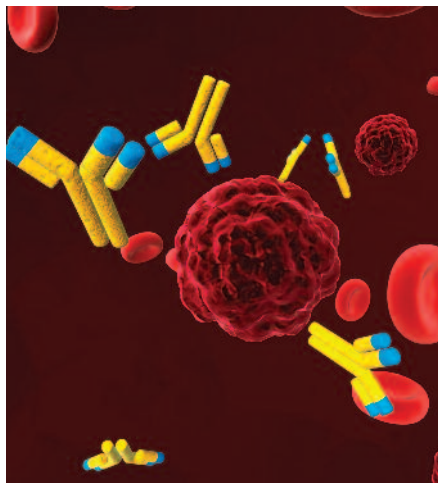
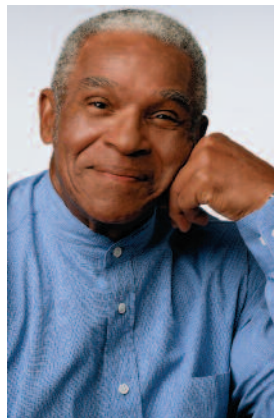


Targeted Therapies in Cancer



Research Advocacy Network

Advancing Patient-Focused Research



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Chapter 1: Introduction to Targeted Therapies

Imagine that you are driving down the road one Saturday afternoon when your car begins to make a knocking noise. You know, of course, that something is wrong so you take your car to the mechanic before the noise gets worse and develops into a potentially dangerous problem. The mechanic says that something is wrong with the engine, but he can't figure out what it is. Your best hope is to have the engine completely replaced, which will likely fix the problem. Clearly, replacement of the entire engine is not optimal. You would prefer that the mechanic identify the one part within the engine that is causing the problem and fix just that, saving you the cost and avoiding replacement of engine parts that are working fine.

This automobile problem illustrates the difference between traditional therapies and targeted therapies. Like the complete engine replacement, traditional drug therapies—known as chemotherapies in cancer—attack the problem in a relatively non-specific way. They may fix the problem, but they also act on many parts of the body that aren't "broken" or that aren't affected by cancer. In contrast, targeted therapies are more specific. They home in on a precise feature of cells or cell pathways that are causing the problem.

Just as the mechanic in our example would like to fix only the specific part of the engine that is broken, physicians would like to prescribe a treatment that affects only cancerous cells. In order to develop such treatments, we first need to understand how cancerous cells differ from normal cells and then capitalize on that knowledge with the development of selective drugs or other therapies.

In this guide, we explore how progress in laboratory research and clinical trials involving humans has led to the development of drugs that are relatively good at seeking out cancerous cells and ignoring healthy cells. We first consider the differences between targeted and traditional therapies for cancer, and then the targets of targeted therapies. Next, we discuss several major categories of targeted therapies. We then describe examples of targeted therapies that are available today and the strategies and methods being used to develop targeted therapies for tomorrow. Targeted therapies are not without challenges, however, and we consider some issues related to the development and clinical use of these drugs. We then explore the future of targeted therapies, including the ultimate goal of matching each patient with the therapy that is best suited to him or her. Finally, we discuss what this information means for advocates and how it can be used to further the goal of providing cancer patients with the best treatment possible.

Traditional Therapies vs. Targeted Therapies in Cancer

For the past half a century, non-surgical cancer treatment has been dominated by two main types of traditional therapies: chemotherapy and radiation therapy. Chemotherapy refers to treatment with drugs that have the potential to kill cancer cells. Radiation therapy refers to the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Targeted therapies are often described in terms of how they differ from traditional therapies such as chemotherapy and radiation therapy. For this reason, we first consider chemotherapy and radiation therapy and then define targeted therapies.

Chemotherapy refers to treatment with drugs that have the potential to kill cancer cells.

Radiation therapy refers to the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors.

Hormone therapies for breast cancer are an exception to the statement that older therapies are non-specific therapies that kill cells. These treatments have been in clinical use for more than 30 years and have been called the first targeted therapies because they act on a specific protein that breast cancer cells use to grow. We will talk more about targeted therapies in Chapter 2 (What Are Targeted Therapies?).

Cancer Chemotherapies

Chemotherapies capitalize on the fact that cancer cells continuously replicate themselves. Like normal cells, cancer cells replicate themselves and proliferate by copying their DNA. Several important classes of cancer chemotherapies are listed in the following table along with their mechanisms of action—the way they act to treat cancer. Although the different classes of chemotherapies may act at different stages of the DNA replication process, the important thing to note is that they all interfere with DNA replication. However, because DNA replication is a common process that all cells use when they want to make more copies of themselves, chemotherapies cannot distinguish between cancerous cells that are being replicated and normal cells that are being replicated. Thus, classic chemotherapy has many side effects because it also tends to kill normal cells that are undergoing replication.

To learn more about DNA replication, you may want to visit the following Web sites:

- Scitable by Nature Education: <http://www.nature.com/scitable/topicpage/mitosis-14046258>
- Genetics Home Reference from National Institutes of Health: <http://ghr.nlm.nih.gov/handbook/howgeneswork/cellsdivide>
- Gene Ed from National Institutes of Health: http://geneed.nlm.nih.gov/topic_subtopic.php?tid=1&sid=2
- Howard Hughes Medical Institute DNA Biointeractive: <http://www.hhmi.org/biointeractive/dna/index.html>

Cell proliferation refers to an increase in the number of cells as a result of cell growth and cell division, which involves replicating its DNA.

