patient population who will stand a better chance of reaping clinical benefit. The development of highly effective cancer vaccines for a variety of prominent cancers is a realistic and achievable goal within the next decade.

Above figure 1: VEGF Peptide Mimic
THE MODERN HISTORY of chemotherapy is controversial, and only really gained acceptance into medical practice during the 1970s. Although hugely successful in stopping progression of - and rarely curing - advanced cancer, these cytotoxic drugs also affect normal, non-cancerous cells, and can cause many toxic side effects. A more specific approach emerged during the early 1980s with the advent of monoclonal antibodies (mAbs), which disrupt the mechanisms that cause uncontrolled cellular mitosis, hence arresting the growth of tumours or rarely eradicating them altogether.

mAbs were initially hailed as a miracle cure for cancer by some experts; nevertheless, it has subsequently become apparent that such a claim is unfounded. As a form of passive immunotherapy, mAbs have a short life span and do not stimulate the immune system to produce its own antibodies. Their clinical use is hindered by issues such as the required frequency of treatment, limited effective duration, undesired immunogenicity and toxicity, and high cost. To illustrate this, Trastuzumab (Herceptin) costs $78,000 per year of adjuvant therapy (in the U.S.), with reports of cardiotoxicity, while Bevacizumab (Avastin) costs $55,000 per course, is associated with hypertension and increased risk of bleeding, and on average increases a patient’s life expectancy by only two months.

THE MOVE TOWARDS ACTIVE IMMUNOTHERAPY

Since passive immunotherapy has been shown to have significant shortcomings, research to find a different solution is well underway. In much the same way as active immunotherapy (vaccination) is used to treat infectious diseases, it is thought that the immune system can be stimulated to automatically elicit anti-cancer antibodies. Professor Pravin Kaumaya, of The Ohio State University, is at the forefront of such research. A peptide/medical chemist who taught himself immunology, Kaumaya has worked with his multidisciplinary team to develop an effective vaccine for cancer, which should fulfill several criteria. “An optimal cancer vaccine must include several components aimed at initiating, strengthening, and sustaining a comprehensive immune response against a patient’s cancer,” he explains.

In a project spanning two decades, Kaumaya’s team has focused their research on peptide epitopes- the amino acid residues on the surface of antigens that bind to antibodies and immune cells (B- and T-cells). Through their preliminary findings, they have pinpointed two suitable B-cell epitopes derived from the HER-2 antigen, which is overexpressed in some types of breast, ovarian, uterine, lung and colon cancers, and is associated with worse prognosis, aggressive disease, and resistance to therapy. HER-2 overexpression is also thought to be associated with the increased expression of VEGF, a glycoprotein secreted by cancer cells, and responsible for angiogenesis (new blood vessel formation), which is essential to the development of large tumours and
metastases. Although HER-2 is expressed by normal cells, an immune response is not normally initiated until it reaches higher, abnormal levels. Unfortunately, some of the antibodies produced by such a response actually stimulate, rather than inhibit, tumour growth. Kaumaya’s work focuses on eliciting an immune response to produce endogenous HER-2 specific antibodies with only an inhibitory function. This has been achieved via the two previously mentioned epitopes, which he has managed to synthesise and fused to a ‘promiscuous’ T-cell epitope.

Despite encouraging progress, Kaumaya’s work has not been lacking in challenges. The complex structure of the epitopes was such that the team had to design models able to mimic their structure in the native protein, and then deliver them to the immune system, without compromising their immunogenicity. That being said, Kaumaya points out that through his extensive work, he has obtained positive results, both in vitro and in vivo in several animal models that mimic human disease: “Our innovative strategy has been shown to be effective in rigorous and extensive pre-clinical testing, and therefore translating it to the clinic was paramount,” he explains.

Consequently, this has manifested as a Phase I trial in human subjects.

THE TRIAL

The Phase I trial of Kaumaya’s vaccine was undertaken to determine the safety, toxicity and maximum tolerated dose (MTD). The study was a dose-escalating trial, with 24 subjects (19 women and three men), all of whom had confirmed metastases and/or recurrent solid tumours, were no longer responding to treatment, and were at least one month free of any chemotherapy, radiotherapy or surgery – not an ideal choice of subjects, as Kaumaya highlights: “The trial was conducted in Stage IV cancer patients that had exhausted all standard treatment, and whose immune system had been severely battered”.

