Cancer Research

Overcoming Challenges
Renewed Focus on Cancer Vaccines

No longer treated as myth, the cancer vaccine field has materialized over the past decade. Researchers have overcome numerous challenges and more vaccines are poised to enter the market. The field is growing rapidly, which makes it an opportune time for graduate and postdoctoral fellows to enter it.

By Jacqueline Ruttimann Oberst

Until recently, Olivera Finn would come across articles or meeting sessions describing her field as “Fact or Fiction.” “It used to drive me crazy,” she says.

Finn, a chair of the Department of Immunology at the University of Pittsburgh, and others who work on cancer vaccines have finally seen their field vindicated. Three vaccines have been approved by the U.S. Food and Drug Administration and five U.S. phase III clinical trials are poised to report data by this year. Worldwide, over a dozen cancer vaccines have been approved.

Cancer vaccines as a field has been slow to emerge but has come into its own. Researchers have learned the reasons, scientific and regulatory, for many past failures and are poised to meet future challenges. Graduate and postdoctoral fellows who choose to enter this field are doing so when it is hitting its stride, allowing the possibility for a rewarding and potentially lucrative career.

FINDING THE PROVERBIAL NEEDLE IN A HAYSTACK: CANCER VACCINE HISTORY

Treating cancer has historically relied on a trifecta of treatments—surgery, chemotherapy, and radiation—known colloquially as “slash, poison, and burn.”

Vaccines have a potential advantage over these three options in that the body’s response is longer lasting (on a scale of years as opposed to weeks or months), which could possibly eradicate the micro-metastases that often linger after standard treatments end. Moreover, cancer vaccines have similar minor side effects to traditional vaccines: inflammation at the injection site and flu-like symptoms.

Some say that this method probably won’t eradicate cancer altogether, but vaccines could enable physicians to manage it more like a chronic disease.

“I anticipate that we’ll get to the point where if you do get cancer, then it will be more manageable or cured more easily,” says Christian Ottensmeier, a medical oncologist and director of the Experimental Cancer Medicine Centre at the University of Southampton in the United Kingdom.

Opines Eric von Hofe, president and CEO of Antigen Express, a cancer vaccine biotechnology company: “We’re not going to replace chemotherapy, radiation, and surgery, but in 5 to 10 years, vaccines will be much more an accepted part of clinical oncology.”

Cancer vaccines require rethinking the term “vaccine.” Most patients are familiar with vaccines given to healthy people to prevent bacterial or viral infections, such as diphtheria and mumps. These traditional vaccines require using weakened or killed viruses, bacteria, or other germs to trigger an immune response in the body via activation of B cells and killer T cells. Although some cancer vaccines (e.g., Gardasil and Cervarix for cervical cancer) work in this fashion and are for prophylactic purposes, others are used as a therapeutic, to retrain the immune system to attack a disease that already exists (e.g., Provenge for prostate cancer). Therapeutic vaccines use cancer cells, parts of cells, or pure antigens—sometimes from the individual patient—in combination with other substances called adjuvants to further boost the immune response. Thus these vaccines all fall under the umbrella of immunotherapy.

The first foray into immunotherapy was in 1893, when William Coley, a New York surgeon, injected a cocktail of attenuated bacteria, Streptococcus pyogenes and Serratia marcescens, into sarcoma patients. Today, this approach is only used in superficial bladder cancers; live Bacillus Calmette-Guérin is injected after surgical resection.

Beginning in the 1970s, the discovery and refinement of techniques to create monoclonal antibodies, which can bind to a single target, has enabled the identification of cancer-specific cell-surface proteins or antigens. Whereas antigens detected by these antibodies offer a whole armamentarium for vaccine creation, most of them are also found in normal cells. This raises the risk of a patient’s immune system turning on itself and creating autoimmunity. Yet all is not lost for this type of treatment: Cancer cells often express more of these antigens than normal cells, and the “friendly fire” or immune-induced injury of normal cells may be reversible. Furthermore, vaccines can elicit antibodies that do not act directly upon the tumor cells; some neutralize growth factors, cytokines, or the blood supply needed by cancer cells to inhibit the tumor’s expansion and

“So much exists that is unknown, and this fact represents a unique opportunity for investigators, especially young scientists, to find a foothold and make very important contributions.”