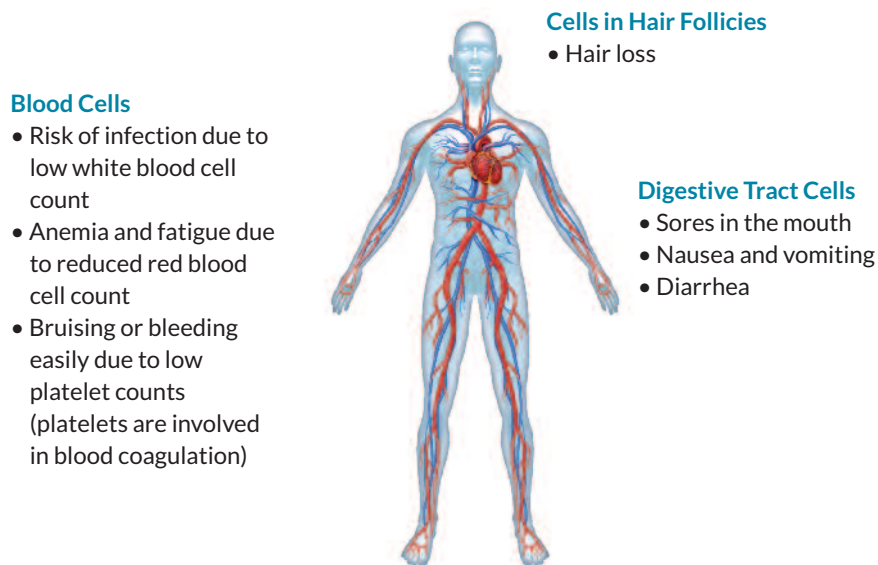
A drug's **mechanism of action** is the method by which it exerts its therapeutic activity.

COMMON CLASSES OF CANCER CHEMOTHERAPIES

| Class of Chemotherapy | Mechanism of Action | Examples of Specific Drugs |
|---|---|--|
| Alkylating agents | Put chemical groups (“alkyl” groups) on DNA causing DNA to break, pair abnormally, or cross link, thus preventing the cell from dividing | Busulfan Cisplatin Cyclophosphamide Melphalan |
| Inhibitors of DNA Replication; also called Antimetabolites | Disrupt DNA replication; some replace natural components of DNA, essentially tricking the cell so that it cannot perform the functions it needs to live and replicate | Fluorouracil Gemcitabine Methotrexate |
| Mitotic Inhibitors <i>Can be further subdivided into taxanes (docetaxel, paclitaxel) and vinca alkyloids (vinblastine, vincristine)</i> | Inhibit cell division by binding to proteins needed for cell division | Docetaxel Paclitaxel Vinblastine Vincristine |
| Antitumor antibiotics Many of these drugs are also classified as anthracyclines (doxorubicin, epirubicin, mitoxantrone [an anthracycline analog]) | Prevent cell division by binding to DNA or inhibiting RNA | Doxorubicin Epirubicin Mitoxantrone Bleomycin |
| Topoisomerase inhibitors | Inhibit an enzyme (topoisomerase) needed for cell division | Topotecan Irinotecan |

If chemotherapies are not specific for cancerous cells, why don't they kill all the cells in our bodies? The answer is that most of our cell populations do not continuously replicate themselves as cancer cells do. For the most part, our organs such as the brain, heart, kidneys, and liver are already formed. Certain cells in these organs can and do replicate, but they do not replicate out of control like cancer cells. Because these cell types are not undergoing repeated, rapid cell division, they are generally not bothered by chemotherapies. Additionally, normal tissues can repair themselves and continue to grow; thus, even if they are injured by chemotherapy, the effects are rarely permanent.

However, not all of our cells escape the effects of chemotherapies. Some normal cell types do continuously replicate and, as you may have guessed, these cell types are susceptible to the effects of chemotherapies. The fast-growing normal cells most often affected by chemotherapy are blood cells in the bone marrow, cells lining the digestive tract (such as the mouth, esophagus, and stomach), and cells in hair follicles. Chemotherapy can also cause side effects by interfering with processes other than cell replication—nausea and vomiting are examples of this. The effects of chemotherapy on these cell types lead to some of the most common side effects, as shown in the following graphic.



Some common side effects of chemotherapy

Radiation Therapy

Radiation therapy for cancer kills cells by breaking apart chemicals in the radiated cells and causing reactions that damage the cells. Radiation therapy damages DNA, which prevents cells from replicating. Radiation therapy is typically administered by directing a beam of high energy x-rays at the site of the cancer. Today's radiation therapy is highly accurate and does not typically cause the severe skin damage seen in years past. However, like chemotherapy, radiation therapy targets both healthy tissue and cancerous tissue.

Radiation therapy is also called radiotherapy.

In order to minimize the effects of radiation therapy on healthy tissue, the area of radiation is carefully mapped out to avoid vital organs and as much normal tissue as possible. However, even with careful planning side effects can and do occur. Fatigue is one of the most common side effects of radiation therapy, increasing over the course of treatment and lasting weeks or months after therapy ends. Nausea and occasionally vomiting are also common side effects. Other side effects can occur depending on the part of the body receiving the radiation; for example, radiation therapy to the head can result in hair loss and radiation therapy to the chest can cause difficulty swallowing and shortness of breath.

Ideally, we would have treatments for cancer that effectively kill only the diseased cells without harming healthy cells, even those that replicate quickly. Basic science research has led to a greater understanding of how cells work and what goes awry in cancer. As a result of this work, investigators have developed a growing list of drugs that are better able to “target” specific features of cancer cells while minimizing effects on healthy cells. These treatments have come to be known as targeted therapies.

What Are Targeted Therapies?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with molecules that are more specifically involved in cancer cell growth and progression than in normal cell activity. These drugs act on cell markers and/or pathways to prevent cells from replicating or proliferating. Targeted therapies are also sometimes called molecularly targeted therapies or drugs.

