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Cancer Immunotherapy—Where Are We Going?

By Ingmar Hoerr | December 23, 2012

The compelling concept of utilizing the patient's own immune system for a stronger and more effective way to attack cancer cells is not a new one. William Coley observed in 1891 that infections produced in patients with inoperable cancer following an injection of streptococcal organisms (Gram-positive bacteria) led to tumor shrinkage especially when the patients developed fever and other signs of a full-blown infection.[1] Since then, research has embraced approaches to "train" the patient's own immune system to recognize certain biomarkers or proteins that are mainly found on cancer cells and to destroy the cells.

After several setbacks the first cellular immunotherapy, Dendreon's Sipuleucel-T (Provenge®), was approved for the treatment of prostate cancer in 2010. Today, new promising cancer immunotherapy approaches are in clinical trials. Most recently, researchers at the 54th American Society of Hematology (ASH) meeting reported early success with a developmental-stage cell-based cancer vaccine for the treatment of leukemia and have shown remission in several patients [2,3], including a 7-year old girl who relapsed twice after chemotherapy.

Cancer immunotherapy can be thought of as either active or passive immunotherapy. The most prominent passive immunotherapies, which have revolutionized cancer therapy, are monoclonal antibodies that either target tumor-specific antigens and receptors or block important pathways central to tumor growth and survival. Therapeutic monoclonal antibodies are the market leader in the targeted cancer therapy space and include blockbusters such as trastuzumab (Herceptin®) or rituximab (Rituxan®).

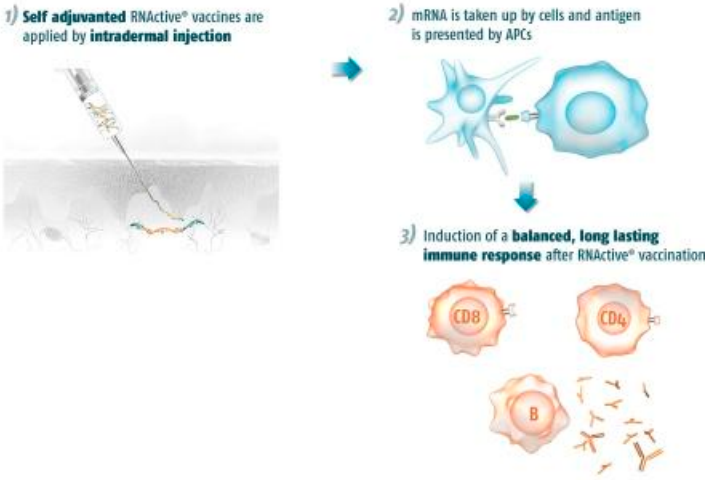
In general, antibodies are significant elements of the body's adaptive immune system. They play a dominant role in the recognition of foreign antigens and the stimulation of the immune response. Therapeutic antibodies target and bind to antigens, usually proteins that are mainly expressed on diseased cells such as cancer cells. After binding, cancer cells can be destroyed by different mechanisms such as antibody-dependent cellular cytotoxicity, the activation of the complement system — an important part of the immune system — and triggering cell death.

Although very successful, especially in oncology, therapeutic antibodies have a significant limitation: they don't generate a memory response by the immune system, and thus, repeated antibody infusions are required. Further, monoclonal antibodies are only able to recognize specific proteins present of the cell surface. Monoclonal antibodies are mostly produced in cell culture systems which are often costly. Humanization of murine monoclonal antibodies by replacing of certain parts of the antibody with human sequences has improved the tolerability of antibodies and made them less immunogenic, but even fully human sequence-derived antibodies can carry some immunological risk.

Novel approaches in the passive immunization strategy include antibody drug conjugates, a combination of targeting antibody with a very potent drug such as the recently approved brentuximab vedotin (ADCETRIS™) for Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL). ADCETRIS comprises an anti-CD30 monoclonal antibodyanti-CD30 monoclonal antibody and a cytotoxic (cell-

killing) agent that is released upon internalization into CD30-expressing tumor cells. Currently, the development of next generations of ADCs is underway.

Alternatively, specific and durable cancer immunotherapies designed to actively "train" or stimulate the patient's intrinsic immune response have been more problematic; however, recent success stories, such as the cell-based immunotherapy Provenge, have revitalized this field. Dendreon's approach modifies the patients' own dendritic cells to present a protein specific to prostate cancer cells.



