Targeted Immune Therapy:

This edition of the LifeTrac Trend Report highlights the history, current state, and future development of cancer therapies and treatments. The rising incidence rate of cancer (and other chronic diseases) due to an aging population has led to the Precision Medicine Initiative, a government-funded research initiative approved in 2015 to develop “the right drug for the right person at the right dose.” Advances in genomics, molecular tools, and information technology have provided much insight into the biological differences that exist between diseases and disease states, and how those differences manifest on population and individual levels. Researchers now have enough evidence to develop “targeted” therapies that take advantage of those molecular and genetic differences. Targeted therapies have the potential to reduce the use of more traditional cancer therapies that are known to have serious adverse side effects. Please continue reading to learn more!

A Brief Primer on Lymphocytes and Cancer

Major cell types of the immune system play a significant role in cellular development, activation, recognition, and destruction. Understanding the foundations of immunology helps case managers and patients stay well-informed about current and up-and-coming cancer therapies.

mAbs and ibs: What’s in a name?

Monoclonal antibody (“mAb”) and small molecule inhibitor (“ib”) drugs are widely used to treat many cancers and immune disorders. Using examples, this article briefly addresses the naming convention of these drugs, common indications/diseases that they treat, their mechanisms of action within the human body, and how monoclonal antibodies and small molecule inhibitors differ from each other.

Disease-Targeted Cancer Therapy Using Genetic Modification: CAR T-cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is one type of targeted immune therapy that is gaining much attention in the field of oncology due to the therapy’s high level of specificity. The therapy is designed to help the immune system differentiate between cancerous cells and non-cancerous cells. This article briefly describes how a CAR T-cell is created, how CAR signaling works, what the pros and cons of CAR T-cell therapy are, and a future outlook of where research into CAR T-cell therapy might lead us.

A Brief Primer on Lymphocytes and Cancer

Basics of Immune Cells

Lymphocytes (white blood cells) play an important role in oncology because they are an integral part of our immune systems. They can also be the source of cancer (e.g. B-cell malignancies) and cause of disease (e.g. autoimmune disorders). All lymphocytes are derived from stem cells in bone marrow, but different subtypes will mature in different stages and locations in the body. It is important to study their mechanisms of action to develop better targeted therapies. The lymphocytes listed below play important roles in tumor recognition.

- **Dendritic cells** are found in tissues with contact to the outside environment, such as respiratory and digestive mucosa, and are able to “capture” foreign particles (antigens), digest them into smaller parts, and present them to **T- and B-cells**. This causes the T- and B-cells to become immunologically activated, which is why dendritic cells are also called antigen-presenting cells (APCs) or accessory cells. In this way, dendritic cells initiate and coordinate both innate and adaptive immune responses.

- **T-cells** mature in the thymus and are responsible for cellular-mediated immunity. Once activated by an APC, Helper T-cells (CD4) will then replicate themselves and the specific antigenic message they carry. They will transmit that specific message to resting macrophages, B-cells, and cytotoxic T-cells (CD8) in order to activate them. Activated cytotoxic T-cells are responsible for secreting cytotoxins at the target site to induce programmed cell death. Helper T-cells can also “license” cytotoxic T-cells to activate other resting cytotoxic T-cells; this is a form of cellular immune memory and allows for a quicker response to repeated exposures of the antigen.

- **B-cells** mature in the bone marrow and peripheral blood and are involved in antibody-mediated immune responses. These cells provide long-term memory for the immune system and can rapidly recreate a response to a specific antigen. When this cell line becomes malignant, it is responsible for the B-cell malignancies such as chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, Hodgkin’s and non-Hodgkin lymphomas, follicular lymphoma and others. B-cells can also produce disease through production of autoantibodies against one’s own cells. Examples of these diseases are systemic lupus erythematosus, scleroderma, multiple sclerosis, rheumatoid arthritis and type 1 diabetes.

