Assessments of Active Specific Immunotherapy That May Provide a Pathway to Immunoprevention of Adenocarcinomas

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Short Communication

Assessments of Active Specific Immunotherapy That May Provide a Pathway to Immunoprevention of Adenocarcinomas

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Considerable attention is being given to immunotherapy as an essential and beneficial arm to cancer treatment. With respect to active and specific immunotherapy, there was over two decades of unsuccessful research using a variety of compositions of cancer vaccines to treat advanced disease [1]. However, in addition, recently the field has created drugs called “checkpoint inhibitors” to induce targeted reversal of immunosuppression which may contribute to disease progression [2]. This treatment has achieved a degree of clinical benefit in a minority of patients.

With all due respect to this current immunological success in cancer treatment, it is logical that we should not have to wait for recurrence and progression of disease to treat cancer. There is much to be gained by staying committed to achieving sustained recurrence-free survival or interval for the majority of cancer patients following surgical resection. Thus, efforts must be accelerated to target cancer specific antigens prior to the establishment of an immunosuppressive environment.

Much attention is still being devoted to a homogeneous, targeted approach to immunotherapy. This is where one picks a mutant gene, characterizes its protein product, then finds a drug that will neutralize it. However, we are beginning to recognize the enormity of genomic heterogeneity, evolving from multiple mutations of tumor cells. Recently, Ling, et al. [3] evaluated a single, approximately 3.5 cm squared hepatocarcinoma by sequencing or genotyping nearly 300 estimated drug resistance to be 1 in 5000 tumor cells of any individual clone. This high probability of drug resistance creates paradoxes that make targeted therapies in solid tumors problematic. It is now an established fact that adenocarcinomas are multi-clonal with inter- and intra-genomic heterogeneity. Yet still, this “inside out” approach of identifying a mutational product from the tumor genome and using it to target drugs, immune cells or antibodies is still the convenient, but less effective paradigm of the research or drug development community. We should now be acutely aware that it is illogical to continue to attempt to treat a heterogeneous disease with a homogeneous approach.

Our, over 30 years of perspective, of patient specific active immunotherapy convinces us that amplifying the patients immune response, arming it with the appropriate tools and relevant targets, will simultaneously increase the patients inherent immunity to the majority of the foreign neoantigens of the tumor cells. This will benefit the clinical outcome by destroying tumors and stave off immunosuppression. This will also benefit the vast majority of cancer patients. We will refer to this as the “outside in” approach, and can achieve it by immunizing the patient with his own tumor. The patient specific, active immunotherapeutic approach has achieved major clinical success in colon cancer and is adaptable to many other forms of adenocarcinomas. Immuno-oncology clinical studies with a patient specific vaccine called OncoVAX, has been performed in hundreds of colon cancer patients [4-6]. This programmed approach has been shown in clinical trials to possess the four Ps necessary for patient specific active immunotherapy, Personalized, Precision, Potency and Prevention of post surgical occult disease. This prevention was seen over a 15-year follow-up of recurrence-free interval and –survival [7]. During the 30 years of our preclinical and clinical development of OncoVAX, we discovered and learned some key fundamental principles of cancer biology and host tumor interactions that must be incorporated in our approaches to treating primary and advanced disease patients [8]. These principles have opened a pathway to developing a vaccine that may be effective in preventing adenocarcinoma formation or progression.

There are three classes of host-tumor interactions which form the tenets to achieving a cancer prevention vaccine. They are:

• If we intend to make progress with cancer immunotherapeutic approaches, we must embrace the limitations established by malignant disease rather than ignore them. In the case of our previous clinical investigations, this involves leveraging the unique inter- and intra-tumor heterogeneity of cancer as a means to prevent cancer recurrence in the post-surgical setting. This process simultaneously addresses the consequences of immunoediting and local immune suppression. In our preclinical animal model and in the colon cancer patients, which we treated with a cancer vaccine consisting of their own live, metabolically active, sterile and non-tumorigenic cells of a specified effective dose, clinical success in the form of recurrence-free survival, recurrence-free interval and overall survival was achieved. However, this was only possible when we treated minimal residual disease following surgery. In fact based in our preclinical studies, using a syngeneic guinea pig tumor model, the limit of the tumor metastasis size that was curable was between 0.1 to 0.2 mm in diameter [8]. These microscopic metastases are below the limit of detection by any visual or radiological detection procedures.

