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Cancer Vaccines: Is There A Future Beyond Trial And Error?

by William Looney

Strong foundational research in immunology and some promising early phase trial results have so far failed to expedite the validation of vaccines to treat cancer. *In Vivo* examines biopharma's enduring optimism about the future of cancer vaccinology, including a closer look at one company's platform to tackle the incurable malignancies that beset the mother of all organs: the human brain.

- There is a substantive academic presence in cancer vaccine research. This makes for more candor in highlighting the challenges of mobilizing potentially beneficial actors to work together in fighting the adaptive heterogeneity of cancer's natural defense mechanisms – and to do so on a uniquely personalized basis.
- [*Immunomic Therapeutics Inc.*](#) is an example of how biotech has leveraged strategic ties to academic leaders in molecular biology and immunology, resulting in a novel nucleic acid vaccine platform, UNITE, that has proved effective against some allergens. UNITE has generated licensing revenues for Immunomic from partners like [*Astellas Pharma Inc.*](#), and holds promise against hard-to-treat cancers like glioblastoma.
- So what? The big question – which no one yet has the answer to – is which of the many immunologically-driven platform approaches to vaccine treatment has the best chance of producing breakthrough results for waiting cancer patients. Clinical evidence is still scant, as most relevant trials remain fixed in Phase I.

The arrival of immunotherapy as a fourth weapon in the armamentarium against cancer – following on the traditional mainstays of surgery, chemotherapy and radiation – has brought fresh attention to the role that vaccines can play in stimulating the body's natural defenses against the abnormal cell growth that leads to malignancies. Vaccines are currently in limited use to prevent viral-based cancers like HPV, but the real promise lies in their potential in

treating and fighting recurrence for patients already diagnosed with the disease. And industry interest in this platform is mounting, as evidenced by the nearly 400 vaccine trials for cancers reported from industry, academia and government through the *clinicaltrials.gov* website.

Vaccinology as a tool to treat cancer is not a new concept. Vaccines complement the immune response and have broad appeal because of their ease of administration and lack of significant side effects. Research dating back to the early 1950s proved a higher incidence of malignant tumors in mice that presented with a weak or compromised immune system compared to those with a normal immune response. This was buttressed by detection of an inherent “immunological surveillance mechanism,” whereby the immune system can be stimulated to recall prior invasive cell activity to better target and enhance the potency of its response to a new tumor threat.

It was not lost on researchers that this is precisely what a vaccine does in inducing immunity against a much wider circle of pathogens. The problem in cancer, however, is the complexity and heterogeneity of cancer cell expression, whose very *raison d’être* is to suppress immunity while also making it hard to identify a single uniform pathway to activate the immune system against a growing tumor. Because cancer cells evolve from a patient’s own healthy cells – and much is still unknown about that process – they have a leg up in escaping detection. And the antigens that signal the presence of a malignancy to the immune system’s frontline of T-cells are multiple, diverse and endlessly adaptable. This reduces the ability of the T-cells to consistently carry out their task to recognize, bind and destroy.

Dr. Catherine Wu, a leader in cancer vaccine research with affiliations to the Dana-Farber Cancer Institute (DFCI), the Broad Institute and Harvard Medical School, notes that researchers face complexities in designing even the simplest vaccines – but the challenge has been compounded in applying the process to cancers. Says Wu, “a lot of juggling is involved in identifying the specific antigen to target, figuring the optimal way to deliver the vaccine and selecting an appropriate immuno-stimulatory adjuvant, while all the time working around the negative immuno-resistance space that tumors create around them, allowing malignant cells to proliferate unchecked.”

However, Wu and many other cancer researchers interviewed by *In Vivo* believe that the fallow period in vaccines discovery may finally be coming to an end, for two reasons. The first is improved understanding of how to target a critical immunologic defense mechanism, the PD-1 checkpoint blockade, that attaches and neutralizes a crucial protein that cancer cells rely on to confuse and counter attacks from the immune system’s “helper” T-cells. This led, in 2014, to FDA approval of the first two drugs – *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab) – in a new therapy class known as checkpoint inhibitors. These genetically advanced biologic drugs are designed to dismantle the cancer cell defense and allow T-cells to recognize and unleash their payloads on cancer cells.

