Cancer vaccines: an overview

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The long-held hope that vaccination strategies might be effective against cancer has motivated numerous attempts over the past century to put the idea to test in the clinic. Although the generally disappointing results have cast a long shadow over the field, advances in cancer immunology growing on the remarkable insights from basic immunology provide a strong foundation and powerful new tools to guide current attempts to fashion effective cancer vaccines. This review covers the scientific basis and rationale for cancer vaccines, the challenges involved in assembling the many ingredients going into the construction of cancer vaccines, and the daunting obstacles confronting academic investigators wanting to transfer their discoveries into the clinical arena. The Cancer Vaccine Collaborative (CVC), a partnership between the Cancer Research Institute and the Ludwig Institute for Cancer Research, represents a new academic model for developing, coordinating, conducting, and monitoring cancer vaccine trials. NY-ESO-1, a prototype cancer-testis (CT) antigen having strong spontaneous humoral and cellular immunogenicity, has been chosen as the initial CVC vaccine target, and the current status of NY-ESO-1 vaccine trials carried at the multiple CVC sites around the world is discussed.

Keywords: cancer vaccines, cancer immunosurveillance, tumor antigens, immunologic monitoring, clinical trials, NY-ESO-1

It is my pleasure to greet you to this 15th annual symposium organized by the Cancer Research Institute. We inaugurated the series to track the progress of therapeutic approaches to cancer based on immunological principles, with a particular focus on the development of cancer vaccines. Efforts to develop effective cancer and HIV vaccines have much in common, drawing upon the same strategies to vaccinate and tools to monitor, and confronting the same challenges of testing our ideas in the clinic. This meeting of experts from both endeavors provides the opportunity to discuss lessons we have learned and aspirations that we share, find ways to procure needed reagents, and seek solutions to barriers that frustrate our success. The CRI is grateful to Dr. Giuseppe Pantaleo for his critical role in the organization of this meeting and we thank all of you for joining us here today.

I will initiate the meeting now with (i) a brief review of the scientific basis for cancer vaccines, (ii) the personal lamentations of an academic investigator wanting to do clinical trials and the way the Ludwig Institute for Cancer Research that I led for 17 years has attempted to deal with this, (iii) a description of the CVC (Cancer Vaccine Collaborative), a clinical discovery instrument created by a partnership of the Cancer Research Institute and the Ludwig Institute for Cancer Research, and finally (iv) a review of the commercial vaccines that are in advanced clinical testing and a summary of the CVC’s experience with vaccines against the highly immunogenic human tumor antigen NY-ESO-1.

Although vaccination against cancer has had a long and controversial history, the field long suffered from the absence of a strong and secure scientific basis. Over the past decade and a half, however, the situation has undergone a remarkable change and this can be directly traced to two sources: (i) the spectacular advances in our understanding of the immune system, and (ii) the validation of widely held but unproven ideas that inspired tumor immunologists.

The first of these, cancer immunosurveillance, the belief that the immune system protects against the development of cancer, a theory put forward by Lewis Thomas and Macfarlane Burnet in the 50s, was broadly accepted then broadly rejected when nu/nu immunodeficient mice did not develop more cancer than their wild-type counterparts. Over the past 5-8 years, the pendulum has swung back and we can now celebrate a formidable body of evidence validating cancer immunosurveillance, from the work of Bob Schreiber, Mark Smyth and their colleagues using mice deficient in individual components of innate and adaptive immunity.

The second deeply held conviction of cancer immunology is that there are specific cancer antigens, the philosopher’s stones of the field, that would serve as targets for immune recognition and attack. The search for tumor-specific antigens has been one of the longest uninterrupted lines of inquiry in cancer research, marked by frustration, controversy and disappointment. However, from work carried out over the past two decades by the laboratories of Thierry Boon, Michael Pfreundschuh, Steve Rosenberg, and colleagues of mine, we can now celebrate enormous progress in the definition of cancer antigens with remarkable specificity for cancer and with the capacity to elicit humoral and cellular immunity. The discovery of these antigens is what provides our aspirations for effective cancer vaccines with such a firm theoretical basis.

