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A pioneer in active specific immunotherapy of cancer

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While a PhD candidate, doing my thesis at the Oak Ridge National Laboratory, Biology Division under Dr. Charles Congdon, my introduction to the immune response was studying graft vs. host (GVH) disease as a consequence of bone marrow transplantation in mice. The sequelae of GVH was impressive, and demonstrated the potential of negative clinical consequences of the immune system. The idea of harnessing this immunological phenomena in cancer therapy was appealing even in the late 1960s. The problem was that at the time T-cells as a component of the immune system were identified but not defined. We moved to soluble antigen stimulation in mice and recognized and described the post antigen stimulation changes in lymphatic tissue germinal centers during the first 48 h after the induction of the humoral immune response. We described the extracellular localization of soluble antigens on the surface of dendritic reticular cells of the stroma, directing a response of B-cells to produce antibody against non-self. The ensuing reaction was the rapid proliferation of B-cells toward antibody secreting plasma cells.

These early histological descriptions described the primary immune response in the early intervals after antigen introduction and how the germinal centers lose their architectural structure as a result of rapid proliferation and migration of B-cells. This is the prelude to detection of circulating specific antibody. The same results were also being described in a rat model by Dr. Gustavo Nossal using salmonella flagella antigens and both studies

were published simultaneously in 1964. In 1965, these two studies were introduced as lectures one and two at the opening of the first major immunology conference in London. In this conference at the Chester Beatty Hospital, international teams of researchers experienced the birth and potential of the total immune system. For many years thereafter, new results in immunology correlating morphology and function were the popular basis in the follow-on Germinal Center Conferences. Also, these histological changes in the first 48 h after an antigenic challenge, based on studies we performed in germ free mice, was one of the critical biologic tests of potential biological contaminants in the core moon dust and moon rock samples brought back by the Apollo 11 and 12 endeavor. I was privileged to be involved with these tests at the lunar receiving laboratory of NASA.

In 1975, I was selected by a scientific advisory committee to the National Cancer Institute (NCI), to be the Director of the Basic Research program at the National Cancer Institute, Frederick Cancer Research Center (NCI/FCRC) and had the opportunity to attempt to harness the immune system to treat syngeneic tumors in Strain 2, guinea pigs using a transplantable L10, hepatocarcinoma. At the time, this was a rare but highly relevant animal model; we shared and collaborated in these studies with Drs. Herb Rapp and Bert Zbar. We basically tried to reproduce the observation defined by Dr. William Coley decades earlier. He hypothesized that the intrinsic defense system that had been mobilized against a pathogenic infection could also affect a tumor. We began

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by injecting dermal transplanted tumors with *Bacillus Calmette Guerin* (BCG) and describing the tumor regression and developed systemic tumor immunity. This was logically followed by creating the same systemic tumor immunity with a tumor-BCG vaccine. It is relevant that later, the early clinical trials of Dr. Alvaro Morales in bladder cancer, which was assumed to be a clinical correlate for the guinea pig model of admixing tumor with BCG, prompted our effort to develop and receive registration for intravesical treatment of pre-invasive carcinoma in situ of the bladder. A follow-on Phase III study in recurring superficial papillary bladder cancer, demonstrated the prevention and progression of disease and a second application and registration.

In 1977, when I was appointed as the first Director of the NCI/FCRC, I had the privilege of working with Dr. Vincent DeVita, then Director of the NCI, in establishing the Biological Response Modifier Program (BRMP) and launching immunotherapy at both a basic research and clinical level. Many clinical investigators passed through this program and several of them were enticed to become entrepreneurs who established some of the early biotech companies. My personal research continued toward the development of a patient specific, cancer vaccine which embraced the genomic heterogeneity of cancer by using autologous tumor cells admixed with TICE BCG.