The second is the steady expansion over the past decade in the ability to sequence the genetic profile of an individual patient, including accurate mapping of cancerous growths and tumor samples, rapidly and at much lower cost. “This has opened the door to us finding better antigens to target, reducing what has been a major barrier to the design of vaccines that could be efficacious against an individual’s specific disease profile,” said Wu. “It’s confirmatory of the promise of personalized medicine because, with sequencing, we can systematically identify the mutations that make each cancer case unique and provide a computational assessment of which mutations have the most potential in stimulating an individual immune response.” Combined, the advances have revived the entire innovative industry’s interest in the immunologic potential of therapeutic cancer vaccines, with sequencing reinforced by the wider understanding of cancer’s underlying biology through the checkpoint blockade therapy response.

Dr. Wu’s optimism is not misplaced, given that her own work on therapeutic vaccines conducted at Dana-Farber has shown promise in boosting immune response in post-surgical melanoma patients deemed to be at high risk of relapse. In a July 2017 paper published in *Nature*, her team from DFCI and the Broad Institute revealed results of a Phase I proof-of-principle trial on a neo-antigen based vaccine, *NeoVax*, in a small cohort of six melanoma patients. Four of the six evidenced expanded regular neo-antigen specific T-cell populations along with a broader repertoire of new T-cell specifications, resulting in enhanced tumor control leading to no recurrence of melanoma 25 months after vaccination. The other two study patients with recurrent melanoma received the anti-PD-1 checkpoint inhibitor pembrolizumab, in addition to *NeoVax*, resulting in complete tumor regression.

“The study confirms the merits of much of what we hope to gain from a therapeutic cancer vaccine, which is the ability to stimulate beneficial sub-types of T-cells that can work collaboratively to eliminate tumors,” Wu said. “If a therapeutic vaccine platform is to succeed, you must be able to mobilize all these beneficial actors for a single-minded assault on the cancer.”

Wu’s group at DFCI will continue to emphasize small path-finding foundational research initiatives, including a study now commencing to improve predictive computational algorithms that can better identify neo-antigens most likely to generate an escalating immune system response. “As an academic, we are well-positioned to test hypotheses and learn the deep biology and mechanisms underlying effective human immune responses. We expect our data to help guide drug developers toward the most efficacious vaccine platform, one with maximum potency and minimal side effects. Immunotherapy as a treatment modality in cancer has now come of age. With so much activity in this space it mandates academia and industry to partner and work even more closely together.”

The important thing is that money continues to flow toward cancer vaccine therapeutics, which benefits as a sidebar to the sustained R&D frenzy around immuno-oncology in general. The VC

community remains bullish on long-term prospects for cancer vaccines – more importantly, so too does big pharma, which has inked a number of collaboration deals with leading-edge biotechs like [Advaxis Inc.](#) (with [Amgen Inc.](#)), [Moderna Therapeutics LLC](#) ([Merck & Co. Inc.](#)), [BioNTech AG](#) ([Roche](#)/Genentech), [CureVac AG](#) ([Eli Lilly & Co.](#)), [Neon Therapeutics Inc.](#) ([Bristol-Myers Squibb Co.](#)) and Transgene ([Merck Serono SA](#)). An *In Vivo* round-up of clinical trials (see *Exhibit 1*) at the active recruiting stage indicates the extent of such contacts, along with evidence that the trial process overall is nascent. With most studies at Phase I, sponsors are unlikely to be able to deliver meaningful data that resonates with patients, regulators – and payers – until well into the next decade.

Yet the underlying science is so promising, the payoff – if and when it occurs – should be enough to satiate the pessimists. “It’s hard to beat the potential of therapeutic cancer vaccines – a personalized treatment that is sustainable and efficacious over time, with minimal side effects and relative ease of administration,” said Les Funtleyder, health care portfolio manager for E Squared Capital Management and a member of *In Vivo*’s Editorial Advisory Board.

Exhibit 1.