- **Natural Killer (NK) Cells** have cytotoxicity, but are not part of the T-cell group of lymphocytes. Their role is to recognize and rapidly respond to tumor formation and virally infected cells. However, they do not depend on the development of antibodies for their actions, but can enhance the antibody-dependent actions of other immune cells and recognize antibody-flagged foreign cells that have been primed for destruction. They are part of the innate immune system and do not need prior exposure to antigens for their activity against foreign cells. They produce various proteins and cytokines, like tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ), which promote cytotoxic effects on tumor and virally infected cells. It is important to note that NK cells also play a role in organ/graft rejection.
A Brief Primer on Lymphocytes and Cancer (con’t)

Cancer Research

The relationship of these cells in protecting the body from infections and cancers and responding to malignancies is becoming better defined each day. Cancer cells are technically ‘self-cells’ and have evolved mechanisms to evade the immune system. Many of these mechanisms help the cancer grow unchecked, develop new blood vessels, or reduce their natural cell death rate.

These “protections” by cancer cells have become the subject of intense research which has led to the development of therapies to “target” specific receptors, cellular processes and the modulators needed by the cancer to survive. Since a variety of mechanisms are involved by the cancer cells that reduce the immune response and downregulate the T-cell response, an “immune-suppressive state” exists, which allows the tumor to continue to grow unregulated.

Hematopoietic stem cell transplantation has become a mainstay of therapy for many cancers. Such transplants depend on the depletion of the B-cells with radiation and chemotherapy prior to transplant and then, an effective engraftment of the transplanted stem cells in order to succeed in establishing a functional immune system.

In essence, the goal of target-cell therapy is to make the T-cells more effective in recognizing the tumor. This so-called “targeted therapy” has rapidly expanded as scientists decode the genetic and molecular makeup of cancer cells and how they evade recognition and destruction by the body’s immune system. Treatments can now be targeted to certain molecules or receptors that are only found on specific cancer cells. Targeted drugs help turn on or off the receptors that are responsible for the survival strategies of cancer cells.

mAbs and ibs: What’s in a name?

Recently there has been an explosion of targeted drugs directed against various cancers and inflammatory conditions. In addition to cancer treatments, some of these drugs have been developed to prevent platelet aggregation and clotting, treat sepsis or serious viral infections, treat diseases such as Alzheimer’s and prevent solid organ rejection. These drugs are being studied under clinical trials to better understand their efficacy and how they should be incorporated into current standard of care protocols. Treatment options for cancer have rapidly expanded as scientists decode the genetic make-up of cancer cells and identify the molecular strategies the cells use to avoid recognition and destruction by the body’s immune system. Treatments can now be targeted to certain molecules or receptors that are associated with specific cancer cells.

Targeted drugs regulate cellular processes responsible for the survival of cancer cells, such as the development of new blood vessels for continued growth, or reduction in natural cell death rate. These drugs are developed to target cellular pathways that lead to cancer and other immune disorders, and their names are often clues to their origin or development. One can tell a drug’s class and its molecular structure by its chemical name. The generic name is given to a drug when it is approved by the FDA and is often a shorthand version of the chemical name. It can be daunting to remember the full generic name of most drugs, but it is helpful to keep in mind a few rules of drug nomenclature – especially in the field of oncology.1

“-mab” drugs

“-mab” drugs are monoclonal antibodies that have been developed from single lineage of cloned immune cells so that only one specific substance (the antigen) is targeted. This allows the “-mab” drug to more effectively recognize a particular cell type or molecule (the antigen) and deliver its targeted effect.2 Additions to the suffix “-mab” provide further indications of the drug’s origin.

For example, “-ximab” drugs are chimeric monoclonal antibodies that have been modified via a technique that links two or more antibodies together, typically of both mouse and human origins. Infliximab (Remicade) is one example of a “-ximab” drug where the monoclonal antibody binds to an inflammatory molecule, like tumor necrosis factor alpha (TNF-α), and prevents it from initiating an autoimmune response. Rituximab (Rituxan) is another example of a “-ximab” drug, but its mechanism of action causes B-lymphocytes to lyse (burst) and is effective in treating non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). Rituximab is also used in combination with methotrexate to treat certain types of inflammatory conditions that do not adequately respond to infliximab or other anti-TNF drugs.3 These types of drugs have been approved for a number of autoimmune and inflammatory conditions, like rheumatoid arthritis, Crohn’s disease, psoriasis, etc.4