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in cell growth and cancer progression.

In biology and medicine, the term “molecular” refers to genes, proteins, and other cellular molecules. A **molecule** is defined as the smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms. Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms.

The goal of targeted therapies is to rid the body of cancerous cells while leaving normal cells unharmed. By focusing on changes in the cell that are specific to cancer, targeted cancer therapies may be more effective than chemotherapy and radiotherapy. Their specific actions may also make targeted therapies less harmful to normal cells than chemotherapy and radiotherapy. However, it is important to note that we have not yet reached the ultimate goal of devising targeted therapies that are completely specific for cancerous cells. Inevitably, some normal cells are still affected by targeted therapies and these drugs still have side effects.

The rest of this booklet considers targeted therapies in more detail, beginning with a discussion of the targets of targeted therapies in Chapter 2.

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Chapter 2: What Are the Targets of Targeted Therapies?

Sarah and Leandra first met in the waiting room of their oncologist's office and they became fast friends, perhaps because they had both just been diagnosed with breast cancer. Both were women in their 50's, had children, and were otherwise healthy. As they communicated over the coming months, it became evident that their doctor had prescribed one drug for Sarah and a different one for Leandra. Given their similarities, Sarah and Leandra wondered why this was the case.

Today, one of the major reasons that different patients receive different cancer treatments is because not all cancers are the same, even if they affect the same organ—in this case, the breast. Analysis of the cancerous tissue from these two women may have indicated that Sarah's tissue had a certain biomarker that Leandra's tissue did not. A drug targeted at the biomarker would be expected to treat Sarah's cancer but not Leandra's cancer.

As defined in Chapter 1, targeted therapies are drugs that act on cell markers (biomarkers) and/or pathways to prevent cells from replicating or proliferating. In this chapter, we explore biomarkers and cell pathways in more detail in an attempt to understand exactly where targeted therapies act and why these cellular biochemicals might be good targets.

Biomarkers

Biomarkers have been defined as anatomic, physiologic, biochemical, or molecular parameters associated with the presence and severity of specific disease states. This definition is a broad one that takes into account the many different forms that biomarkers may take today and in the future. However, in the context of targeted therapies for cancer, biomarkers usually refer to biochemicals or molecules in or on cancer cells. These biomarkers are usually genes or proteins. For a more detailed consideration of the different types of biomarkers and some examples of each, you may want to consult document entitled *Biomarkers in Cancer* available for download from the Research Advocacy Network Web site (www.researchadvocacy.org).

Biomarkers have been defined as anatomic, physiologic, biochemical, or molecular parameters associated with the presence and severity of specific disease states.

It is important here to distinguish between biomarkers with different uses. When talking about biomarkers in general, several potential uses can be described as shown in the following table.

USES OF BIOMARKERS IN CANCER

| Use of Biomarker | Description |
|------------------|---|
| Risk assessment | To help a person determine how likely he or she is to develop cancer; can be used to help decide whether a person should undergo more intensive screening or take preventive measures |
| Screening | To help identify cancer at an earlier stage than would have happened without the test |
| Diagnostic | To help diagnose a cancer, perhaps before it is detectable by conventional methods |
| Prognostic | To forecast how aggressive the disease process is and/or how a patient can expect to fare in the absence of therapy |
| Predictive | To help identify which patients will respond to which drugs |
| Monitoring | To determine how a patient is doing over time, either on or off therapy |

Biomarkers used as targets for drug therapies fall into the category of predictive biomarkers. However, not all predictive biomarkers are targets for medical therapy. For example, tumors produce many types of proteins. Some of the proteins may be involved in the cancer process, whereas others may be by-products. Both proteins may help predict which patients will or will not respond to a certain treatment. However, drugs that target the by-product may not actually treat the cancer, whereas drugs that target the protein involved in the cancer process may treat the cancer.

The other uses of biomarkers listed in the table are also important, but are not considered in this booklet because the focus here is on therapies. For more information about the different types of biomarkers, you may want to download the booklet entitled *Biomarkers in Cancer*, available at the Research Advocacy Network Web site (www.researchadvocacy.org).

USES OF BIOMARKERS IN CANCER MEDICINE

| Prior to Cancer | Diagnosis | After Cancer Diagnosis | | | Post Treatment | |
|------------------------------------|--|---|--------------------------------------|---|--|---------------------------|
| Risk Assessment | Diagnosis | Prognosis | Predicting Treatment Response | Pharmacokinetics | Monitoring Treatment Response | Recurrence |
| Am I at increased risk for cancer? | Do I have cancer? What type of cancer do I have? | What is the expected course of my cancer? | Will my cancer respond to this drug? | Should I receive a normal or lower dose or no dose? | How is my cancer responding to this treatment? | Will my cancer come back? |