Therapeutic Cancer Vaccines In Active Clinical Trials

[Click here to explore this interactive content online](#) ✎

Source: Trialstrove; clinicaltrials.gov

Building A Vaccines Business: The Calculus Of Chance

Given the long legacy of failure in targeting vaccines as a treatment pathway for cancer, it is important to underscore how new science, entrepreneurial drive, and unconventional, cross-disciplinary partnerships are contributing to current clinical progress in this field. A case in point is Immunomic Therapeutics, a privately held start-up founded in 2005 and focused on gene-based antigen vaccines against hard to treat cancers like glioblastoma. That it exists today is due to an informal encounter several decades ago between its founder and CEO, Dr. Bill Hearl, a bench scientist, inventor and early biotech entrepreneur, and Dr. Tom August, a professor of pharmacology and molecular science at the Johns-Hopkins Medical School.

At the time, the two were among around 10 researchers interested in ways genetic immunotherapy could mobilize powerful antigen-presenting cells against invasive pathogens like viruses and allergens or even cancerous tumors. Hearl, in an interview with *In Vivo*, said “We

were both drawn to the fact that cell-based antigens and antibodies were not being effectively sequenced and deployed to attack these invasive threats – a lost opportunity in immunization. What was needed was a specialized, ‘professional’ antigen-presenting cellular cohort to amplify the response to an invasive threat by teaching ‘amateur’ (i.e. helper) immune cells to improve their disease targeting and containment capabilities. This concentrated set of weaponry could form the basis for a more structured, sustainable and safe immune response in the individual patient.”

As it turned out, August had already established a pathway toward this goal through his Johns-Hopkins research on protein structures, which in 1985 led to the discovery of the lysosome-associated membrane protein (LAMP). LAMP is a class of proteins with unique properties that facilitate the delivery of gatekeeper antigens to optimize the antibody response in fighting invaders. “When I looked at what Tom August had in LAMP, a light literally went on in my head. I realized this platform could help direct the histocompatibility complex of task-oriented, antigen-presenting cells – such as dendritic, macrophage and endothelial cells – to activate the immune system’s front-line of T-cells to identify and dispatch a malignantly transformed regular somatic cell, eliminating it as a threat to normal cells. LAMP has the potential to use the body’s natural biochemistry to help develop a complete immune response, aided by simplified vaccine design and delivery.”

August’s breakthrough thesis was compelling enough for Hearl to invite him to co-found a company together to pursue work on a new class of vaccine therapies, all driven by the LAMP platform. Hearl believed the greatest potential for this technology lay in oncology, a view reinforced by the discovery that LAMP had already been evaluated in studies in HPV at Johns Hopkins University and in clinical studies on several cancers – prostate, melanoma, acute myeloid leukemia and glioblastoma -- conducted at Duke University, Emory University and by a research team at Brussels University in Belgium. It turned out that August had shared his LAMP research with them and several other academic labs but by 2005 had stopped promoting the work and lost touch with the recipients.

Nevertheless, according to Hearl, the fact that some of the research had been peer-reviewed and published demonstrated the clinical versatility of LAMP in addressing not only cancer, but a wide variety of other conditions demanding an immune response, including potentially lucrative applications against common environmental and food allergies. There was another lead-in from studies August conducted in his own lab at Johns-Hopkins on the HIV virus and pest-borne flavivirus infections like dengue and yellow fever. In all such cases, vaccines were the obvious and most efficacious delivery vehicle.

The first thing the new company did was to secure intellectual property rights in 2006 to August’s platform under the trademark LAMP-Vax. To raise money, Hearl orchestrated an early sub-licensing deal for the LAMP-Vax platform with [Geron Corp.](#), a clinical-stage drug developer

applying LAMP-Vax to treatment for hematologic malignancies. “I have always believed that oncology held the most promise under the LAMP-Vax platform,” Hearl notes, “but the stumbling block was we lacked the means to raise the large sums of money required to do clinical studies in cancer. Hence we launched the new company by looking back to allergy vaccines, whose development costs were very inexpensive in comparison to cancer yet still presented us with an attractive market opportunity.”