Techniques have been developed to fully or partially “humanize” monoclonal antibodies in order to eliminate some of the adverse side effects caused by mouse cells. These techniques have resulted in a drug class name ending with the suffix “-umab” and “-zumab,” which respectively denotes a “-mab” drug of fully human origin and of partial human or “humanized” origin.5 An example of an “-umab” drug is adalimumab (Humira), which has similar anti-TNF effects to aforementioned infliximab. An example of a “-zumab” drug is elotuzumab (Empliciti), which is designed to enhance natural killer (NK) cell activity and is the first drug proven effective for relapsed multiple myeloma.6

Monoclonal antibody drugs number in the hundreds and are used or being further studied to treat many types of cancer and diseases.

References:

mAbs and ibs: What’s in a name? (con’t)

“-ib” Drugs

“-ib” drugs are small molecule inhibitors that block the actions of enzymes. A subclass of “-ib” drugs are tyrosine kinase inhibitors (TKIs), denoted by the suffix “-tinib,” that specifically block tyrosine kinase enzymes. Tyrosine kinases are an integral part of many cell functions, including cell signaling, growth, and division. In some types of cancer cells, these enzymes may be over-active or found in higher concentrations. The main enzymatic mechanism of tyrosine kinases is to facilitate phosphorylation, which is the transfer of a phosphate group from adenosine triphosphate (ATP) to the substrate or target molecule to be activated. TKIs are designed to block phosphorylation, thus inhibiting further cell functions. Imatinib (Gleevec) is a commonly used TKI that is effective against progression of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs). Other “-ib” drugs target specific enzymes and exhibit different inhibitory effects.

Like “-mab” drugs, research and trials continue to uncover and refine uses for the “-ib” class of drugs. Small molecule “-ib” drugs are capable of passing through the blood brain barrier and cellular membranes, while larger “-mab” drugs cannot. This means that “-ib” drugs can target any molecule, regardless of cellular location. But “-ib” drugs are highly specific and bind tightly to secreted molecules or molecules expressed on cell surfaces, and for this reason, they have shown great effectiveness against circulating cancer cells such as blood disorders and cancers.9

Summary

Both classes of drugs (“-mab” and “-ib”) can target the same molecules, albeit through different mechanisms of action. The “-mab” drugs are monoclonal antibodies that target specific antigens, while the “-ib” drugs are inhibitors that interfere with the actions of enzymes. The former helps the immune system recognize and destroy cancer cells, while the latter helps stop further growth of cancer cells. These targeted drugs, and even newer immune-modulating ones, will continue to undergo trials to better refine their clinical roles, timing and sequencing with cytotoxic chemotherapy, and for use in adjunct therapies related to hematopoietic stem cell transplant.

Disease-Targeted Cancer Therapy Using Genetic Modification: CAR T-cell Therapy

It has long been recognized that if immune cells could be modified to recognize a tumor as foreign, they could then be effective against tumors. Over the past 20 years, several types of immune cell therapies have been developed which utilize the various cell types and their roles in immune response. It is the reversal or unbundling of this immune-suppressive state that has been the focus of much research and recent breakthrough results in clinical trials.

A recent approach to genetically modify the T-cells of cancer patients is demonstrating significant clinical results. This approach adds “chimeric antigen receptors” (CARs) to the T-cell surface.21 These cellular and genetic modifications create chimeric antigen receptor T-cells, or CAR T-cells, which can reproduce with the new proteins attached to their surface. These receptors enhance recognition of tumor cells as foreign and can then attach to the cancer cells directly.

While the initial work with chimeric antigen receptors was disappointing due to limited activity against tumors11, newer generations of CAR T-cells (“2nd and 3rd generation” CAR T-cells) have the addition of multiple internal co-stimulatory molecules which activate the T-cell to become more cytotoxic to the cancer cells.12 It is these next-generation cell modifications that are beginning to demonstrate dramatic results in clinical trials. While none of these therapies have gained FDA approval yet, the results are creating much excitement in hematology and oncology circles.