This approach was strongly influenced by what is now recognized as breakthrough tumor biology research published in *Science* in 1976 by Drs. I.J. Fidler and Margaret Kripke, two members of the NCI/FCRC basic research program. They described the first significant evidence of phenotypic heterogeneity in tumors. They demonstrated that various clones of murine melanoma cells could be derived in vitro which varied greatly in their ability to produce lung metastases in syngeneic mice. This suggested that the parent tumor initially displayed a high degree of heterogeneity and clones with various metastatic potentials preexisted in the parental population. However, a competing view around this same time, posited that cancer is a disease arising from a surviving mutant clone which progresses into



About Dr. Hanna

Dr. Michael G Hanna, Jr. received his PhD in experimental pathology and immunology from the University of Tennessee (TN, USA) in the 1960s. He was a consultant with NASA for the lunar receiving laboratory during Apollo 11 and 12, for which his expertise in immunology was used in the testing of the lunar core powder for immunogenic or pathogenic materials. Dr. Hanna served during 1974–83 as Director of the National Cancer Institute, Frederick Cancer Research Center (MD, USA).

He was Chief Operating Officer during 1985–94 of Organon Teknika/Biotechnology Research Institute and Senior Vice President of Organon Teknika Corporation, a subsidiary of Akzo Nobel, Netherlands. He developed and obtained approvals for TICE BCG for the treatment of carcinoma in situ (CIS) bladder cancer, which remains the standard of care for prophylaxis of recurrence of superficial bladder cancer and therapy of CIS. Subsequently, Dr. Hanna founded PerImmune Inc., for which he served as President and Chief Executive Officer before it merged with Intracel Corp. in 1998. He continued to work for Intracel Resources as Chief Scientific Officer and Chairman.

In 2007, Dr. Hanna founded Vaccinogen Inc., where he served as Chairman and CEO. Currently, Dr. Hanna is Chairman Emeritus. The company is a pioneer in the field of cancer vaccines and is developing OncoVAX, an autologous vaccine designed to elicit a specific immune response against cancer cells. The Phase 3 vaccine is being investigated for treatment mainly of colon cancer, but also for melanoma and renal cell carcinoma.

In addition to cancer therapy research and development, Dr. Hanna has been involved in Homeland Security. He served as Chairman of the Department of Commerce Biotechnology Advisory Committee (1984–9) and also participated in the Department of Defense Technical Working Group for Biotechnology (1988–9). PerImmune completed a Department of Defense contract to manufacture the current effective therapeutic for Botulinum toxin, an equine heptavalent anti-toxin.

Dr Hanna's research resulted in over 225 publications in international peer-reviewed journals and book chapters, and he holds 10 patents related to immunotherapy. Dr Hanna has been the recipient of numerous honors and awards and has served on many editorial boards, including for *Human Vaccines & Immunotherapeutics*.

an established tumor with a high degree of homogeneity reflecting its clonal origin. Clearly, the latter hypothesis has been well-represented in the majority of failed cancer vaccine clinical trials. What was recognized was that these observations would benefit from molecular biology. Fortunately, improvements in DNA sequencing technology have been able to definitively address this debate.

As our knowledge of inter-tumoral and intra-tumoral heterogeneity has expanded with improved DNA sequencing technology, we have simultaneously gained

a greater appreciation for the troubling degree of difficulty which challenged the cancer vaccine trials of the past. Also, intratumor heterogeneity, challenges the concept of “personalized medicine,” the as of yet unfulfilled, promise. The major focus of this was profiling patient-specific mutations such that appropriate targeted agents can be used in a rational manner to clear primary disease. Given the degree of intratumor heterogeneity, this approach is extremely problematic; how can a randomly chosen biopsy be expected to adequately represent the complexity of

the entire tumor? How many biopsies are required? What clones with known drug resistance lay undetected in the remaining tumor? This leads to the provocative yet critical question: is tumor heterogeneity of any practical value and how does one embrace heterogeneity in cancer treatment? With respect to cancer vaccines, the answer is employing a means of antigen discovery that is highly adaptable and exquisitely sensitive utilizing the entire array of parenchymal tumor cells as source material.