Immunomic progressed its work on allergens, resulting in an investigational vaccine to treat various tree pollens, including *cupressus japonica*, the most common tree-borne allergen in Japan. The efforts culminated in two licenses, including a landmark agreement in 2015 with Japan’s Astellas Pharma Inc., in which Immunomic granted Astellas global commercial rights to any product for human allergy diseases derived from the LAMP-Vax platform. Under terms of the deal, Immunomic received a \$300 million up-front payment from Astellas as well as a 10% royalty on net sales of all future Astellas medicines for these diseases, including a Phase I trial program on peanut allergy. Most important, in addition to giving Immunomic access to a predictable revenue stream to fund future research, the company kept ownership rights to the LAMP-Vax platform for other disease applications – including cancer immunotherapy vaccines.

Hearl emphasizes the relationship with Astellas continues, with Immunomic retaining responsibility for manufacture of the Japanese red cedar pollen product now owned by Astellas. It also can receive another \$55 million in milestone payments from Astellas under the original deal. “We value it as an additional revenue-producing resource for Immunomic going forward, one that fuels our work in oncology and which most other early-stage biotech innovators don’t have.”

Clearly, the LAMP technology remains the centerpiece of Immunomic’s value proposition to the provider community, investors and patients. The emphasis, however, has changed, from the early work in allergy to embrace therapeutic vaccines in immuno-oncology, and involving new science, patents, and other complementary tools and methods. “We are tackling much more, at the enterprise level, in terms of our capacity to apply new knowledge and expertise,” says Hearl.

To reflect this evolution, the company has repositioned the LAMP platform under a new descriptive acronym called UNITE – the Universal Intracellular Targeted Expression platform -- which management sees as an appropriate marker for Immunomic’s move to capture the immune-oncology vaccine space. “UNITE correctly describes what the company has built over the past decade, and signifies our move beyond the original LAMP design to a combination of intracellular and molecular biology methods for enhanced MHC-II presentation, along with potent adjuvant and delivery technologies that result in a unified and complete immune system response. That’s why we now call it UNITE.”

Immunomic’s current agenda centers on development of a vaccine for newly diagnosed

glioblastoma based on the UNITE platform. The other priority is building and growing a pipeline around other virally driven and neo-antigen based cancers.

The company is supporting a Phase II 150-patient trial – known as ATTAC-II – conducted by researchers from the University of Florida and Duke University (with funding from the National Cancer Institute) to determine if its investigational dendritic cell vaccine (pp65+LAMP DC) is effective for treatment of glioblastoma, when administered with standard of care chemotherapy and radiation. The randomized, blinded and placebo-controlled study intends to show that the vaccine will increase the effectiveness of the powerful immune-boosting dendritic cell by helping it educate those “helper” immune and cytotoxic T-cells to attack and neutralize the brain malignancy. In other words, by giving the pp65+LAMP DC vaccine as a shot under the skin, the immune system could be activated in a full-blown attack on the malignant tumor cells, while leaving normal cells alone.

“This is a long-term exercise, dating as far back as 2006, to establish the clinical merits of our platform in advancing gene-based vaccine therapy against hard-to-treat cancers like glioblastoma,” said Immunomic’s SVP for R&D Dr. Teri Heiland in an interview with *In Vivo*. In addition to its academic partners at the University of Florida and Duke, Immunomic has ties to small commercial partners like [Annias Immunotherapeutics Inc.](#), from which Immunomic obtained certain IP rights to enhance the LAMP-Vax platform. Heiland relates that the Duke researchers, in an earlier study dubbed ATTAC-1, demonstrated that a dendritic vaccine built around the proprietary LAMP-Vax platform, when combined with radiation and chemotherapy, could prolong survival for newly diagnosed glioblastoma patients. “While the ATTAC-II study seeks to establish proof of concept for the dendritic cell-based immunotherapy approach in the clinic, my R&D team has developed an upgraded, direct nuclei acid based version of the vaccine that we plan to translate directly into clinical trials later in 2019,” Heiland said. Meanwhile, Heiland and Heiland expect a readout of preliminary data from ATTAC-II in 2020 or 2021, with a final result due in 2024. There are also plans to launch another company-sponsored clinical study later this year designed to support proof-of-concept for the pp65+LAMP DC vaccine and validate the approach to manufacturing and commercialization.