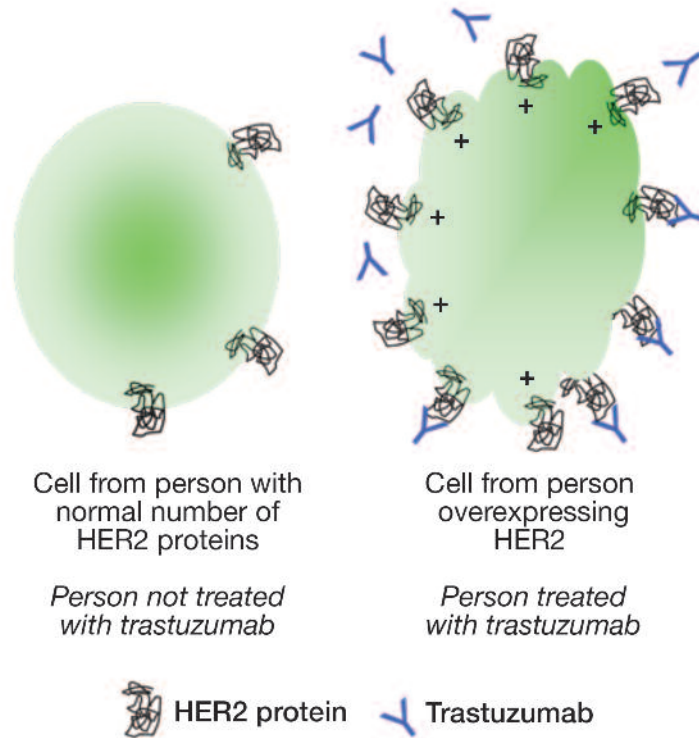
EXAMPLES OF SOME BIOMARKERS

| Biomarker | Type | Condition |
|---------------------------------|-----------------------|--|
| C reactive protein | Molecular/biochemical | Inflammation |
| High cholesterol | Molecular/biochemical | Cardiovascular disease |
| S100 protein | Molecular/biochemical | Melanoma |
| HER-2/neu gene | Molecular/biochemical | Breast cancer |
| BRCA genes | Molecular/biochemical | Breast and ovarian cancers |
| Prostate Specific Antigen (PSA) | Molecular/biochemical | Prostate cancer |
| CA-125 | Molecular/biochemical | Ovarian cancer |
| Cerebral blood flow | Physiologic | Alzheimer disease, stroke, schizophrenia |
| High body temperature | Physiologic | Infection |
| Size of brain structures | Anatomic | Huntington disease |

An example of a targeted cancer therapy directed at a biomarker is trastuzumab (Herceptin®). This drug is directed against a protein known as HER2, which stands for human epidermal growth factor receptor 2. Approximately one sixth of all breast cancers have too many copies of the HER2/neu gene, which go on to produce too much HER2 protein. This protein participates in a pathway that causes breast cancers to grow and divide more quickly. Blocking the HER2 protein with trastuzumab can reduce cell division in cancer cells that have too much HER2 protein and, in this way, can help treat breast cancer.

In biology, **overexpression** means to make too many copies of a protein or other substance.

Overexpression of the HER2/neu gene is not only used as a predictive biomarker, but also as a prognostic biomarker whose presence indicates a more aggressive cancer. This example illustrates that a biomarker may have more than one use.



Example of a therapy targeted against a biomarker: trastuzumab. The graphic on the left shows a cell from a person with a normal number of HER2 proteins (squiggly black lines) and a person whose cells overexpress HER2 (right). The person on the left has not been treated with trastuzumab, whereas the person on the right has been treated with trastuzumab. On the right, trastuzumab (“Y” shapes) has just been injected into the blood, where it travels to cells, binds to HER2 proteins, and helps prevent the cells from proliferating. HER2 also interacts with other signals coming into the cell to amplify their effects on growth—this action is shown in the graphic as “plus” signs.

Human epidermal growth factor receptors are expressed not only by certain breast cancer cells, but also by many types of normal cells in our bodies. Like the cancerous cells, the normal cells use these receptors to transmit information telling them to grow and proliferate. However, normal cells do not go overboard in their production of HER2 protein and thus cell growth and proliferation is controlled. Thus, HER2 protein is not a “bad” protein in and of itself. Instead, it is part of a normal cell process that is hijacked by cancer cells, permitting them to grow and proliferate out of control.

Receptors are molecules inside or on the surface of a cell that bind to specific substances and cause specific effects in the cell.

Cell Pathways

Although the signaling pathway in which HER2 participates is important in initiating cell growth and replication, it is not the only pathway through which these effects can occur. Growth, replication, and many other cellular processes are mediated by cell pathways—chains of events that involve many molecules and interactions that allow cells to communicate with their environment and with one another. Cell pathways are designed to provide information to the cell and they often influence some aspect of the cell’s behavior. Activation of cell pathways can alter a cell’s behavior by influencing whether certain genes are turned on (expressed) or off (suppressed). It can also influence a cell’s behavior by altering the levels of a key protein that regulates a critical cellular process.

Cell pathways are a little like traveling to Paris. There are many ways to get there—by boat or by plane, with parts of the trip taken by train or car. You may travel from Seattle to London first, or you may fly from Memphis to New York City to Paris. The different molecular players in the various cell pathways represent different ways of getting to the same destination, which can be compared with cell growth. For example, HER2 can be likened to the flight you take from Memphis to New York City. It represents