Autologous cancer vaccines or the process of using a patient's own tumor as source material for an individualized treatment is not a new endeavor. However, given what we now know about tumor heterogeneity, we are primed to deploy these tools in the appropriate way. Using powerful, genomic sequencing technology and an updated understanding of tumor-immune system interactions, we now have the ability to design tools capable of addressing the biological realities of cancer. We are at the cusp of a renaissance for active specific immunotherapy (ASI), assuming we follow a basic set of guidelines:

1. While antigen discovery platforms of the past emphasized the use of common antigens, based on tumor homogeneity, there is now indisputable evidence cancer is comprised of extreme genetic diversity from an inter- and intra-tumoral standpoint. It is now illogical to treat a heterogeneous disease with homogeneous tools.
2. As immunologists, we are aware of one highly adaptable, exquisitely sensitive tool provided by evolution to address the magnitude of cancer diversity - the immune system.
3. No longer can we use cancer vaccines to inappropriately treat established or advanced disease. We must be focused on preventing recurrence in the adjuvant setting by curing minimal residual disease (MRD). In this way, latent disease which has not yet established a tumor microenvironment, but is certainly capable of doing so later, would be the therapeutic target. This has the opportunity of significantly

impacting cancer mortality as the majority of cancer patients (~80%) die due to recurrence.

4. In the clinical setting described above, extending recurrence-free survival (RFS) should be the primary endpoint of autologous cancer vaccines. Overall survival will serve as a secondary clinical endpoint.

Our approach to ASI is a patient-specific (personalized) vaccine composed of sterile, live, irradiated, but metabolically-active, autologous tumor cells compounded with TICE® BCG, a live, attenuated mycobacterium which serves as a potent adjuvant. Using a proprietary method for dissociating and purifying cancer cells from a resected tumor, this autologous vaccine induces a robust and functional immune response. By using the entire tumor and relying on the immune system to determine which epitopes are unique, the vaccine provides a treatment in which no preconception of "known" or shared tumor antigens is needed. This approach is compatible with the current understanding of the host-tumor interaction.

Most of the contemporary effort involves the compelling results of targeted agents designed to reactivate the immune system by manipulating the PD-1/PD-L1 and CTLA-4 pathways. By blocking these recently identified suppressor molecules, these targeted therapies are designed to unleash the immune system either as monotherapies or in combination with traditional cytotoxic chemotherapy. The ultimate result of either strategy could improve the treatment of established, late stage disease, a patient population that has yet to be adequately addressed with modern modalities. While these investigations have provided a novel direction for enhancing cancer treatment, additional technologies still are essential to identify and present the full array of tumor-associated antigens (TAAs) to harness the full power of the immune system. Active, patient specific immunotherapy has the potential to be that transformative technology by embracing the recently demonstrated genomic heterogeneity of tumor cells, through the use of live, metabolically active, autologous tumor cells which

represent the entire antigenic diversity of each patient's primary tumor.

The OncoVAX® Solution

In a dose and regimen optimized phase III trial, OncoVAX® decreased the risk of stage II colon cancer recurrence at 5 y post-surgery from 1 in 3 to 1 in 10. The protective effect with OncoVAX® treatment is durable with up to 15 y of patient follow-up. While these results are certainly exciting, they serve as an initial proof of concept. A second, FDA approved phase III trial, with a granted SPA and Fast Track designation, in Stage II colon cancer is underway. Because OncoVAX® is a process and not a single product; this treatment paradigm could potentially be applied to many other types of cancer, greatly broadening the global impact of this technology

An ancillary benefit to evaluating OncoVAX in human patients was the isolation, during a narrow window of time, circulating, diploid B-cells which produced an array of cancer-specific human monoclonal antibodies (HuMab). In fact, we were able to isolate 36 HuMabs which positively recognized colorectal adenocarcinoma cells and tissues. Furthermore, roughly half of these antibodies appear to recognize cell surface antigens and have immediate potential for cancer diagnosis and treatment. While OncoVAX was originally designed with tumor heterogeneity in mind, it is thrilling this process may ultimately yield a suite of tools which will allow us to standardize this disease. The degree to which these colon cancer-specific tools will be broadly applicable to other cancers remains to be seen; however, autologous cancer vaccines utilizing renal, breast, and lung tumors should be able to produce similar tumor-specific antibodies for their respective cancer subtypes. In the future, it is very possible that newly developed immunomodulatory agents may serve to enhance the efficacy of ASI therapeutic regimens. In the meantime, novel strategies for ASI and immunomodulation need to be developed in parallel as it is clear these modalities are far from mutually exclusive.