—Philip Vernon

UPCOMING FEATURES

Bioclusters: Eastern United States—April 6
Bioclusters: Western United States—May 4
Biotech/Pharma: Navigating Mergers/Acquisitions—June 8
others target the connective tissue or stroma between tumor cells. The discovery of cancer-testis antigens, whose expression is limited only to cancer cells and immune-protected sperm cells, has opened up new immunotherapy approaches that avoid healthy cells altogether.

The late 1980s and early 1990s ushered in better cell culturing techniques, allowing immune cells, such as killer T cells, to be retrieved from the patients and grown in the lab. In the 1990s and 2000s, the development of spontaneous mouse tumor models closed the loop from bench-to-cage-to-bedside. Instead of using xenographs or transplantable tumors in immunocompromised mice, researchers can now observe tumorigenesis in the context of an intact immune system. These improvements have facilitated better preclinical testing of cancer vaccines and their safety.

“The development of synthetic vaccines via genetic engineering over the last decade has [also] been a game-changer,” says Philip Arlen, president and CEO of Neogenix Oncology, another prominent cancer immunotherapy company. “Previously vaccines came from the tumors themselves. Now we are using peptides and vectors and not introducing biologic material from the tumor itself to humans.”

According to many in the field, it will take a village of researchers to help create these vaccines. “This is a very active field of translational research requiring clinical investigators as well as scientists in both academia and biotech as it increasingly attracts big pharma attention,” says von Hobe. “At the practical level, biomarker discovery, including gene profiling and the study of immunological parameters, are clearly areas in need of candidates with bioinformatics expertise, as well as a tumor immunology background, to help guide the discovery of second generation cancer immunotherapeutics.”

Finn, whose students are part of an interdisciplinary graduate program at the University of Pittsburgh School of Medicine, admits that she’s “shameless about convincing new students to choose immunology.”

“We teach students the power of the immune system and how the immune system operates. One can’t do anything nowadays that doesn’t involve the immune system. It affects such ailments as obesity and stress,” adds Finn, claiming that as a result, psychology, and bioengineering students have entered the immunology department to work in the cancer vaccine field.

Tumor biologists and immunologists are not the only experts that are required for this field. “A whole slew of skills are needed,” says Arlen. “There’s the issue of discovery in which tumor biologists and immunologists contribute, but then there’s sequencing of proteins or peptides for which molecular biologists are needed. Virologists and microbiologists can contribute to design of viral vectors, and those with regulatory and peptide synthesis skills are desired for production/manufacturing work.” He adds that individuals with vivarium expertise are also in demand, as various animal models, such as mice, dogs, pigs, and monkeys, are needed for preclinical studies.

STICKING POINTS: CANCER VACCINE CHALLENGES
Over the years, numerous tumor immunotherapies have had “false starts,” with early-stage successes but failing in phase III clinical trials. Many reasons account for these failures, including insufficient knowledge of the biology and inappropriate patient populations.

“The understanding of the immune system 30–35 years ago is archaic compared to what we know today,” says Arlen. “We now have a much more comprehensive understanding of the checks and balances of how the immune system works—the subsets of cells, how they function, and how immunocompetency can be compromised or lead to autoimmunity when the immune system is not in check.”

“Although immunologists are still needed, someone versed in regulatory affairs is also required,” continues Arlen. “We’ll need someone who can go through the IND process, understands the rationale for treating patients, and who has expertise in developing animal studies.” Those who possibly fit the bill include physicians, nurses, and veterinarians.

According to Finn, the earlier clinical trials have taught cancer vaccine researchers two things: “One, there really is no window of opportunity; patients with cancer are already immunocompromised to varying degrees so they might not respond well to a vaccine. Second, we have learned more about the specifics of how a tumor changes the immune system. For example, too many regulatory T cells observed in many cancer patients will prevent an immune response to the vaccine, so we need to get rid of these. Likewise, if there are too many exhausted T cells, we need to help them by interrupting their negative signaling pathways.”

This knowledge has spurred the vaccine field into a new industry: immunotherapeutic antibodies that prime the cancer patient’s immune system so vaccines can work. One example is the emerging class of anti-inhibitory antibodies called checkpoint blockades, such as anti-CTLA-4 and anti-PD-1, which bypass the immune system’s natural off switches, sustaining the cellular immune response long enough to make an impact on cancer. To aid in the construction of these antibodies, biochemists and researchers with expertise in X-ray crystallography are also highly desired.