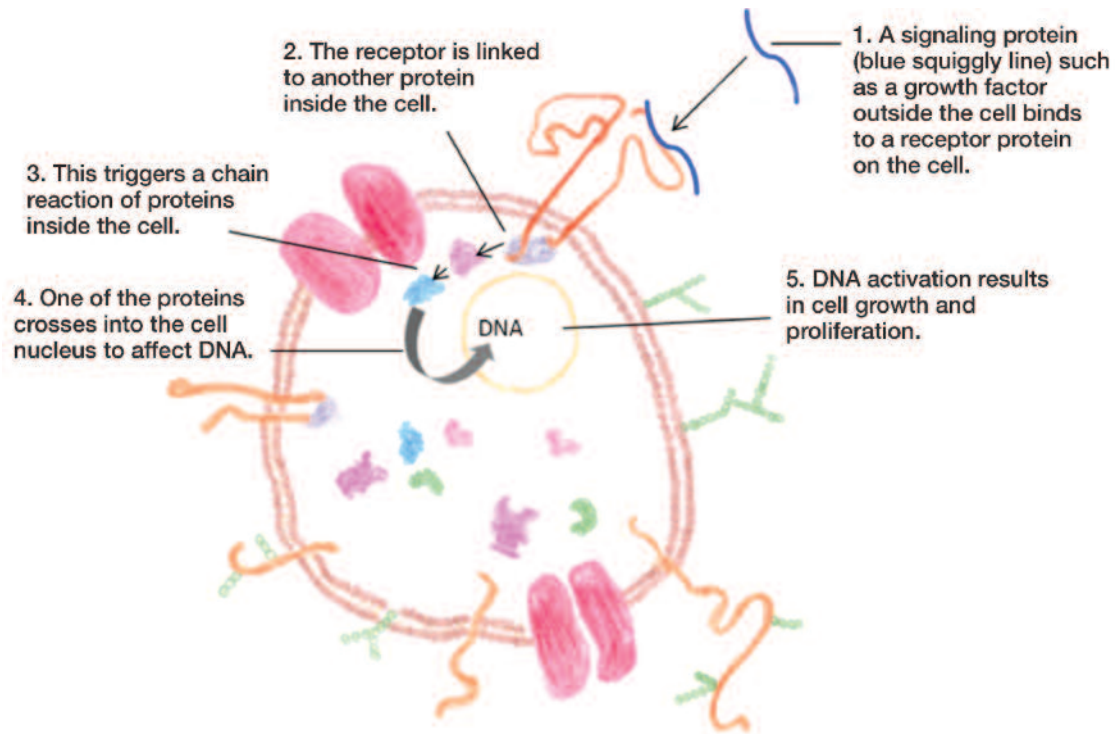
only part of your journey and is only one way to get there. However, once you get to Paris you can affect cell growth. Some ways of getting to Paris can turn off cell growth, whereas other can turn it on. Similarly, traveling to Madrid may represent another cell process such as replication. There are many cities and many ways of getting there, just as there are many cell processes and many pathways by which they can be affected.

Cell pathways are chains of events that involve many molecules and interactions that allow cells to communicate with their environment and with one another. They are sometimes referred to as cell signaling pathways or signal transduction pathways.

An example of how a pathway may influence gene expression is shown in the graphic on the next page.. Cells can release proteins that affect the behavior of other cells. These include proteins such as growth factors and hormones. Some of these proteins released into the space around cells bind to receptors in the cell membrane. These receptors are often proteins as well. Binding may cause a change in the receptor protein, such as a change in shape. This change may lead to the release of another protein that was bound to the receptor. The released protein may go on to interact with other cellular components, including other proteins. Some of the proteins may be chemically altered, which affects their behavior. Eventually, a protein that normally influences gene expression is activated or inactivated. The resulting change in gene expression may then change something important in the cell, such as causing it to proliferate.

A cell pathway is a little like a relay race in which one runner hands off the baton to the next runner. The baton represents the information that is being carried to the cell nucleus, such as “a growth factor bound to its receptor.” This information is passed from one runner – protein – to the next until it eventually reaches the finish line, represented by changes in gene expression in the cell nucleus. For excellent descriptions and visual representations of cancer pathways, you may want to visit the DNA Learning Center website called Inside Cancer sponsored by Cold Spring Harbor Laboratory (<http://www.insidecancer.org/>).

Although many biomarkers play roles in cell pathways, it is possible to have biomarkers that are not involved in pathways. Conversely, not all members of cell pathways are biomarkers.



Example of a cell pathway. Cells communicate with their environment and with one another in several different ways. One method of communication is for a cell to release chemicals that affect other cells. The chemicals that cells release are often proteins, which include growth factors and hormones. These chemicals bind to receptors, which may be located on the outside of cells. This binding initiates a series of events designed to affect some aspect of the cell. These events occur along multiple pathways and involve many different proteins and other chemicals inside the cell. The activation of these pathways often results in altered gene expression or protein metabolism. That is, the proteins involved in the pathways eventually carry information to the cell nucleus where genes are either activated or suppressed (inhibited). Alternatively, pathways may affect key proteins that regulate important aspects of cellular behavior such as survival and growth.

In our example, a growth factor binding to its receptor is the signal that activates the pathway responsible for growth and replication. By blocking this receptor, targeted therapies such as trastuzumab prevent activation of the growth pathway so that cancer cells cannot grow and replicate. Trastuzumab belongs to a class of targeted therapies known as monoclonal antibodies, which we consider in more detail in the next chapter.

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Chapter 3: Monoclonal Antibodies – One of the Major Classes of Targeted Therapies in Cancer

Throughout the latter part of the 19th Century, a German physician named Paul Ehrlich worked diligently in the area of immunology, attempting to develop treatments for a variety of human diseases. Dr. Ehrlich received the Nobel Prize in Physiology and Medicine in 1908, the capstone of a prolific career that included developing the first modern antibiotic, coining the term “chemotherapy,” and conducting essential research that would lead to the use of penicillin and sulfa drugs.

Dr. Ehrlich made two contributions that are particularly relevant for our discussion of monoclonal antibodies: first, that our immune system helps fight off cancer and second, that it should be possible to develop compounds specifically targeted against diseased cells. Decades later, scientists trying to develop such drugs faced a vexing problem. Normal immune cells produce different antibodies that are directed against multiple parts of a target. Some of these antibodies may be potent, while others may be weak. Additionally, some of these antibodies may bind to things other than the cancer. What was needed was a single cell that could produce a single type of antibody—a monoclonal antibody (from “mono” meaning one)—that could be selected for its potency and specificity. It was not until 1975 that researchers found out how to solve this problem, but the importance of their discovery was immediately recognized and the three pioneering scientists won the Nobel Prize in 1984.