The third idea that has permeated immunological thinking about cancer comes from the observation that human cancers are frequently infiltrated by cells of the immune system. This was of course postulated to reflect a defensive reaction on the part of the host, but there was little or no proof for this belief. We can now say with confidence from work with several tumor types, including colon cancer, bladder cancer and ovarian cancer, that CD8+ T cells in close contact with tumor cells have highly significant positive prognostic value. Microarray analysis of human tumors has also shown that immunological parameters, such as levels of gamma-interferon, can have a stronger prognostic correlation than the expression of genes generally associated with transformation.

Finally, clinical observations from the time of William B. Coley on the beneficial effect of bacterial infection and bacterial products on the course of human cancer have been interpreted to be due to strengthening immunological reactivity to cancer. This has its counterpart in the current use of BCG (bacillus Calmette-Guerin) as a successful treatment for superficial bladder cancer. The anti-tumor effect of IFN and IL-2, and the capacity of adoptively transferred T cells to cause regressions of...
large tumors, emphasize the power of the immune system to destroy cancer. Most profound to me, however, is the striking anti-tumor activity of anti-CTLA-4. This antibody to a single molecule on T cells can bring about total regression of tumors in patients with advanced melanoma, a Lazarus effect to be sure. The development of anti-CTLA-4 by Jim Allison is a striking example of how the study of a basic immunological question in mice can be exploited for therapeutic benefit in humans.

Because of these advances in cancer immunology – validation of the theory of cancer immunosurveillance, definition of a large number of tumor antigens as targets for immune recognition, prognostic significance of immunological parameters, such as CD8+ T cells infiltrating human tumors, and therapeutic benefits of immune-related therapies from BCG to anti-CTLA-4 – we now have a firm theoretical basis to test the validity of cancer vaccines as a therapeutic strategy. People who say cancer vaccines have been tested and failed are simply wrong. We only now have the knowledge and tools to put this powerful idea to test.

With our increasingly secure scientific base, how do we go about fashioning effective cancer vaccines? Clearly the model we have for basic research doesn’t fit the complex inter-disciplinary, inter-institutional, and regulatory hurdles and requirements involved in an undertaking of this magnitude. The AIDS field confronted this precise challenge some years ago and we can ask at this point how effective the eminently reasonable plan at the time to form a consortium of government, academia, philanthropy and industry as the coordinating and facilitating core of this effort was – how effective was this in achieving the goal of an HIV vaccine? From the onset, the problem with this noble idea was that the component elements had different agendas, different timelines and different cultures – business had intellectual property and bottom lines on their mind, government by its nature is bureaucratic and lacks flexibility, philanthropy tends to be fractionated and uncoordinated, and academics find themselves in a chronic state of underfunding and in an environment that stresses and celebrates individual, not team or programmatic achievements.

The biggest problem, of course, and here I am talking specifically about Phase I clinical entry trials, is the extraordinary challenge confronting any academic wanting to put their ideas to the test in the clinic. Words like “daunting, insurmountable, nightmarish, career-wrecking” are what you hear from the countless investigators who have aspired but failed to scale the barriers separating the laboratory and the clinic. Just how difficult is it? Do a thought experiment with me. Imagine if every experiment we did in our laboratories involved myriad approval steps, was burdened with the extraordinary cost of making and testing the reagents we used, required an IND (Investigational New Drug) submission to the FDA (US Food and Drug Administration) for each experiment, and an additional cost of $500,000 - $1,000,000 to carry out the experiment - just how many discoveries do you think we would have made in our laboratories? The frustration is that never before have we had so much to test in the clinic and never before has it been so difficult or costly to do so.

So industry would seem to be the answer to the academics’ prayer – they have the financial resources, the infrastructure to deal with the FDA and other regulatory requirements, and a large staff to initiate and monitor the trials. The problem is that industry, confronting the dictates of the commercial world, follows a different rule book than the academic world. In the real world, industry decides what to test, how to test it, where to test it and when to stop testing. Under these circumstances, the role of the academic becomes essentially a contract researcher, if he or she is lucky enough to be included in conducting the trial. What we need is a new rule book linking academic and commercial aspirations in this early phase of clinical testing.