Clinical trial designs also need revamping in the cancer vaccine field. With traditional drugs, clinical trials tend to include individuals whose cancer is at an advanced stage to prove efficacy. This is often because these patients are more willing to try the treatment. Essentially, they have nothing to lose, having already been treated with other agents that have failed. Moreover, companies have found that treating this population often results in positive effects showing up more quickly than in patients with either early-stage or fully-resected tumors.

However, Ottensmeier says, “cancer vaccines have forced clinical trial design to stand on its head” because clinical trials have indicated that vaccines will likely work best in patients with earlier-stage cancers or in those whose tumor burden has been reduced to the microscopic level by surgery or chemotherapy. continued »
Cancer Research

“After decades of using in vitro culture systems and animal models, it is fantastic to now have access to samples from patients that can provide us with truly informative answers. Our findings may indeed improve the treatment or even cure cancer patients one day.”

—Angelica Cazaly

Finn’s lab is testing early intervention in patients with premalignant lesions such as advanced colon polyps. Her group has seen that vaccinating patients who have had these polyps removed elicited a robust immune response never before seen in patients with colon cancer. She hopes that this strong immune response will prevent the polyps from either recurring or reverting to colon cancer.

MAGIC BULLET OR NOT?

Most researchers in the cancer vaccine field believe that because cancers are ever-changing in their nature, adopting a one-size-fits-all approach for cancer vaccines is not likely.

“The future is in two directions: vaccines as one more addition to a very complex and comprehensive therapy for cancer patients, or alone as prophylaxis,” predicts Finn.

Combining vaccines with chemotherapy might prove to be a formidable match.

“There’s a long-held belief that any chemotherapy has a negative impact on the immune system. However, low-dose chemotherapies actually release antigens that trigger cancer-specific immune responses and can give a whole new set of markers to monitor,” says Jill O’Donnell-Tormey, CEO and director of scientific affairs at the Cancer Research Institute, a non-profit organization dedicated to advancing the field of cancer immunology. She adds that there is a need to optimize cancer vaccines (i.e., dosing, timing, alone or in combination, and the identification of prognostic and diagnostic biomarkers that can be modulated by cancer vaccines)—as such, epidemiologists and those studying public health are in high demand in the field.

Arlen points out that the chemotherapy agents may change their spots: Many of the drugs used to damage cancer cells, once thought to be immunosuppressive, appear to have unexpected beneficial effects on the immune system. “When used at a proper dose, [chemotherapy] can reduce or lower regulatory T cells that block tumor response, making the tumor more susceptible to the immune responses generated by cancer vaccines,” he says.

WHY GO INTO THIS FIELD?

For Ottensmeier, a medical oncologist and immunologist, this field has the best of all worlds.

“It’s an interplay of learning in a lab, testing in people, and going back to the lab,” he says. And because patients understand the general concept of vaccines, they also get excited to see their lab results and whether their bodies are fighting the cancer, he adds.

His postdoctoral fellow, Angelica Cazaly, agrees: “After decades of using in vitro culture systems and animal models, it is fantastic to now have access to samples from patients that can provide us with truly informative answers. Our findings may indeed improve the treatment or even cure cancer patients one day.”

The field is also not a fait accompli, yielding more opportunities for students to contribute.

“It’s a great field to enter because of how much we still have to learn about how the immune response to tumors is initiated, the complex interplay of molecules and cells that render it effective, and how it can contract appropriately. Knowledge of all these processes increases the opportunity for therapeutic intervention,” says Adam Farkas, Finn’s graduate student.

Laboratories that focus on cancer vaccines are becoming abundant at university cancer centers and at government facilities such as the National Cancer Institute (NCI) and the National Institutes of Health. There are also positions in the cancer vaccine field for M.D.s. Many U.S. medical oncology training programs provide physicians with either training in the laboratory or developing clinical trials and treating patients with experimental cancer vaccines. Furthermore, now that the industry is focusing on developing these therapies, basic research laboratories in both pharmaceutical and biotechnology companies provide a basis for additional training in this cutting-edge oncology field.

“So much exists that is unknown, and this fact represents a unique opportunity for investigators, especially young scientists, to find a foothold and make very important contributions,” says Philip Vernon, another graduate student in Finn’s NCI-sponsored training program. “This reality allows scientists to pursue their own ideas because of the relative paucity of established ‘dogma.’”

This latitude of scientific exploration, as well as preliminary positive results has steered the field, according to Arlen, from “‘this is really voodoo’ to now being validated and approved.”

Jacqueline Ruttimann Oberst is a freelance writer living in Chevy Chase, Maryland.

DOI: 10.1126/science.opms.r1200116