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The latest in cancer immunotherapy

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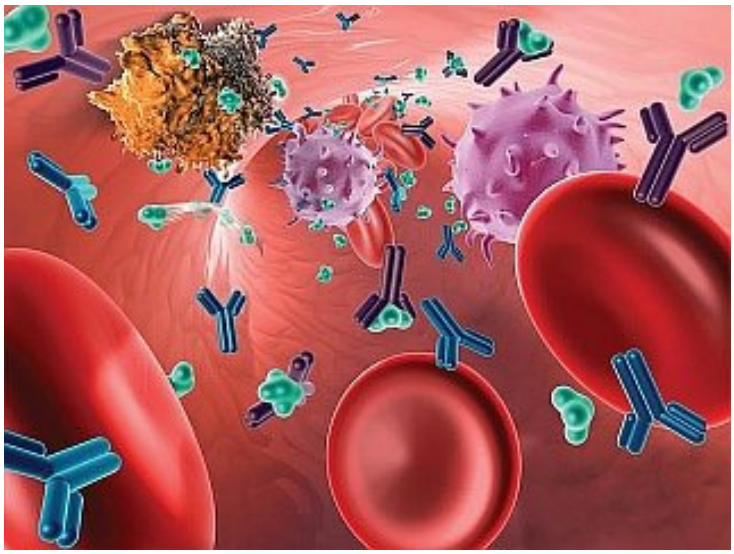

Guest Column

Dr Sanjay Singh, Head-Biotechnology, Sun Pharmaceutical Industries Limited, is a technocrat who has over two decades of varied and in-depth experience in biotechnology.

Immunotherapy is a very active area of cancer research wherein the treatment makes the immune system fight against cancer. Scientists around the world are studying new ways to use immunotherapy to treat cancer. Some of these have been discussed here which are based upon various strategies, such as boosting the immune system to aggressively attack cancer cells, training the immune system to specifically and effectively attack cancer cells and driving the drugs to attack cancer cells among others.

What does the immune system do?

The immune system basically works by recognizing and fighting out any foreign substance invading or found in the body. But the immune system's normal ability to fight cancer is limited, because the cancer cells are not different enough from that of normal cells. To overcome this, researchers have designed ways to help the immune system recognize cancer cells and strengthen its response so that it will destroy them.

What's new in immunotherapy research?
Predictions for the future of cutting-edge antibody technologies for the treatment of various cancers are very high and robust growth will continue despite the many roadblocks and uncertainties in the overall picture of drug development. While the market will continue to be dominated by whole antibody molecules, it is anticipated that multi-specific antibodies and antibody-drug conjugates will be a growing component of the overall market.

Newer monoclonal antibodies
Monoclonal antibodies (MAbs) have already become an important part of the treatment for many cancers and continuous effort is being made to develop MAbs for new targets. Newer forms of mAbs, such as multispecific antibodies and the antibody conjugates to make them more powerful, are also under advanced stage of development. The commercial clinical pipeline for antibodies is growing at a rate of 50-to-55 new mAbs per year. Today, about 314 mAb products are in clinical trials worldwide.

Multi-specific antibodies
Multi-specific antibodies present a new edge technology platform for the disease treatment. There is substantial interest in multi-specific antibodies as a means to overcome some of the shortcomings of conventional recombinant antibodies that have slowed their successful performance and prevented FDA approval. Today, numerous multi-specific antibodies are in clinical trials and may provide a new generation antibodies. Researchers are mostly trying to target both the antigenic sites on the tumor as well as activating CD8+ T cell to specifically attack the cancer cells.

Immunoconjugates
Antibody conjugates, historically, consisting of a cytotoxic agent linked covalently to an antibody or antibody fragment directed towards a specific cell surface target expressed by tumor cells which faced several hurdles particularly poor conjugate in-vivo stability that have been identified and overcome in the new developments. A number of targets, drugs, and linkers are being evaluated. The last few years have seen a remarkable momentum in the development of antibody-drug conjugates which are expected to get approval in next few years.

Researchers have explored four main avenues using antibodies to target cytotoxic agents to malignant cells, including antibody-protein toxin (or antibody fragment-protein toxin) recombinant fusion conjugates; antibody-chelated radionuclide conjugates; antibody-small molecule drug conjugates and their nano-particles and nano-vesicles; and antibody-enzyme conjugates administered along with small-molecule prodrugs that require metabolism by the conjugated enzyme to release the activated species.

So far, only antibody-radionuclide conjugates and antibody-drug conjugates have reached the regulatory approval stage, and nearly 20 antibody conjugates are currently in clinical trials. It seems this technology might bring a new hope for the cancer patients.

