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CANCER VACCINES: GETTING READY FOR A DECADE OF BIG BREAKTHROUGHS AND NOVEL TREATMENTS

A Frost & Sullivan Virtual Think Tank

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INTRODUCTION

Frost & Sullivan recently invited industry leaders in cancer vaccine research to participate in a new and unique thought leadership forum, our Virtual Think Tank series. This forum brought together leading minds in this emerging field to discuss challenges related to antigen and adjuvant selection, vaccine design, immune response improvement, and future treatment options. The key opinion leaders who contributed to the discussion included:

Moderator:



Barbara Gilmore
Senior Consultant,
Transformational Health
Frost & Sullivan



Aude-Hélène Capietto, PharmD, PhD
Senior Scientific Researcher,
Cancer Immunology
Genentech



Sam Landry, PhD
Professor of Biochemistry,
Department of Biochemistry &
Molecular Biology
Tulane University
School of Medicine



Chelsea Pratt, PhD
BioPharma Market
Development Manager
Bio-Rad Laboratories



Michael Har-Noy, MD
CEO
Immunovative Therapies



Nathaniel Wang, PhD
Chief Scientific Officer
Replicate Bioscience



Alessia Melacarne, PhD
Postdoctoral Researcher
Humanitas University

HISTORY OF CANCER VACCINES

In 1891, the first attempt to use a cancer patient's immune system to improve their prognosis was performed by Dr. William Coley. At the time, his work using inactivated bacterium injections on cancer patients was viewed with skepticism, but science would eventually show that the underlying principles were indeed correct.¹ The development of therapeutic vaccines has since made great advances. The mention of cancer vaccines may bring to mind prophylactic vaccines for viruses that can cause cancer, such as Hepatitis B virus and Human Papillomavirus; however, cancer vaccines also encompass therapeutic cancer treatments which utilize the patient's own immune system. These therapeutic vaccines use either cell-based, protein/peptides, or DNA, RNA, or viral delivery systems, and attempt to train the patient's immune system to identify otherwise evasive tumor cells. This is accomplished by inducing antigen cascades or epitope spreading to enact distant and durable immune responses.

In 2010, Dendreon made history when it launched Provenge, a new cell-based immunotherapy cancer vaccine for prostate cancer. This milestone revealed that complex treatments tailored to individual patients could receive FDA approval. However, a combination of supply constraints and limited demand prevented Provenge from catching on. This has intensified the focus on research and development of a peptide- or protein-based vaccine using either tumor-specific antigens (neoantigens) or tumor-associated antigens (TAA).



¹ McCarthy, Edward F. "The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas." *The Iowa orthopaedic journal* vol. 26 (2006): 154-8.

DIFFERENCES BETWEEN TRADITIONAL PROPHYLACTIC VACCINES AND THERAPEUTIC CANCER VACCINES

“One of the big differences between traditional vaccines and cancer vaccines, first and foremost, is they typically target non-self, different types of pathogen genes that are seen as foreign by the immune system, whereas cancer vaccines have traditionally targeted more self-proteins,” explained Dr. Wang. “Although, with neoantigens, that’s increasingly changing.”

Dr. Har-Noy further discussed the need for “a robust cellular immune response against the neoantigens.” He expanded on the obstacles to developing a cancer vaccine in contrast to traditional vaccine development, highlighting “the immune cascade that needs to occur before you get protective immunity and then the additional issue of conditioning the microenvironment of the tumor to reverse or counter-regulate the immunosuppression and immunoavoidance.” This challenge underscores the complexity inherent in both the immune system and a tumor’s ability to avoid detection and eradication.