From Many, One?

Hearl is not worried about that lengthy timeline to commercialization of his principal asset, contending that everyone in the therapeutic cancer vaccine space shares an awareness of the extent of the scientific challenge. “It’s a function of resources – where I believe we are competitive with the rest of the trade – and the ability to differentiate in producing a genuine treatment advance, beyond the lab,” he says. While numerous other biotechs are involved in vaccine-based research directed at brain malignancies, Hearl insists the UNITE platform is precedent-setting because it engages all four standard elements of the immune response, including expedited activation of “helper” T-cells necessary to produce a prolonged attack on a cancerous growth. “Solving for cancer from an immune system approach absolutely requires that

global response, which in our asset is reinforced because UNITE supports delivery of an additional, upgraded cytotoxic payload.”

In addition, UNITE mimics a key attribute of the standard vaccine – an immunological “memory.” This enables the immune system to recognize and address successive waves of malignant cell invaders, in much the same way that a tetanus shot can stop a pathogen introduced when you step on a nail, years after it was administered. “UNITE technology will know what the relevant antigen looks like and activate the T-cells to respond directly. It’s a very important piece of the puzzle – you want that strong initial wave of attack to shrink and disappear the tumor, but it’s also critical to have that immunological memory so that, if and when the cancer reappears, the immune system will quickly crank up without having to initiate an entire new course of treatment. It amounts to an ongoing enhanced process of immune system monitoring, although Hearl admits this is also the intent behind other therapeutic cancer vaccines being tested by competitors. “With the UNITE platform, the pieces of that puzzle just fit together better, in our view.”

UNITE is agnostic in terms of the distinction that researchers sometimes make between DNA vaccines and those based on mRNA. “We are not constrained by the format of the nucleic acid – UNITE allows us to pursue any format we choose,” responds Hearl. “In fact, the vaccine we are currently testing for glioblastoma is an mRNA treatment.” The conclusion he drew was that Immunomic had the capability to compete – or partner – with any of the big players in cancer vaccine, including the segment’s acknowledged leader, Moderna Therapeutics, which focuses on the mRNA approach. “Each of our competitors, which, in addition to Moderna, must include our fellow publicly-traded biotechs Inovio, BioNTech, and Cure Vac, have had some biologic success,” Hearl notes. “In my view, this gives the entire science behind immunologic vaccines credibility and validation. Of course, we’d like to see them using our UNITE technology to stimulate the best possible immune system response. But ultimately what’s most important for patients and society is to have that success in multiple areas – there are no boundaries on disease.”

Immunomic claims that early studies reliant on the platform showed significant improvement in survival compared to the normal 20-month course of glioblastoma in patients, post diagnosis. While the small study population and focus on early stage cancer renders this research preliminary by nature, it nevertheless piqued Hearl’s interest in making glioblastoma the company’s first venture in the cancer vaccine space. In addition to the obvious medical need, Immunomic believes that a vaccine workable against glioblastoma – cancers of the brain are among the most difficult to treat—could serve as a model for addressing many other types of cancer going forward. “We intend to use this project to develop a strategy to identify what particular type of antigens might fit UNITE best, which is the essential step in expanding our anti-cancer portfolio beyond glioblastoma.” As CEO, Hearl has set this as a priority for the company over the next 12 to 24 months.

Overall, Immunomic is confident it inhabits some of the most fertile terrain in the expanding landscape of immuno-oncology, with FDA approval of several effective, personalized therapeutic cancer vaccines projected as a probability in the next decade. few years. Hearl was particularly excited by the potential of vaccines in conjunction with combination therapies involving the many new checkpoint inhibitor drugs now becoming available to clinicians. “There will be a next wave of checkpoint inhibitor drugs for use in combination with treatment vaccines – thoughtful, individually tailored combinations of therapies that boost the capacity of the immune system to educate itself in finding and killing tumor cells,” he says. “We can finally say goodbye to the past of throwing everything against the wall and just seeing what sticks. Cancer vaccines will be a real business – and a boon for patients.”