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Recombinant cancer vaccines and new vaccine targets:

Interview by Jenaid Rees, Commissioning Editor

Jeffrey Schlom

Author for correspondence: Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, NIH, 10 Center Drive, Bethesda, MD 20892, USA, js141c@nih.gov

Abstract

Jeffrey Schlom obtained his PhD from Rutgers University (NJ, USA). After obtaining his PhD, he worked at Columbia University (NY, USA) before moving in 1973 to the National Cancer Institute, National Institutes of Health (MD, USA). Since then he has served as the Chief of several sections, including his present position as the Chief of the Laboratory of Tumor Immunology and Biology in the Center for Cancer Research which he has held for the past 30 years. During this period, he has worked as an Adjunct Professor at George Washington University (Washington, DC, USA), served on the Editorial Board of several journals and holds membership in a number of committees. He holds over 30 patents and patent applications in the areas of vaccines, tumor antigens and monoclonal antibodies and has received honors and awards throughout his career. Jeffrey Schlom has been involved in translational research involving the immunotherapy of a range of carcinomas and predominantly works in the areas of tumor immunology, mechanisms of tumor cell–immune cell interactions and immune mechanisms. He has recently been working on the design and characterization of recombinant vaccines for cancer therapy.

What inspired you to specialize in the field of cancer vaccine development?

There was a lot of evidence that the immune system plays an important role in the eradicating of human tumors. It has been shown that patients who were immunosuppressed following transplants, patients with AIDS, or patients who received high doses of radiation had a higher incidence of cancer. This tells us that when you are immunosuppressed, you have more tumors and that means that the immune system is playing a role in tumor surveillance. I think this is a pretty well-established phenomenon. But we also know that some tumors are poorly immunogenic in patients and that the immune system does not recognize the antigens expressed by the tumor. Therefore, the goal was to answer the

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question: How does one increase the immunogenicity of these weak antigens? There have been a lot of studies, previously and ongoing, to show how to do this. That was the main reason I thought this would be a good way of intervening in cancer management. Another reason is that vaccines, in general, have a very low level of toxicity, as it is the patient's own immune system fighting the tumor or the pathogen, and I thought this would be a very good modality to use as a monotherapy or in combination therapies.

You have been working in the field of recombinant cancer vaccines; could you kindly outline your advancements in this field?

I would put the advances into two major categories: the knowledge gained from preclinical studies and the knowledge gained from clinical studies. Let me talk about preclinical studies first. One of the things we have found is that even though the host is tolerant to a particular antigen that is found in the tumor, one can enhance the immunogenicity of that antigen by placing the gene for that antigen into a vector. Also, you can add immunostimulatory molecules into the mix to increase the immunogenicity of the antigen. So it is not necessarily that the tumors are expressing antigens that the immune system will never attack; if you know how to enhance the immune response to the tumor antigen, then you can get a better attack of the tumor. Dr James Hodge in our laboratory and others have demonstrated how well combination therapies work with vaccines. There are now preclinical studies with checkpoint inhibitors, hormones, chemotherapy, radiation and targeted therapies that show that vaccines can act synergistically with these modalities. These other modalities can either have a direct effect on the tumor to render the tumor more susceptible to T-cell attack, or can have an effect on the immune system by inhibiting immunosuppressive elements to make the vaccine more effective.

There is another phenomenon we call antigen cascade. This occurs when the immune system, activated by a vaccine, attacks a tumor with some degree of tumor destruction and lysed tumor cells are presented to the immune system. The immune system then recognizes other antigens that are not in the vaccine itself. This spreading of immune attack against multiple tumor antigens also addresses the issue of tumor cell heterogeneity. That is another advantage of vaccines.

In terms of advances for the clinical work, there is one vaccine now approved by the U.S. FDA and that is PROVENGE for prostate cancer. We have extremely good results in many clinical trials conducted by my collaborators at NCI, Drs James Gulley, Ravi Madan and Christopher Heery, with our PROSTVAC vaccine that is a poxvirus vaccine for prostate cancer. Also, there have been some very exciting results with a vaccine we developed called PANVAC in a multicenter trial (headed by investigators at Duke) in patients with metastatic colorectal cancer. Other studies have shown that we can use these vaccines in combination with nonimmune therapies such as hormone therapy, chemotherapy and radiation therapy. The PROSTVAC and PANVAC vaccines are being studied as part of a Cooperative Research and Development Agreement (CRADA) between our laboratory and Bavarian Nordic, Inc. Additionally, we have shown that one of the issues that always comes up when using vaccines is that they do not necessarily shrink tumors, but patients are simply living longer.