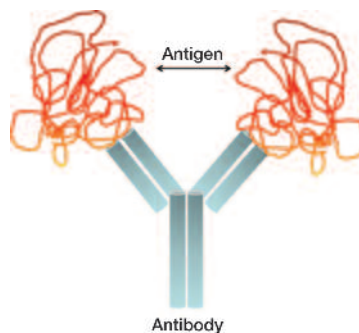
What Are Monoclonal Antibodies?

Monoclonal antibodies are proteins made in the laboratory that can bind to substances in the body, including components of cancer cells. Each type of monoclonal antibody is designed to bind to one substance. Monoclonal antibodies attach themselves to the substance (often a protein) on cancer cells, thereby blocking the signals for cell growth and proliferation. In some cases, the attachment of monoclonal antibodies to cancer cells leads to death of the cells. As large proteins, monoclonal antibodies cannot typically enter cells. For this reason, they usually bind to substances or parts of substances that are located on the cell surface or in areas outside cells such as in the liquid part of the blood.

Monoclonal antibodies are sometimes abbreviated as “mAbs”.

Structure and Binding of Antibodies

Antibodies are “Y”-shaped proteins that bind to substances known as antigens. Antigens are the substances that cause the immune system to develop antibodies. Each tip of the “Y” binds to a specific part of an antigen, so that the two fit together like a key in a lock. Different antibodies show differences in the tips of their “Y”s, which gives them specificity for their antigens.



Antigen binding to an antibody

Antibodies are proteins made by plasma cells (a type of white blood cell) in response to an antigen (a substance that causes the body to make a specific immune response).

Antigens are the substances that cause the immune system to develop antibodies. They are the substances to which antibodies bind.

How Are Monoclonal Antibodies Made?

Under normal conditions, our immune systems respond to the presence of foreign “invaders” such as bacteria, viruses, fungi, or unknown proteins by mounting an immune response. The goal of this immune response is to get rid of the invader. As part of this response, white blood cells known as plasma cells or plasma B cells may make antibodies. The antibodies made by normal plasma cells are not all the same. Although each antibody binds to a specific part of the antigen, different antibodies may bind to different parts. These antibodies are known as polyclonal antibodies.

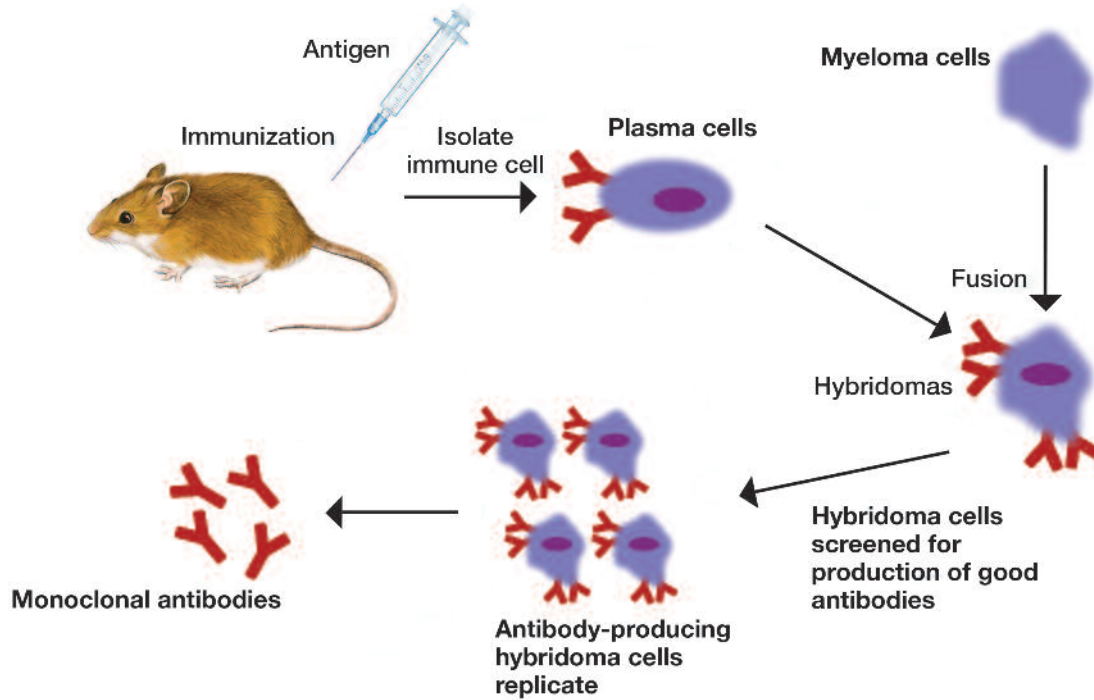
Polyclonal antibodies are not ideal treatments for several reasons. First, some of the polyclonal antibodies bind better to the antigen than others. Additionally, some antibodies may bind a little bit to healthy cells and proteins; this is not optimal because it can interfere with their normal activity. The goal for antibody treatment of cancers is to specifically target certain proteins involved in maintaining the cancer, while avoiding healthy cells. For this purpose, it is most useful to have a single type of antibody that binds tightly and specifically to cancer cells. This is the goal behind monoclonal antibodies. Monoclonal antibodies are antibodies that are identical because they are produced by one cell, or clones of a single parent cell.

Monoclonal antibodies are identical because they were produced by one type of immune cell, all clones of a single parent cell.

Polyclonal antibodies are derived from different cell lines.

A typical way to make monoclonal antibodies is to begin by injecting animals—usually mice—with the antigen. For example, if you wanted to generate monoclonal antibodies that would bind to the HER2 protein, you would inject that protein into mice. Just as humans sometimes need more than one injection to develop immunity against certain diseases, the mice need more than one injection of the antigen to develop plenty of antibodies.