The results of this first trial have been remarkably positive, and the findings have been published in the Journal of Clinical Oncology. The vaccine was found to be safe, with the MTD established at 1.5mg, and it elicited an antibody response in 62.5 per cent of patients. There were no incidences of serious adverse events, autoimmune reactions, or cardiotoxicity. Four of the subjects (with adrenal, colon, ovarian and squamous cell carcinomas) were reported to have stable disease, two (with endometrial and ovarian cancer) had a partial response, while 11 had progressive disease. As Kaumaya observes, these results are somewhat unexpected, since only one of the patients who experienced benefit from the vaccine was shown to overexpress HER-2: “Some patients had exceptionally high levels of antibodies to the vaccine”. However, putting these results in context, he does recognise the limitations of the study: “Given that this was a limited Phase I study with 24 patients, the safety of the vaccine can only be validated in a large cohort of patients in

FIGURE 3. ENGINEERED VEGF PePTIDE MIIMIC

Phase II trials.” He continues: “We are exploring avenues to license this vaccine to a company that can conduct these trials”.

FUTURE DIRECTIONS

That Kaumaya’s research has yielded such positive results over the last two decades is due in no small part to the funding from the National Institutes of Health and the National Cancer Institute. He has also been supported by the Susan Komen Foundation and more recently the FORE Cancer Research Organization. This has allowed him and his team to explore further innovative new avenues for research. They have already developed a second generation version of the vaccine, which is due for human trials in July 2010. Kaumaya believes that this not only has the potential to target solid tumours that overexpress HER-2, but also those that are HER-2-negative and EGFR-overexpressing, including breast, ovarian, lung, colon, pancreatic, and head and neck cancers. Presently, he is completing extensive new studies on combining HER-2 and VEGF peptide mimics with low-dose Taxol that is providing new insights on cancer immunotherapy strategies of the future.

Working in an area of medical research with such a controversial history, Kaumaya has experienced a wide range of opinions regarding his work. “Some of my peers thought my work was exceptionally innovative and some thought it had very little merit,” he reflects. “That’s the paradox and beauty and of peer review. Being in an academic environment is also important as it allows the freedom to develop innovative ideas without the constraints that exist in Big Pharma. One can then follow one’s intuition, even if a proportion of the community at large believes otherwise.”

Kaumaya remains optimistic about the future, and is keen to share his thoughts on the subject. “Unlike most other current forms of cancer treatment, cancer vaccines can generate a specific attack on tumour cells, target genetically predisposed patients, even those that may be clinically undetectable, without harming normal cells,” he states. “Cancer vaccines have the potential to revolutionise cancer treatment by enabling patients to live longer with full immunological control of their disease.”

INTELLIGENCE

PHASE I TRIAL WITH TWO HER-2 B CELL EPITOPE VACCINE IN PATIENTS WITH SOLID TUMOURS

OBJECTIVES

To develop an optimal cancer vaccine from B-cell epitopes derived from the HER-2 antigen, and comprising several components aimed at initiating, strengthening, and sustaining a comprehensive immune response against a patient’s cancer.

FUNDING

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DR KAUMAYA received his BSc (Hons) in Biochemistry at the University of Central London, UK and PhD in Medicinal Chemistry at the University of Portsmouth, Hants, UK in 1981, was a postdoctoral associate at University of Texas at Austin, Research associate and Assistant Professor at Northwestern University. He joined the department of Ob/Gyn as Professor in 1989as well as Director of the Peptide and Protein Engineering Laboratory within the Comprehensive Cancer Center and College of Medicine. He assumed the Directorship of the Division of Reproductive Biology and Vaccine Research in 2004. He is a member of several Professional societies (FAIC, AAAS, APS, AAI), and was elected as a fellow of the American Association for the Advancement of Science (AAAS). Dr Kaumaya is the primary inventor on several issued and pending patents for Peptide Vaccine and Therapeutic Technologies.