CAR T-Cell Therapy and B Cell Cancers

One of the best examples of CAR T-cell therapy is with B-cell cancers. The CD19 protein on the surface of B-cells is one of the most exciting targets of this type of therapy, and early research success is cause for oncologists to rethink standard of care protocols for these malignancies. It is well recognized that the CD19 protein is specific only to B-cells,13 which makes it an attractive target antigen for CAR T-cell targeted therapy. The greater the specificity between the antigen and the engineered CAR T-cell receptor, the fewer the side effects from “off-target” interactions.

A CAR T-cell is created by extracting the patient’s T-cells through leukopheresis and cell sorting and then genetically modifying those T-cells to express a receptor specific to an antigen. The engineered cells are then grown in culture to expand the number of cells into a living drug that can be re-infused into the patient. Thus, a new weapon is created to attack the cancer cells with the patient’s own lymphocytes. The 2nd and 3rd generation modifications to the T-cell seem to allow for superior proliferation and persistence after re-infusion into the patient and are producing some of the exciting results.14 This creates the potential for a memory T-cell line that can provide long-term immunity against the cancer cell and thus protection from future relapses.

The advantage of CAR T-cells is that they directly combine the antigen-binding site of antibodies with the T-cell activating machinery necessary to produce an immune response. This means that the structure and functionality of CARs are engineered to traverse the cell membrane, with the antigen-binding antibody region on the outside of the cell and the T-cell activating machinery on the inside of the cell. Combining these two, typically independent, mechanisms into one structure allows for a quick and highly specific immune response and removes the barrier of requiring a major histocompatibility complex (MHC) linkage molecule between the T-cell and the antibody-flagged target.

**Side Effects and Treatment Risks**

While there is no risk of a graft-vs-host reaction, there are some risks of the infusion for the patient. These risks require close monitoring of the patient during and after the infusion.

**Cytokine-release syndrome and tumor lysis syndrome:** Due to the potent nature of these cells against the tumor and the rapid destruction of the tumor cells, the release of their internal cytokines and other products of cell destruction can result in fevers, rigors, nausea, diarrhea and hypotension. This is a common reaction to the infusion of the CAR T-cells as they attack the tumor and occurs in nearly all patients. The severity of the reaction is related to the overall tumor burden (i.e., number of tumor cells, size of tumor and amount of cancer in the body) at the time of infusion. These patients can also develop renal and pulmonary insufficiency and altered mental status. Managing these side effects is a standard practice for oncologists already. However, new treatments are emerging to treat cytokine-release syndrome with other targeted therapies that block the cytokine effects.

**B-cell aplasia:** Since the CD19 protein is expressed on normal B-cells as well as cancerous B-cells, infused CAR T-cells engineered to bind to CD19 will affect both normal and cancerous B-cells. This results in a B-cell depletion, or aplasia, as a complication. This is an accepted side effect of the treatment and is a marker for a successful CAR T-cell treatment, as it indicates on-going surveillance and activity against B-cells. The patient may need periodic infusions with immunoglobulin to help provide immunity against infections.

**Off-tumor reactivity:** The modified CAR T-cells may sometimes develop reactivity to other cells of the body with the same or similar protein receptors in addition to the targeted cells of the tumor. The best studied antigen is the CD19 antigen, but as other cellular antigens for other tumors are developed and tried; the modifications might allow the cells to react to the person’s own cells with similar receptors. The cells might be cardiac cells, lung tissue or brain cells. Thus, the CAR T-cell is specific to the tumor antigen (“on-target”) but also acts against other cells that may not have been identified at the time with the same antigen (“off target”). Strategies to combat this side effect are to identify and link two different tumor antigens to the T-cells, thus making the likelihood of cross-reactivity much less likely.

---


---

**Role of pharmaceutical companies:**

The cost and complexity for these individualized treatments is very high. Specialized labs and research facilities are the only centers that have the capacity to utilize this type of therapy at this time. Pharmaceutical companies are investing huge amounts of capital and resources into these therapies to help develop their potential. As a result, many research organizations and centers have entered into agreements with pharmaceutical companies to maximize their financial resources dedicated to research and rapidly advance clinical trials and treatments.