The ability of tumors to evade detection is through genetic alterations, including nucleotide insertions, deletions, or substitutions. These types of mutations are responsible for tumor-specific neoepitopes. These neoepitopes can then be exploited to distinguish healthy and cancer cells if they are successfully presented to the major histocompatibility complex (MHC) for ultimate T-cell recognition. This is essential to the success of neoantigen-directed cancer vaccines, as evidenced by studies showing that better outcomes are associated with high neoantigen load.²

The generation of personalized vaccines that induce neoepitope-specific immune responses based on a patient’s human leukocyte antigen (HLA) type is now considered possible.

Better understanding the mechanisms allowing cancer cells to evade the immune system, coupled with advances in cancer treatment, has generated hope that cancer vaccines may yet play an important role in immunotherapy. Research suggests that cancer vaccines should be included in combination therapy strategies to enhance overall efficacy.³ Dr. Melacarne noted, “The combination of immunotherapy with checkpoint inhibitors can make a great difference” in patient outcome.

² Ott PA et al. “An immunogenic personal neoantigen vaccine for patients with melanoma.” *Nature*. 2017; 547: 217–21.

³ Pan C et al, “Next Generation immuno-oncology agents: current momentum shifts in cancer immunotherapy” *Journal of Hematology & Oncology* (2020); 13:29.

ADVANCES OVER THE LAST FIVE YEARS

Although previous attempts to develop effective cancer vaccines were met with disappointing research and commercial results, therapeutic cancer vaccines still offer a promising treatment methodology. Current approaches to improve the efficacy of cancer vaccines include targeting novel antigens and combining cancer vaccines with standard of care treatments, with the goal of generating new immune-based platforms. These new platforms require additional randomized clinical trials to investigate the use of vaccines in combination with current therapies. In addition, work is underway to determine the optimal treatment sequence and identify novel biomarkers to monitor the success of directed immune responses.

DNA sequencing technology has also contributed to the identification of potential neoepitopes in recent years. Dr. Landry explained, “Many of the ideas and technologies existed before [DNA sequencing], but the targets weren’t available . . . now with DNA sequencing so cheap and fast, that’s really been the big breakthrough.”

For many cancer vaccines to be effective, the antigen needs to be both present in the tumor cells and presented on the cell surface to generate an effective antitumor response. Strides have also been made in this area, with many ongoing studies seeking to better understand and elucidate the epitopes presented on the cell surface using mass spectrometry. This data is then analyzed and fed back into the predictive algorithms in order to offer better future predictions. Dr. Capietto remarked, “There have been huge advances, including machine learning and neural networks in artificial intelligence ... [to address] the challenges remaining for predicting these new antigens.”

Finally, Dr. Landry noted the desire for an mRNA delivery mechanism rather than peptides for cancer vaccines. Though regulatory approval is still pending, several mRNA vaccines for SARS-CoV-2 have demonstrated the speed and agility with which this type of vaccine can be developed. Dr. Landry states, “This major new advance has rapidly, enormously accelerated the possibilities for delivery of novel vaccines. It’s far more feasible now for new epitope vaccines to be constructed on an adequate scale and with great complexity in short times.”

Despite many advances in the last few years, Dr. Har-Noy noted that much work is still needed, both technically and commercially, to translate potential cancer vaccines into viable products.



FOCUS ON ANTIGEN SELECTION CHALLENGES

The key to the successful development of a cancer vaccine rests on the identification and characterization of either TAAs or neoantigens that induce cytotoxic T lymphocyte (CTL) expansion.

While there have been many setbacks in the field of cancer vaccines due to the lack of success of monotherapies, many of the early targets investigated may still have clinical validity in a combination therapy approach. Dr. Wang acknowledged that “[T]here were a lot of things that failed in oncology as monotherapies, which does not mean the underlying target that was being studied should be discarded.” However, the question still remains, what does ‘correct’ mean when referring to an antigen or target for cancer vaccines?

Dr. Har-Noy commented, “I think you can develop a neoantigen vaccine and vaccinate and even be able to show you get very high titers of [neoantigen-specific] CTL response and still not get a clinical response in the patient. Does that then meet the definition of a correct antigen? I don’t think so.”