Do cancer vaccines hold the promise?
Most cancer vaccines usually prime the immune system to attack cancer cells in the body to treat cancer or to prevent it from coming back. Some cancers are caused by viruses, which can be prevented by prophylactic vaccines that help protect against infectious viruses such as some strains of human papilloma virus (HPV), linked to cervical, anal, throat and some other cancers and chronic hepatitis B virus (HBV) probably linked to liver cancer.

The prophylactic vaccines for HPV and HBV are successfully in the clinics for several years. Researchers are trying to explore the other prophylactic vaccines which could modulate the immune system to regret the cancers. So far, the BCG vaccine has been approved for urinary bladder cancer as an adjuvant therapy.

But most cancers, such as colorectal, lung, prostate, breast, lymphoma, leukemia, glioma, kidney and pancreas cancers are not caused by infections. Researchers are trying to invent effective therapeutic vaccines employing cytotoxic T cells, in conjunction with different cytokines and different adjuvants, trigger the antigen presentation along with MHC- I which could activate CD8+ T cells to specifically attack cancer cells. Several therapeutic cancer vaccine candidates have shown some promise in clinical trials, but yet to be approved.

Several types of cancer treatment vaccines are being studied with a few reaching late
stage clinical trials, including tumor cell vaccines, antigen vaccines, dendritic cell vaccines and DNA vaccines.

How far non-specific immune boosts are successful?

Non-specific boosts do not target a certain cell or antigen but they stimulate the immune system against cancer cells. The following immune boosters are prominently used to treat cancer.

Interleukins
Interleukins are a group of cytokines that act as chemical signals between white blood cells. Interleukin-2 (IL-2) helps immune system cells to grow and divide more quickly. IL-2 is so far approved to treat advanced kidney cancer and metastatic melanoma either as a single drug or in combination with chemotherapy or with other cytokines such as interferon-alfa. It is also being studied for use as an adjuvant along with some vaccines.
Other interleukins, such as IL-7, IL-12, and IL-21 are now being studied for use against cancer too, both as adjuvants and as stand-alone agents.

Interferons
IFN-alfa is a cytokine used to treat cancer. It boosts the ability of certain immune cells to attack cancer cells. It may also slow the growth of cancer cells directly as well as the blood vessels that tumors need to grow. The FDA has approved IFN-alfa for use against various cancers.

G-CSF and GM-CSF
These cytokines that causes the bone marrow to make immune and blood cells, thereby reducing the risk of infection in patients receiving chemotherapy. These are also being tested against cancer as a non-specific immunotherapy and as an adjuvant given with other types of immunotherapy. Clinical trials of these cytokines, alone or with other immunotherapy, are under way for different various cancers.

Some other drugs such as thalidomide, lenalidomide, imiquimod and levamisole also boost the immune system in a non-specific way, similar to cytokines.

Other ways to boost the immune system
Some other forms of immunotherapy are being studied to boost the specific parts of the immune system. These types of treatments have shown promise, but they could be very complex in operation. Following approaches are being studied.

Lymphokine-activated killer cell therapy
Scientists can make large numbers of active, cancer-fighting T cells in the lab by treating a small number of a patient's T cells in a test tube with the IL-2. After being returned to a patient's bloodstream, these special cells, now called lymphokine-activated killer cells (LAK cells), are more effective against cancer cells. Researchers are now testing several ways to use these very active cancer-fighting cells.

LAK cell therapy has shown promising results in animal studies, where it shrunk tumors in animals with lung, liver, and other cancers. Although clinical trials in humans have not yet been as successful, researchers are constantly improving LAK cell techniques. They are testing these newly improved methods against melanoma, brain tumors, and other cancers.

Tumor-infiltrating lymphocyte therapy
Researchers have found immune system cells deep inside some tumors and have named these cells tumor-infiltrating lymphocytes (TILs). These cells can be removed from tumor samples taken from patients and made to multiply in the lab by treating them with IL-2. When injected back into the patient, these cells can be active cancer fighters.

Treatments using TILs are being tested in clinical trials in people with melanoma, kidney cancer, ovarian, and other cancers. Early studies of this approach have been promising, but its use may be limited because clinicians may not be able to get TILs from all patients.

Dendritic cell-based cryo-immunotherapy
The cryo treatment damage the tunor which liberates the antigen and follows with an injection of millions of the patient's own dendritic cells into the gland which may allow dendritic cells to capture the released tumor antigens and present the antigen alongwith MHC-I to activate cytotoxic T cells which in turn attack tumor cells.

Hopes for the future
Since, the treatment of cancer is still an unmet clinical need of humanity, it is a big challenge to have control over it. The scientists are very hopeful about the future of cancer therapies using various technology platforms that remain a very dynamic area of research. There are many clinical trials under way today that could hopefully lead to better treatments for many types of cancer.