Dendritic cells are the most potent, "professional" antigen-presenting cells. They process the antigen material and present it on their surface to other cells of the immune system. Once activated, the dendritic cells migrate to the lymphoid tissues where they interact with T-cells and B-cells — white blood cells and important components of the immune system — to initiate and shape the adaptive immune response. To develop Provenge, each patient's own dendritic cells are harvested and then loaded *ex vivo* with the tumor-associated antigen. Now "presenting" the antigen, the dendritic cells are administered back into the patient to induce a potent, cell-mediated anticancer immune response resulting in tumor shrinkage and clinical benefit.

In another experimental approach for the treatment of leukemia, patients' own modified T-cells were infused back into the patients. Prior to this, the T-cells were transduced with a lentivirus to express the CD19-specific chimeric antigen receptor. CD19 is an antigen which is found on B-cell neoplasms, cancerous B-cells, and the lentivirus was the vehicle to transfer the genetic material for CD19 into the cells. A case report published in the *New England Journal of Medicine* stated that a patient with chronic lymphocytic leukemia (CLL) was in ongoing remission 10 months after treatment.[3]

These promising results have spurred continued research for new and safe ways to achieve effective tumor vaccination, and drug developers have explored many cancer immunotherapy strategies. To generate an effective antitumor immunity, therapeutic intervention should drive several functions; specifically, it should promote the antigen presentation functions of dendritic cells, promote the production of protective T-cell responses, stimulate B-cells and overcome immunosuppression characteristics that are common to tumor cells.[4]

Cell-based therapeutic vaccines are most frequently produced outside the patient's body and involve isolation of the specific cells, such as dendritic cells, and the introduction of preselected antigens, often with the use of specific vehicle, into the cells. The antigens can be encoded in viral vectors (frequently DNA) or administered as peptides or proteins in a suitable adjuvant and carrier through a long and cumbersome process.

During my doctoral thesis, I conducted immunization experiments using RNA as a negative control, assuming that the RNA would be degraded during the experiment thus making it impossible to use as a vaccine. The physiological role of messenger (m) RNA is to transfer genetic information from the nucleus to the cytoplasm where this information is translated into the corresponding protein. mRNA is known to be very unstable and has a relatively short half-life. But astonishingly, we were able to measure a solid T-cell immune response. We repeated the experiment and confirmed that the RNA we had produced had the potential to be used as a vaccine. Importantly, we didn't need to isolate the patients' cells: mRNA-based vaccines can be injected directly into the skin (intradermal). The mRNA-based vaccines are then taken up by antigen-presenting cells, such as dendritic cells, and are then able to induce an immune response. Importantly, mRNA-vaccines can also be synthesized quickly for any antigen sequence identified.[5]

The first mRNA-based vaccines (RNActive®) are now in the clinic for the treatment of prostate cancer and lung cancer and have demonstrated that they do what they are supposed to do – induce a balanced humoral, as well as T cell-mediated, immune response that is entirely HLA independent. The HLA (human leukocyte antigen) system is used to differentiate the body's own cells (self) and non-self cells. Additionally, RNA-vaccines do not need a vehicle such as a virus for delivery to the cells, nor do they contain virus-derived elements that are often found in DNA-vaccines. These attributes make RNActive a very safe therapeutic.

The risk of integration of the RNA into the host-genome is minimized (RNA would have been transcribed first to DNA, and then it has to be transported to the nucleus), as is the residual risk of DNA-based vaccines for inactivating or activating genes or affecting cellular regulatory elements, which can induce oncogenesis. Thus, the favorable safety profile of mRNA-based therapies broadens their potential use not only for the treatment of diseases but for use as prophylactic vaccinations. A recent proof-of-concept study using mRNA-based vaccines (RNActive) in animal models for influenza was published in *Nature Biotechnology*.[6]

Therapeutic cancer immunotherapies and vaccines have come a long way, and novel, promising approaches give hope for safe and effective treatment options. This may one day lead to the treatment of all cancers as chronic diseases.

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About the Author: Ingmar Hoerr is co-founder and CEO of CureVac, an integrated biopharmaceutical company in the field of novel vaccines for infectious diseases and cancer. CureVac has secured about €65 million in equity financing in three financing rounds and currently employs more than 100 people. During his scientific career, Ingmar laid the foundation of CureVac's unique RNA-based technology platform, RNActive®, enabling the development of a new class of cancer vaccines. With a background in both biology and business management, he decided to set-up CureVac in order to advance his findings to their full therapeutic and commercial potential. Ingmar Hoerr's scientific track record includes works in the laboratories of Professor Günther Jung and Professor Hans-Georg Rammensee, both renowned scientists in organic chemistry and immunology, respectively. As well as one year of field studies on leprosy and HIV in collaboration with the World Health Organization (WHO) at Madurai Kamaraj University, India. Ingmar Hoerr received his PhD in biology from Tübingen University (1999), and a MBA from Danube University in Krems, Austria (2001).
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