This has been shown with PROVENGE and with the checkpoint inhibitor ipilimumab and with some of our own vaccines, in particular PROSTVAC and PANVAC. We have found that the vaccines are altering the growth kinetics of the tumor, thereby slowing down the growth of the tumor so that patients are simply living longer.

Where do you feel the field of viral-based vectors for cancer vaccines is headed?

There is a lot coming up on the horizon that is very exciting. Vaccines are now being used earlier in the disease stage, they are used more in combination therapies and there are new targets. In particular, we have just started a vaccine trial at NCI that is targeting a transcription factor (termed Brachyury) that is involved in cancer cell ‘stemness’, that is, cells that are more drug resistant; this is a phenomenon called epithelial–mesenchymal transition.

A potential drawback for cancer vaccines is that the tumor microenvironment & other immunosuppressive entities can limit the effectiveness of these vaccines – how do you feel this can be best overcome? And which strategies do you feel are most promising?

One of the areas that is very exciting is in the field of immune checkpoint inhibitors. For example, anti-CTLA-4 ipilimumab has been approved by the FDA. There are other trials going on with anti-PD-1 and anti-PD-L1, which are both checkpoint inhibitors. PD-L1 is a molecule found on tumor cells that has been shown to suppress the ability of T cells to kill the tumor, so the use of a molecule that blocks PD-L1 should overcome this immunosuppressive entity. And indeed, we and others are conducting clinical trials with an anti-PD-L1 antibody. Second, it has also been shown that certain targeted therapies, such as the tyrosine kinase inhibitors, for example, sunitinib, can alter the microenvironment, that is, the vasculature in the tumor to enhance T-cell-mediated killing. These are two major pathways that researchers are studying.

You have recently been working on cytokine biology as it integrates with cancer immunotherapy; could you elaborate on any recent hopeful implications this may have for cancer vaccines?

There are three interesting cytokines that are currently being studied by Dr Jack Greiner in our laboratory and others. There is granulocyte–macrophage colony-stimulating factor (GM-CSF), and indeed in our ongoing Phase III trial with PROSTVAC, we have three arms: a control arm, a vaccine arm and then vaccine plus GM-CSF. There are conflicting results in the field as to how GM-CSF works and whether it can potentially be harmful or helpful. It probably depends on the dose and the dose scheduling, so we hope to answer this in a large Phase III trial.

Another cytokine that is very promising is IL-15; we and others are conducting preclinical studies with IL-15 and other groups are starting clinical work with IL-15. Another very important cytokine is IL-12. One of the issues with IL-12 is that it has been shown previously to be quite toxic. We have just started a clinical study at NCI in collaboration with our CRADA partner EMD-Serono, where IL-12 has been linked to an antibody that targets tumors, so that it should reduce toxicity and increase its effectiveness. All three of these cytokines are extremely important. Others include reagents directed against TGF- β , which has been shown to be immunosuppressive. The ongoing anti-TGF- β studies are mostly preclinical.

You have been involved in the development of the TRICOM cancer vaccine; how have the TRICOM trials progressed & what are your hopes for this vaccine?

The trials have progressed extremely well. The TRICOM vaccine is composed of two different vectors: the recombinant vaccinia virus, which is the priming vaccination, and boosting with recombinant fowlpox, the avian pox virus that can be given multiple times. Both vectors have been shown to be extremely safe in patients. We have been able to load up these vectors with one or two tumor antigen transgenes and trans-genes for multiple costimulatory molecules, that is, where the term ‘TRICOM’ comes from, a triad of costimulatory molecules. Through a lot of preclinical work, we found that these three costimulatory molecules work synergistically to enhance immunity against tumor antigens.