In response to these injections, mice make many different types of antibodies against the antigen; in other words, they make polyclonal antibodies. In order to obtain just one type of antibody, spleen cells are collected from the animals. These spleen cells are kept alive and functioning in the laboratory and are a good source of antibodies. However, normal cells die after replicating a certain number of times. In order to keep the spleen cells alive, they are fused with cancerous cells such as myeloma cells, which can keep replicating themselves. Myeloma cells are cancerous plasma cells that form bone marrow tumors. These fused cells reproduce indefinitely in the laboratory, turning what is an undesirable property when in the body (unchecked replication) into a desirable property in the laboratory (indefinite replication means indefinite source of antibodies). The antibodies produced by these so-called “hybridoma” cells are then tested to identify those that are best at binding to the antigen.



Production of monoclonal antibodies. This graphic shows how monoclonal antibodies are produced. First, mice are injected with the antigen, which may be a growth factor receptor such as HER2 or another target that is an important biomarker for cancer cells. The plasma cells are isolated from the mouse's spleen and fused with cancerous plasma cells such as myeloma cells. The resulting cells are called hybridomas. The hybridoma cells are then screened to find those that produce the best antibodies—the antibodies that bind the best to the antigen. These cells are induced to make exact copies of themselves (cloned) to create a population of identical cells that make plenty of monoclonal antibodies.

Even after isolating the spleen cells and fusing them to the myeloma cells, there is still an important problem with the monoclonal antibodies produced by mice or other non-human species. When injected into humans, these monoclonal antibodies will be recognized as “non-self” foreign invaders, and attacked and eliminated by the immune system. In past years, some patients had severe reactions to these antibodies, experiencing rashes, joint swelling, kidney failure, and even death.

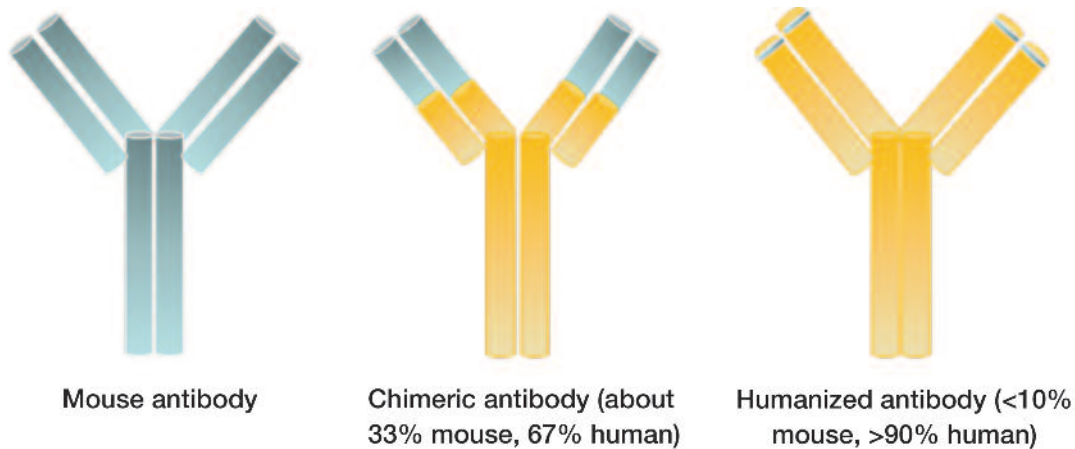
In order to keep these things from happening, one of two strategies is undertaken to replace part of the mouse protein with human protein. One strategy is to chimerize the antibodies. This means that the antigen-binding parts of the mouse antibody are combined with other parts of a human antibody. The word chimerize comes from the Greek mythological character, a chimera, which was an animal made up of parts from several different animals: a lion, serpent, and goat.

A chimera from Greek mythology. The creature is part lion, part serpent, and part goat.



The other strategy to reduce the immune response to mouse monoclonal antibodies is to humanize them. With this strategy, as many parts of the antibody as possible are replaced with human portions via genetic engineering. The basic idea in both of these strategies is to minimize the immune response to the antibody by making part of it human. Humanized antibodies have more human parts than chimerized antibodies, but both strategies are successfully used today.

Chimeric or humanized monoclonal antibodies are monoclonal antibodies that are part human and part another species, such as mouse or rat. Humanized antibodies contain a higher percentage of human parts than chimeric antibodies. The mouse or rat part of the antibody binds to the target antigen, and the human part makes it less likely to be destroyed by the body's immune system.



Comparison of chimerized and humanized antibodies. An antibody that is 100% mouse is shown in blue. Chimeric antibodies are about 33% mouse (blue) and 67% human (yellow). Humanized antibodies are less than 10% mouse (blue) and more than 90% human (yellow).

Scientists are now developing monoclonal antibodies that are completely human and do not contain any mouse parts. These antibodies are referred to as fully human monoclonal antibodies and are made either by human cells in the laboratory or in mice that have been genetically altered to carry human antibody genes.

Naming Monoclonal Antibodies

Monoclonal antibody products that are available for clinical use typically have two names, one is a non-proprietary name that is not owned by the manufacturer and a proprietary name that is owned by the manufacturer (also called trade name). The non-proprietary names of monoclonal antibody products are assigned by the World Health Organization and the United States Adopted Names (USAN) Council in order to facilitate identification of the product's active ingredient(s).

According to the naming conventions developed by these organizations, the non-proprietary names of all monoclonal antibodies end in -mab. Humanized monoclonal antibodies end in -zumab. An example is trastuzumab, the humanized monoclonal antibody against HER2 that we discussed earlier. In contrast, the non-proprietary names of chimeric monoclonal antibodies end in -ximab. An example of this is rituximab, a chimeric monoclonal antibody used for the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia. Other suffixes are -momab, which indicates a mouse monoclonal antibody and -mumab, which indicates a human antibody.