• There is a window of time during the course of the autologous tumor cell vaccination when we can identify, isolate and characterize antibody forming B-cells that make a variety of tumor, neoantigen, specific, human monoclonal antibodies. These have been characterized and determined to react with the multiple mutagenic neoantigens [9,10]. Thus, a characterization of the antibodies across a wide variety of colon tumors and many other adenocarcinomas surprisingly revealed that there was a cohort of antibodies generated that are not just tumor class specific but also are broadly cross reactive with adenocarcinoma from various
organisms. These conserved antibodies show no reactivity with non-adenocarcinoma tumor cells or normal tissue.

- The immune system can function as an additive or subtractive variable in the equation for cancer development. Immune surveillance subtracts cancer risk while immunodediting adds cancer risk. The first key host tumor interaction that is responsible for these unique and important reagents are immunodeediting [11] of the highly immunogenic neoantigens while poorly immunogenic tumor cells eventually escape immunosurveillance. Immunodediting is actually created by normal immune function through a long-term process of clonal selection. Thus, the immune system plays a dual role in cancer: it can suppress tumor growth by destroying cancer cells but also promote tumor progression by actively selecting clones of weakly immunogenic tumor cell neoantigens which can thrive in an immunocompetent host. The latter function while seemingly paradoxical is an essential and mandatory component of tumor development driven by antigenic competition [12]. When we take the tumor at surgery and produce a tumor cell vaccine to which the host is tolerant, by injecting the vaccine intradermally with a strong immunostimulant, we break tolerance and create a more tumor specific immune response with long-term immunological memory.

If we can learn anything from the important medical breakthroughs of the past, we understand the most effective vaccination strategies rely on prevention over treatment; cancer is no different. What are needed to obviate the need for advanced cancer treatment are compositions and methods for appropriately utilizing immune-based products provided by patient-specific, active immunotherapy. In other words, through the "outside in" approach the immune system is allowed to identify molecular determinants which can be used to recapitulate effective immunogens for the prevention of malignant disease. Through active, patient specific immunotherapy as described, these antibody tools are created by an agnostic immune system to affect immediate clinical benefit and establish long-term immune surveillance. While it has been proven that antigenic heterogeneity and early intervention is required for effective cell-mediated cancer treatment, the humoral homogeneity discovered by these methods is the subject of a pending patent application, by Michael G. Hanna Jr., PhD and Jason D. Howard, PhD, that may provide a pathway for developing a generic adenocarcinoma prevention vaccine.

This pending patent relates to methods of characterizing antigenic determinants which broadly define adenocarcinomas with the guidance of human monoclonal antibodies (HuMabs) reactive to such epitopes. These antibodies are generated by patient specific tumor cell immunization and harvesting the antibody forming B-cells during a specific interval of time in the course of treatment. We have characterized one aspect to the critical antigenic determinants (epitopes) with a high degree of inter- and intra-tumoral cross reactivity to a broad range of adenocarcinomas. What was most enlightening was the nonadenocarcinomas that these antibodies did not cross react. We currently have a cohort of antibodies with known specific cross reactivity with colon tumors and more broadly with a representative variety of adenocarcinomas. The research plan is to expand the cohort by developing more HuMabs from future OncoVAX treated patients and skin testing the epitopes and or the peptides in other OncoVAX immunized patients.

Evaluating and characterizing the humoral and cell-based responses within our previous and upcoming clinical trials, we intend to identify the molecular determinants most suitable to accomplish that goal. No current tools exist which can match the specificity and long-term surveillance the immune system provides. We simply need to utilize these tools in the most appropriate way. By way of comparison, if a patient were to contract smallpox today, modern medicine can provide little more than supportive care. However, by appropriately training the immune system to prevent infection, we have eradicated the problem from our species. By focusing on prevention, rather than treating advanced disease, smallpox has been completely eliminated and similar infectious agents (i.e. polio, guinea worm disease, etc.) and hopefully cancer will be soon to follow.

We find ourselves in an exciting time in cancer immunotherapeutic research. Through the diligent work of many, we are finally establishing a complete and comprehensive picture of how cancer emerges and evolves with respect to immune function. This renaissance is occurring in parallel with advancements in technology designed to identify and exploit these pathways for clinical gain. As a field, we must grasp this opportunity and broaden our focus from curing cancer to preventing cancer, relegating malignant disease to the same designation as smallpox and polio: problems that simply went away.

Clearly we have a long trek ahead to develop a prophylactic vaccine for presumably non-virus related adenocarcinomas. We now have some insight into the possibility and potential of a cohort of conserved neoantigens that are in these tumors that could provide the basis of immunosurveillance of adenocarcinoma formation, prior to detectable disease levels. It is just a pathway, but we are motivated to follow it since the result will be of greatest clinical benefit and pharmacoeconomics of cancer.

References