With D. K. Ludwig’s magnificent gift to the world of cancer research and the creation of the Ludwig Institute for Cancer Research, it was possible to construct a new model that allowed the Ludwig Institute to take responsibility for the initial clinical testing of its discoveries. Before describing the Ludwig Model, let me share a principal rule with you from my rule book for the academic clinical investigator. If I wanted to articulate a guiding mantra for individual academics and academic institutions wanting to control the fate and entry of their discoveries into the clinic, it would go something like this overarching statement: “Control the IP (intellectual property), and you control the clinical reagent. Control the reagent, and you control the clinical trial. Control the clinical trial and you control the field”.

The Ludwig Institute translated these principles into (i) the development of a strong IP program, (ii) the construction of two facilities - one in Melbourne and one in Ithaca, NY - capable of producing GMP (good manufacturing practice) grade clinical products, (iii) the creation of a clinical trials management team to sponsor and conduct clinical trials but under industry standards, (iv) the assembly of a team of clinical investigators around the world to carry out Phase I/II trials, and (v) linking the licensing of LICR IP to the clinical goals of the LICR. Those of you who have not been involved in the clinical trial arena may wonder why I so stress the issue of IP. I assure you it’s not about profit - that’s always a toss of the dice. Rather, it has to do with having some control over the fate of your discoveries and having a say in how the validity of your ideas are initially tested in the clinic.

A pivotal event in the development of the cancer vaccine field was the decision of LICR and CRI to form a partnership that created the Cancer Vaccine Collaborative or CVC. This brought together two institutions with different strengths and different histories, but with a common commitment to the exploration of cancer vaccines. The CVC, which I direct, has 24 sites at leading academic institutions in 11 countries around the world and has evolved into a magnificent instrument for clinical discovery. The CVC is centrally managed and coordinated by a CVC Coordinating Committee, and CVC trials are sponsored by the LICR. There is a strong interaction between laboratory and clinical scientists at each site and there is a great deal of inter-site collaboration. Each site has strong expertise in immunological monitoring. Now one of the formidable challenges of creating cancer vaccines is the number of variables that need to be brought together and tested individually in the construction of a successful vaccine. If these are tried serially, one after another, progress would be extremely slow. In contrast, the coordination of CVC activities allows parallel trials that test each variable, and thus a rapid way to decide which is best. Finally, the CVC has established a free online journal – Cancer Immunity – to serve the needs of the cancer vaccine community.

Figure 1 is a global view of the present structure of the CVC and a listing of participating institutions in Australia, Asia, Europe and the USA. There is a strong possibility that the CVC and another organization with the same objective, the Cancer Vaccine Consortium, will join forces and merge. This is an exciting prospect because it will create a single strong voice in the cancer vaccine arena.

Now where are we in the current development of cancer vaccines? As background to our CVC efforts, let me show you a list of the most advanced commercial vaccines in clinical trials...
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Figure 1

Cancer Vaccine Collaborative structure.

Figure 2

Cancer Vaccines in Advanced Stage Clinical Trials

<table>
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<th>Defined Antigen</th>
<th>Tumor Type</th>
<th>Company</th>
<th>Trade Name</th>
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<td>Prostate</td>
<td>Call Garasys</td>
<td>GVAX™</td>
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<tr>
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<td>Antigenics</td>
<td>Oncophage®</td>
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<tr>
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<td>5T4</td>
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Commercial cancer vaccines in advanced stage clinical trials.

(Figure 2). As you can see, they range from whole cell vaccines and heat shock protein vaccines to defined antigen vaccines, including PAP, 5T4, MUC-1 and MAGE-3. The risk, of course, of large scale trials is that they may fail, and if they do, this can have a profound negative impact on the field. The Merck adenovirus HIV vaccine is a good example of this, as was the Therion vaccinia/fowlpox CEA vaccine in pancreatic cancer. There is a strong feeling in the academic community that such large trials should be conducted only if there are compelling indications from early stage trials, a precaution that companies do not always heed.

