CANCER IMMUNOTHERAPIES AND VACCINES: PIPELINE ANALYSIS AND COMPETITIVE DYNAMICS

An Interview with Arthur M. Krieg, MD

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Although the improvement of cancer therapies has been a major focus of researchers and pharmaceutical companies for decades, cancer is still the second leading cause of death in the United States. Traditionally, three approaches have been available for treatment of cancer: surgery, radiation therapy, and chemotherapy. A large number of smaller biopharmaceutical companies and a more limited number of major pharmaceutical companies are developing immunotherapies or vaccines for treatment of cancer. They are investigating a wide range of different approaches that can be used to try to overcome a cancer's ability to evade surveillance of the immune system and to stimulate the immune system to respond to and kill a patient's tumor cells. In ***Cancer Immunotherapies and Vaccines: Pipeline Analysis and Competitive Dynamics***, a new report from CHI Advances Reports, author Lucy Sannes, PhD, assesses the efforts under way and offers a comprehensive analysis of the R&D picture today. Expert interviews make up one chapter, from which this excerpt was taken. For a full table of contents, visit: http://www.advancesreports.com/all_reports/2006_73_CancerIM/table_of_contents.html.

Advances Reports: *Please briefly describe the work your company/laboratory is doing in the area of cancer immunotherapies and vaccines.*

Dr. Krieg: Coley partnered its TLR9 [Toll-like receptor 9] agonist technology in the field of oncology with Pfizer. PF-3512676 (formerly CPG 7909) is now in two Phase III international, randomized trials in non–small-cell lung cancer (NSCLC), in combination with platinum-based doublet chemotherapy, and several Phase II trials, in combination with chemotherapy and/or targeted agents for first- and second-line NSCLC. Pfizer has also indicated its interest in the potential use of PF-3512676 in breast cancer. Earlier in the compound's clinical development, we completed monotherapy trials in melanoma, renal cell carcinoma, non–Hodgkin's lymphoma, cutaneous T-cell lymphoma, and others.

We give a once-weekly injection of this synthetic TLR9 agonist to patients with lung cancer. This activates the immune cells in the body that have TLR9. In essence, we are tricking the immune system into thinking that an infection is present. This "wakes up" the immune system, which looks around for something dangerous to attack. We believe that the immune system then sees the tumor and attacks and rejects it. Our program is based on stimulating a class of immune proteins called Toll-like receptors. This class of proteins was originally discovered in fruit flies. At least 10 of these Toll-like receptors have been identified in humans. Each of them functions to detect a different class of molecules that are present in pathogens but not in our own body. This gives the immune system a way to detect infection. Our technology stimulates TLR9 using synthetic DNA molecules (TLR9 agonists). TLR9 detects a subtle difference in the structure of DNA

between bacteria, viruses, and human DNA, called CpG motifs, which are absent from our DNA. We mimic this difference by making synthetic oligonucleotides containing CpG motifs. To use this technology with vaccines, you simply add low amounts of this TLR9 agonist (VaxImmune) to the vaccine. This tricks the immune system into thinking that the vaccine is a real infection. We know historically that real infections stimulate a much stronger response from the immune system than artificial vaccines. This is why we think that VaxImmune is such a strong vaccine adjuvant. It has been used in multiple vaccine trials. Today, Coley is partnered with GSK [GlaxoSmithKline] for cancer vaccines, which include breast (which is in Phase II), prostate (in Phase I), and lung cancer (which is at the proof-of-concept stage). In addition to the GSK cancer vaccine trials, this technology has been used in clinical trials with infectious disease vaccines for anthrax, flu, and hepatitis B vaccines. The NIH [National Institutes of Health] is using it in a malaria vaccine program. Coley has a collaboration with Chiron (now Novartis Vaccines), which plans to use VaxImmune as part of its infectious diseases vaccines. AVANT Immunotherapeutics, Inc., licensed VaxImmune from Coley for planned inclusion in a cholesterol management vaccine. The advantage that CpG brings is better and faster responses.

Advances Reports: *Other than your own research/development activities, what cancer immunotherapies or vaccines are the most promising (in your opinion)? Why?*

Dr. Krieg: I am a fan of the anti-CTLA4 approach. The data that have been presented at meetings show that it can induce impressive clinical responses in patients with advanced melanoma. I am also a fan of the T-cell approaches to therapy, where patients have been treated with large numbers of tumor-specific T cells. What has been shown is that if you stimulate production of enough T cells that are specific to the tumor, or if you take individuals with a tumor and inject into them enough highly activated T cells of the right specificities to attack the tumor, you can cause regression of even large, advanced tumors. This suggests that what has been holding back the efficacy of immunotherapies has been not getting enough of these highly activated T cells.

Where the field of immunotherapy is moving, in my opinion, is with the various approaches that provide a lot of T cells. A key question is: How do you get them? Anti-CTLA4 is one way to remove one of these “brakes” of the immune system and allows you to get these cells. Another approach that is promising is the dendritic cell vaccine. Dendritic cells are the master regulatory cells that determine what the immune system will make T cells against. If the dendritic cells determine that you need to make T cells that are specific for the tumor, they stimulate their production. A problem with dendritic cell vaccines, like many of the T cell–based therapies, is that they are very cumbersome, expensive, and difficult to produce. Only certain types of dendritic cells can be successfully made into vaccines. And, even then, there is still a problem in directing the vaccine to the appropriate place in the body. This is where our approach comes in. TLR9 is expressed on a set of dendritic cells called the plasmacytoid dendritic cells. TLR9 appears to have a key role in the immune system for determining what the body will make a T-cell response to. Our TLR9 agonist therapy activates dendritic cells in situ (in the body). Unlike the previously mentioned approaches, we do not have to take the dendritic cells out of the body, grow them, pulse them with a tumor antigen, inject them

back into the patient, and hope that they get to the right place and stimulate the right response. We just activate them in situ. The tumor antigens are already there, in the patient with cancer. The theory is that the dendritic cells induce a response against the tumor.