In terms of our prostate program, we have gone from Phase I to multiple Phase II studies, which have provided evidence of clinical efficacy and we have a global Phase III PROSTVAC vaccine study ongoing. Although this trial focuses on patients with metastatic prostate cancer, we also have promising results with patients with early prostate cancer and we are about to start some clinical studies in prostate cancer with this vaccine in combination with a new antigen-deprivation therapy agent. There is also a clinical study, which has just been published by Drs Morse and Lyster at Duke, in metastatic colorectal cancer patients who received PANVAC that has two tumor antigens – CEA and MUC-1 – and TRICOM in it. This regimen has provided evidence of increased survival in these patients. The patients in this trial had their metastatic tumor in the liver or lung removed, after which they were given the PANVAC vaccine. Compared to contemporary controls, this has been extremely exciting in terms of the increased survival in the vaccine group.

You are also working on the development of novel immunoassays to define immune responses to vaccines from patients enrolled in vaccine trials; how do you feel this will impact on the success of trials & the subsequent development of cancer vaccines?

One of the issues that has not been resolved is whether the patient’s immune response is a surrogate for clinical efficacy. Although there are trends that patients who mount greater immune responses to the vaccine do better, this is not at the point where it is going to be

considered a surrogate. I doubt it ever will be a surrogate. I would attribute this to a couple of different reasons. Number one is that in almost all of the trials being evaluated, investigators are looking for immune responses in the peripheral blood. Except for melanoma, which is easy to biopsy, or leukemia, very few biopsies are taken so it is difficult to determine which immune cells are in the tumor; this is the business end, as opposed to what is in the blood. So we are only seeing a very small part of the picture.

Number two is that preclinical studies, and now clinical studies, are showing that often patients are mounting immune responses postvaccination to antigens that are not in the vaccine, and these responses are actually stronger than the immune responses to the antigen in the vaccine. This is due to the phenomenon of antigen cascade where some tumor cell destruction is initiated by vaccine-induced T cells. This leads to an antigen cascade where lysed tumor cells are taken up by host antigen-presenting cells. These cells in turn activate immune cells that are actually more potent than the initial immune cells in killing tumor.

You are also involved in collaborations to define novel target antigens for tumor immunotherapy: what do you feel are the most promising areas here? How are things progressing with agonist TAA epitopes for use in clinical vaccine development?

We feel it is very important to make enhancer agonists to these antigens. What is an agonist? An agonist is a modified tumor antigen that becomes more immunogenic. We have had these agonist epitopes in all our vaccines.

There are two other targets we are very excited about. The first is brachyury, which is a driver of drug resistance or stemness or epithelial–mesenchymal transition. This work is led by Dr Claudia Palena in our laboratory. We just initiated a clinical study with a recombinant yeast vaccine to target Brachyury through our CRADA with GlobeImmune. The other target we are very excited about is the C-terminus of the oncogene MUC-1C. This gene has been shown by Dr Kufe at Dana Farber in many studies to be an oncogene and to correlate with drug resistance. We are hoping to start clinical studies very soon targeting this particular oncogene.

Of your scientific achievements to date, which one do you feel will have the biggest impact on the field of vaccines?

I think the Phase III trial with PROSTVAC, which is now ongoing, may have a very big impact in prostate cancer management, as well as the trial that was conducted with PANVAC in metastatic colorectal cancer patients. I also think that the trials we will start soon in early prostate cancer and in metastatic prostate cancer as well as other cancers with vaccine in combination with novel-targeted therapies are going to be very important.

In your eyes, where do you feel the field of cancer vaccines will be in the next 5 years?

I am optimistic that there will be several vaccines approved by the FDA. They will be used early in the disease process and in combination therapies, and we will see the use of combinations of different vaccines together. This is because each vaccine targets a different antigen and/or enhances the immune system in a different way.

Do you have any words of advice you would give a young researcher entering the field of cancer vaccines?

I think this is the absolutely perfect time to get involved in the field of cancer vaccines and immunotherapy. When the field of monoclonal antibodies was in its infancy, it took about 10–12 years before clinical trials started to look promising. And now, monoclonal antibodies represent some of the biggest blockbuster anticancer drugs. I think we are clearly at a tipping point right now in the field of cancer vaccines where some of the early work has been done; it has taken many years to show the safety of these vaccines and learn how to use them, what the appropriate endpoints are and how they can be used in combination therapies. I think this is really an excellent time for the clinical development of cancer vaccines both as monotherapy and in combination therapy.

Biography