Now how does an academic enterprise such as CVC contribute to the goal of creating cancer vaccines? At the onset, we had several critical questions to answer. Should we choose a single antigen and use it to compare the multiplicity of different vaccine strategies or choose several antigens and select a single vaccine platform. How critical is immunological monitoring and having a secure base for understanding the immunological response to the vaccine? And when do you have sufficient evidence to justify going after a therapeutic endpoint?

We chose to focus on a single antigen and that antigen was NY-ESO-1, a member of the cancer/testis or CT family of tumor antigens, and one of the most fascinating tumor antigens found to date. There are over 90 CT gene or gene families with an expression pattern that makes them ideal vaccine targets. CT antigens are expressed in spermatogonia, fetal ooblasts and trophoblasts, but with no or highly limited expression in normal adult somatic tissues. In cancer, CT antigens are expressed in a wide range of different tumor types, and their aberrant expression appears to be due to cancer-related hypomethylation. Over 50% of the CT coding genes are located on the X chromosome and make up over 10% of the coding sequences on that chromosome.

NY-ESO-1 was discovered by Yao Chen and our group in NY, and as a consequence of international collaborative efforts of CVC investigators in Germany, Japan, Australia, the United Kingdom and the USA, we now have a comprehensive view of the immunogenicity of this antigen, with our knowledge of NY-ESO-1 rivaling understanding of HIV and influenza immune responses. NY-ESO-1 ranks as the most immunogenic tumor antigen we know, eliciting a strong integrated humoral and CD4+ and CD8+ T cell immune response in patients with advanced NY-ESO-1 expressing tumors.

Monitoring the immune response to NY-ESO-1, both occurring spontaneously and following vaccination, is central to the CVC mission and, because of its strong immunogenicity, robust and standardized monitoring methodologies have been developed, allowing valid comparisons of immunological monitoring results at different sites.

This centrality of monitoring is exemplified by a maxim I developed for the CVC: "If you want to know how to vaccinate, you need to know how to immunize. And if you want to know how to immunize, you need to know how to monitor". This means that if you haven't defined and maximized the immune
response to a vaccine, you probably shouldn’t risk going after a therapeutic endpoint. The problem is that we are still learning how to monitor.

Figure 3 is a summary of the CVC sponsored NY-ESO-1 vaccine trials carried out to date. Over 34 trials with different NY-ESO-1 vaccine formulations have been or are being conducted. You will hear from a number of speakers at this meeting about the results of these trials, particularly the detailed immunological studies of these vaccines. The key finding is that NY-ESO-1 peptide, protein and pox-NY-ESO-1 vaccines can all induce strong NY-ESO-1 humoral and cellular immunity in patients with no pre-existing NY-ESO-1 immunity. The NY-ESO-1 Protein/ISCOMATRIX® trial conducted by Jonathan Cebon showed sufficient evidence for possible therapeutic benefit that a Phase II randomized trial is now ongoing, a trial entirely funded and sponsored by the LICR/CRI partnership. The salmonella/NY-ESO-1 vaccine, which shows remarkable therapeutic effects in mice, is now being prepared for the clinic and every effort is going into developing NY-ESO-1 adenovirus constructs for vaccination.

Figure 4

CVC Priorities

- Prime/Boost Strategies
- Multivalent CT Vaccines
- Control Tregs
- Block CTLA-4 and other immunological restraints
- Novel adjuvants
- Therapeutic endpoints

Priorities of the Cancer Vaccine Collaborative.

I’m certain that it doesn’t escape anyone’s attention that everything on this list is about or depends on reagents, and in my opinion the three major obstacles to our continued success are reagents, reagents, and reagents. We must find ways to combat the chilling territoriality of reagent control, because putting together and testing the necessary ingredients for the construction of effective vaccines requires crossing all sorts of impenetrable IP and commercial boundaries. My hope is that by joining forces, the HIV and cancer vaccine effort will have a much more effective voice in overcoming obstacles to achieving our shared objectives. What we need to say is that our quest to construct effective vaccines against HIV and cancer is only beginning.

Abbreviations

CT, cancer/testis; CVC, Cancer Vaccine Collaborative; IP, intellectual property; LICR, Ludwig Institute for Cancer Research

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