Although advances are being made in terms of antigen selection and presentation, this progress has not yet translated to the clinical level. This makes one consider what it may take for a neoantigen vaccine to be deemed successful.

One factor may be the disease stage in which the neoantigen vaccine is administered. Dr. Wang hypothesized, “[T]he timing in which you are targeting a specific antigen also matters. It could be that an antigen is really good at a certain stage in the tumor and completely dispensable and quickly immuno-edited out at another stage of the tumor. I do think that the timing of the kinetics and evolutions of tumors over time, needs to be taken into account.” Therefore, a target or neoantigen could be the ‘correct’ one if targeted early in the disease, but might not have any effect if used in a later stage, even if the tumor types and mutations are the same in both instances.

CANCER VACCINES — THE NEXT TEN YEARS

Immunotherapy research is moving at an exhilarating pace toward new frontiers in cancer treatment. The past decade has seen tremendous advances in the areas of both cellular therapy development and antibody-based protein therapies, with cancer vaccines beginning to play a larger part. Recent studies have shown that peptide vaccines have enhanced the activity and proliferation of CAR-T cells, which may improve the cells' efficacy against solid tumors.^{4,5}

Still, these findings are preliminary, and the consensus is that we may have set our expectations for cancer vaccines too high, too soon. Dr. Wang noted, "Some of the failures of the past in the field have just been a matter of not having adequate biomarkers in place and having unrealistic expectations of the types of responses you are going to be getting." Despite setbacks, the field of cancer vaccine development is moving in the right direction.

Another challenge the field has faced is lack of commercial success. As declared by Dr. Har-Noy, "Developing an effective therapeutic vaccine for cancer in any indication, which becomes a commercial success, will be the one event that will be the most significant for the whole industry of neoantigen vaccines. Proof of commercial success brings the investment and excitement to try all kinds of different ideas."

This success is thought to be just around the corner, thanks to artificial intelligence. With advances in predictive algorithms and artificial intelligence, neoantigen vaccines can be designed for tumor mutation prevention rather than via the current reactive approach. Dr Wang remarked, "This will take cancer vaccines [closer] to where vaccines tend to succeed in general, where you generate T-cell or B-cell responses in some kind of target even before it occurs within the body itself." The ongoing challenge extends from the fact that immune responses are at present very hard to forecast. Fortunately, the ongoing development of new algorithms, the identification of optimal antigens and adjuvants, and research into new T-cell therapy strategies may soon change all of this. Despite continued challenges, cancer vaccines hold great promise in cancer treatment, either alone or as part of combination therapies.

4 Tanaka M et al, "Vaccination Targeting Native Receptors to Enhance the Function and Proliferation of Chimeric Antigen Receptor (CAR) modified T Cells" *Clinical Cancer Research* (2017); 23:3499.

5 Majzner RG et al, "Tumor Antigen Escape from CAR T-cell therapy" *American Association for Cancer Research* (2018); 8(10):1219-26

NEXT STEPS

- **Schedule a meeting with our global team** to experience our thought leadership and to integrate your ideas, opportunities and challenges into the discussion.
- Interested in learning more about the topics covered in this white paper? Call us at 877.GoFrost and reference the paper you're interested in. We'll have an analyst get in touch with you.
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Silicon Valley

3211 Scott Blvd
Santa Clara, CA 95054
Tel 650.475.4500
Fax 650.475.1571

San Antonio

7550 West Interstate 10
Suite 400
San Antonio, TX 78229
Tel 210.348.1000
Fax 210.348.1003

London

Floor 3 - Building 5,
Chiswick Business Park
566 Chiswick High Road
London W4 5YF
Tel +44 (0)20 8996 8500
Fax +44 (0)20 8994 1389

✉ myfrost@frost.com

☎ 877.GoFrost

🌐 <http://www.frost.com>

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Frost & Sullivan

3211 Scott Blvd

Santa Clara, CA 95054

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