Interview

Dr Charles Drake speaks to Laura Dormer, Editor

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Dr. Charles Drake is currently an Assistant professor in the Departments of Oncology, Immunology and Urology at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center. He was awarded a BS and a Masters Degree in Biomedical Engineering from Rutgers University, and pursued a career in integrated circuit design before entering the combined MD/PhD degree program at the University of Colorado in Denver. He was extremely productive during his thesis work with Dr Brian Kotzin, a leading immunologist in the field of autoimmunity at the National Jewish Hospital in Denver. Dr Drake's thesis work involved the analysis of genetic loci predisposing to the development of autoimmunity in murine models of systemic lupus erythematosus. This work and his appreciation for the links between autoimmunity and tumor immunity led him to become interested in the area of cancer immunology. After completing a residency in internal medicine on the Osler Medicine Service at Johns Hopkins, he joined the laboratory of Dr Drew Pardoll, where he began to study aspects of T-cell tolerance relative to cancer immunity. This work led to two important observations. First, in a physiologically relevant model of prostate cancer, Dr Drake and his colleagues showed that androgen-ablation leads to a mitigation of systemic tolerance to a tumor-associated antigen. These results were recently published in *Cancer Cell*, and form the basis for a clinical trial that is currently under development with the Eastern Cooperative Oncology Group. Secondly, Dr Drake and his associates showed that LAG-3, a T-cell molecule with a previously obscure function, is involved in processes that downregulate an immune response. By blocking LAG-3, antitumor immune responses can be augmented in several systems. The Drake laboratory is currently working towards translating these findings into a clinical trial as well. Overall, the goal of the Drake laboratory is to understand the basic mechanisms by which the immune system fails to recognize and eliminate an evolving tumor, and to translate these findings to the clinical setting.

Your current research is focused on developing vaccine strategies for patients with prostate cancer. What led you to focus your research on this area?

I was trained as a basic immunologist, so when I started to work in tumor immunology I was hoping to begin preclinical studies with a truly physiologically relevant animal model. To that end, Adam Adler (when he was with Drew Pardoll) developed a transgenic model that expresses a model antigen in a tumor-restricted manner – this allowed us to study the immune response to a tumor antigen as accurately as possible *in vivo*. I felt that if we could understand the immune response in the context of a tumor that developed slowly over the life of an animal (rather than the typical implanted models), we'd get a much more accurate picture of what happens in patients with developing solid tumors. So, our initial model happened to involve an autochthonous model of prostate cancer, but as our studies evolved we began to realize that, for many reasons, human prostate cancer might be an ideal target for immunotherapy in the clinic.

What is the main research focus of you and your team at present?

The most exciting studies in our laboratory involve a new cancer vaccine technology based on an attenuated strain of *Listeria monocytogenes* (LM) engineered to express tumor antigens. These vaccines are incredibly immunogenic – in our models a single dose of these vaccines can break tolerance to an evolving tumor. Although these studies are in a fairly early developmental stage, we are eager to eventually test such approaches in the clinic. The laboratory is also focused on understanding the mechanisms that limit an antitumor response *in vivo*, to that end we've discovered that the T-cell surface molecules LAG-3 and PD-1 both seem to attenuate the functional capability of anti-tumor CD8 T cells. By combining antibodies to these 'checkpoints' with active vaccines we seem to be able to maximize an antitumor response.

You mention in a recent publication that current treatments for hormone-refractory prostate cancer are limited, and that immunotherapy might fill this gap. Is prostate cancer well-suited for targeting with immunotherapy?

For several reasons, prostate cancer might prove an ideal target for immunotherapy. First, these tumors arise in a specialized population of secretory epithelial cells, which express a spectrum of unique proteins that can serve as tissue/tumor antigens. In many cases, successful immunization to a tumor antigen can initiate a bystander response in which normal tissues that are similar to the target cells undergo immune destruction. The best example of this is the association of vitiligo with vaccination for melanoma. Since the prostate gland is not essential for survival, bystander damage to the normal gland should not prove especially dangerous. In early-stage disease, androgen-ablation is a remarkably effective therapy, and by eliminating a tolerogenic tumor burden one might be able to reverse CD8 T-cell nonresponsiveness. Finally, it should be noted that prostate cancer usually develops in the sixth decade of life – thus, successful immunotherapy would not have to remain effective for decades in order to produce an appreciable benefit in terms of patient survival

As well as developing immunotherapies, your research also involves determining how prostate cancer evades the existing immune system. Will immune evasion pose a problem for possible vaccine therapies?

To date, clinical experience with vaccine therapies has been somewhat disappointing. An increasing body of evidence indicates that the failure of single-agent immunotherapy is most likely due to immune evasion by a variety of mechanisms, including immune checkpoints, regulatory T cells and suppressive antigen presenting cells (and others). So, for vaccine therapy to be successful in the clinic, vaccination will almost certainly need to be combined with strategies that target these evasion mechanisms. The NIH group has been particularly productive in this area, combining the ProstVac® VF vaccine platform with radiotherapy, androgen-ablation, and most recently with checkpoint blockade using a monoclonal antibody against CTLA-4.

Are there any other foreseeable downsides to immunotherapy?

I think that as our immunotherapy strategies become more effective, we might begin to see a degree of autoimmunity in our patients. This is probably unavoidable on a population basis. The other major challenge to immunotherapy will be widespread acceptance; while medical oncologists are quite comfortable managing chemotherapy-induced toxicity, managing autoimmune toxicities from immunotherapy might involve a bit of a learning curve.

You are currently involved in a Phase III clinical trial of the vaccine GVAX®. What is the aim of this trial?

This Phase III trial was a fairly ambitious and well-designed trial aiming to show that treatment with prostate GVAX improves patient survival as compared with standard-of-care treatment with docetaxel. Patients were randomized 1:1 to a 6-month treatment with either immunotherapy or chemotherapy. At the end of the 6 months, patients who appeared to derive clinical benefit from immunotherapy were allowed to stay on a monthly boost program. This was quite a large trial, involving 600 patients, and was sufficiently powered to show a survival benefit. I'm using the past tense here because the trial completed accrual in July of 2007, and Cell Genesys has announced that data from an interim data analysis might be available in Q3 or Q4 of 2008. As you might expect, we are eagerly awaiting these data.

Finally, where do you think your efforts will be focused over the next 5 years?

Well, I think that the former Soviet Union showed that 5-year plans can be a little risky! On a serious note, on the basic science side, we're going to really try to understand the relative importance of the immune checkpoints mediated by LAG-3 and PD-1, as well as the molecular mechanisms by which these molecules mediate their negative function. We also have an ongoing research program trying to understand the mechanism(s) by which tumors induce regulatory T cells. From a clinical standpoint, we hope to be able to bring these attenuated *Listeria*-based vaccines forward in a Phase I trial for patients with prostate cancer. Finally, I have to admit that I'm really no longer very interested in single-agent immunotherapy. Few chemotherapy regimens in widespread use today involve a single agent, so there is absolutely no reason why treating tumors with immunotherapy will not also require rationally designed, multi-agent approaches.

Financial & competing interests disclosure

C Drake received research funding from Cell Genesys to support a postdoctoral fellow in his laboratory who is studying combinations of GVAX with chemotherapy. In addition, he is a co-inventor on a patent to use LAG-3 blocking antibody to augment anti-tumor immunotherapy. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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