One problem with this approach is that most patients have big, bulky tumors by the time they seek treatment, and the tumors are suppressing the immune system. It has only been in recent years that we have begun to understand how the immune system is "turned off" by the tumor. One of the key things that we now realize must be done is to disrupt the tumor or to block its protection against the immune system. One way to do this is to use chemotherapy. Recent studies have shown that chemotherapy can sensitize tumors to immunotherapy.

I think that one reason why so many immunotherapies have failed in the past is that people were trying to develop these therapies by themselves instead of in combination with some other therapy that would synergize with them. In our program, a key aspect that has generated very positive data in Phase II randomized trials is our use of TLR9 agonists in combination with effective chemotherapy.

Advances Reports: *How are cancer immunotherapies or vaccines likely to fit into the overall treatment regimens for cancer?*

Dr. Krieg: The conventional wisdom with immunotherapy is that you need to treat patients who have earlier-stage disease or minimal residual disease. There are logistical problems with this, predominantly financial, especially for small biotechnology companies. Where the field has to move is to find effective ways to use these treatments in people with bulky disease, even though that is not the obvious indication where it is most likely to be effective. Based on our experience, we believe that immunotherapies will be used in combination with other treatments, like Coley's experience in synergizing with chemotherapy.

Advances Reports: *What are the potential benefits of immunotherapies and/or vaccines compared to other novel cancer therapies in development?*

Dr. Krieg: Compared to other novel therapies that are in development, immunotherapy could be a safer and better tolerated form of treatment. Of equal importance in terms of advantages is that cancer immunotherapies may have the potential to target a wide range of tumors.

Advances Reports: *What are the likely limitations of immunotherapies and/or vaccines?*

Dr. Krieg: Depending on the type of immunotherapy, you may induce autoimmune disease. This is one of the limitations of anti- CTLA4 therapy. At least one of the anti-CTLA4 antibodies that is in development has been associated with some very clinically significant and serious autoimmune diseases. They have been treatable, and this may not be inevitable for the treatment of cancer. However, it could be a limitation.

We have not seen this in our TLR9 agonist development program. One of the fundamental differences between these two approaches may be that CTLA4 is one of the critical checkpoints in regulating immune responses. Normally in nature, this checkpoint is not overcome in the way that antibodies do so. Thus, the antibodies do something that normally is never done in nature. In contrast, TLR9 activation is something that we think happens every time you are infected with certain types of pathogens. Therefore, this is a more natural way to activate the immune system that leaves the checks and balances in place, thereby making the development of autoimmune disease unlikely.

Advances Reports: *Is this likely to vary with different types of cancer? If so, how?*

Dr. Krieg: Historically, it was thought that immune activation was only effective in melanoma, renal cell carcinoma, and maybe lymphoma. This was because the immunotherapies that were tried only succeeded in these types of cancers. In fact, when we announced our results in lung cancer, we were met with surprise by many oncologists because the conventional wisdom was that lung cancer does not respond to immune activation. In fact, one of the lessons we have learned is that, depending on how you activate the immune system, we may be able to treat types of cancer (like lung cancer) that did not respond to previous generations of immune stimulation. This may be a new approach for immunotherapy—to focus on activating the dendritic cells in situ as a way to direct T cells against the tumor. Therapies that try to activate dendritic cells in the body, and that harness their ability to direct a strong T-cell response, could allow us to treat types of cancer that did not respond to the earlier generations of immunotherapy.

Advances Reports: *Companies have been working to develop cancer immunotherapies and vaccines for many years, yet no cancer-specific immunotherapies or vaccines have reached the market. (Agents such as interferon and interleukin-2 are available, but are immunomodulators that affect the immune system as a whole and are not specific to cancer.) Why is it taking so long to develop cancer-specific immunotherapies and vaccines? What are the challenges, issues, or hurdles being faced by companies developing immunotherapies or vaccines for cancer?*

Dr. Krieg: When I look at all of the failed approaches, it is sobering. However, one of the things that we have realized when we looked at all of the failed Phase III trials of immunotherapies in cancer is that a lot of these trials were not based on proper Phase II data. In every case, there was no controlled Phase II trial. Rather, there was typically just a single-arm Phase II trial that used historical controls, and then the sponsors convinced themselves that something good was happening. They thus went into a Phase III trial and found that when they did a trial with proper controls, the treatment was not working. I think that one of the lessons from these failures is to do a controlled Phase II trial. Also, in some cases the design of the past trials changed when going from Phase II to Phase III, sometimes in major ways, and the effects of the changes were not evaluated. Also, there were other issues such as failing to define the dose and schedule of the regimen. Sometimes there were problems with the purity or characterization of the reagent if it was a biological.

Advances Reports: *How do the challenges/issues/hurdles vary with different cancers?*

Dr. Krieg: For non-Hodgkin's lymphoma, treatment and progression-free survival have improved to the point where it is very difficult for new therapeutics to show superiority over the current therapy in a time frame that most biotechnology companies can survive. Usually you only have a couple of years of funding. If your 5- year survival with current therapy is 80%, you are not likely to show an improvement over this before you run out of money. This was one of the factors that we considered when we chose lung cancer as the indication for our Phase II trials. We focused on stage III and IV lung cancer. The median survival for this population in past trials has ranged between 7 and 10 months with chemotherapy alone. In our randomized Phase II trial, we achieved a median survival of 12.3 months with chemotherapy plus PF-3512676, which was a very encouraging finding.