A good site to consult for more information on naming of targeted therapies is maintained by the Vanderbilt-Ingram Cancer Center: <http://www.mycancergenome.org/content/other/molecular-medicine/overview-on-targeted-therapies-for-cancer>. This site contains an up-to-date list of the approved targeted therapies for cancer, as well as a diagram illustrating how generic names for targeted therapies are derived.

A list of stems used in creating nonproprietary names is available at the American Medical Association Web site under Resources: <http://www.ama-assn.org/resources/doc/usan/stem-list-cumulative.pdf>

Naked Versus Conjugated Monoclonal Antibodies

So far in this chapter, we have been talking about monoclonal antibodies that, by themselves, are the treatment. As we have already seen, naked monoclonal antibodies can attach to antigens on cancer cells, interfering with their growth and proliferation or causing cell death. These are the most common types of monoclonal antibodies in use today.

However, it is possible to attach the monoclonal antibody to a substance that potently kills cells. In this way, the monoclonal antibody acts as the arrow that targets the cancerous cells, while the substance attached to the arrow acts as a cell poison. Scientists have named monoclonal antibodies that work by themselves “naked monoclonal antibodies” and those that are joined to another substance “conjugated monoclonal antibodies.”

Naked monoclonal antibodies work by themselves. There is no drug or radioactive substance attached to them. Sometimes these antibodies are referred to as unconjugated.

Conjugated monoclonal antibodies are joined to a chemotherapy drug, radioactive particle, or other toxic substance. Conjugated antibodies may also be called tagged, labeled, or loaded antibodies.

Conjugated antibodies can be divided into several groups depending on the type of substance attached to them. The three main classes of conjugated antibodies are radiolabeled (attached to radioactive particles), chemolabeled (attached to chemotherapy drugs), and immunotoxins (attached to cell toxins). The following table provides some examples of these three types of conjugated monoclonal antibodies.

MAIN CLASSES OF CONJUGATED MONOCLONAL ANTIBODIES

| Class of Conjugated Monoclonal Antibody | Description | Examples | Target |
|---|---|---|---|
| Radiolabeled | Monoclonal antibody attached to small radioactive particles | Ibritumomab tiuxetan (Zevalin®), Tositumomab (Bexxar®) | CD20 antigen on certain white blood cells |
| Chemolabeled | Monoclonal antibody attached to chemotherapy drug | Brentuximab vedotin (Adcetris®) | CD30 antigen on certain white blood cells, attached to a drug known as MMAE |
| Immunotoxin | Monoclonal antibody attached to a cellular toxin | No products approved yet | No products approved yet |

Although no immunotoxins are currently available for the treatment of cancer, many are under study. A related drug that consists of an immune system protein that is not an antibody is attached to a toxin made by the organism that causes diphtheria. This drug is known as denileukin diftitox (Ontak®) and is used to treat some types of cancers.

Treatment with Monoclonal Antibodies

At least nine different monoclonal antibodies are approved by the United States Food and Drug Administration (FDA) for the treatment of cancer. These products are listed in the following table along with their target, the type of antibody, and the type(s) of cancer they are used to treat.

**** MONOCLONAL ANTIBODIES FOR THE TREATMENT OF CANCER ****

(Chart is located in back pocket)

We've already discussed how trastuzumab works by binding to the HER2 protein. Let's consider two of the other monoclonal antibodies in more detail: alemtuzumab and bevacizumab.

Alemtuzumab (Campath®)

Alemtuzumab is a humanized, unconjugated monoclonal antibody used to treat some patients with chronic lymphocytic leukemia. Alemtuzumab binds to a protein called the CD52 antigen, a protein located on certain white blood cells known as B cells and T cells. Following attachment to the CD52 antigen, alemtuzumab initiates the destruction of the cell by the immune system.

The abbreviation CD stands for "cluster of differentiation" and refers to a group of antigens on the surfaces of white blood cells that react with different antibodies. Each type of white blood cell expresses a pattern of CD antigens that can be used to help distinguish it from other types of white blood cells that are at different stages of maturity or perform different functions. The antigens themselves have a variety of different functions such as allowing cells to adhere to one another, acting as receptors, and regulating immune responses. Many different CD antigens have been identified and more are still being discovered. As you can see from the table listing the current monoclonal antibodies in clinical use, many of them target CD antigens such as CD20 and CD33.

Bevacizumab (Avastin®)

Bevacizumab is a humanized, unconjugated monoclonal antibody directed against vascular endothelial growth factor (VEGF, pronounced "vej-F"). As its name implies, VEGF is a growth factor that helps vascular endothelial cells to grow. Vascular endothelial cells make up the inside of blood vessels. As we will see in a subsequent chapter, cancers need a constant blood supply to bring them oxygen and nutrients so that they can grow and proliferate. VEGF is a growth factor that stimulates new blood vessel formation, which helps tumors grow.

Bevacizumab binds to VEGF to form a complex that prevents VEGF from binding to its receptors on the surface of cells. VEGF is the signal that initiates the growth pathway in vascular endothelial cells. Without the VEGF signal, the growth pathway is not activated. No growth of these cells, no new blood vessels. Without new blood vessels, cancers cannot grow. That is, all tumors need a blood supply and VEGF is a key factor needed for generating this blood supply. For this reason, it seems that all tumors would be sensitive to antibodies against VEGF. This is not always the case, in part because the body uses several different pathways to generate new blood vessels.

The timeline of discoveries that eventually led to the development of bevacizumab dates back to the late 1930s:

1939: Dr. Gordon Ide suggests in a publication that new blood vessel development is essential in cancers to provide oxygen and nutrients for tumor growth.

1971: Dr. Judah Folkman suggests that the inhibition of angiogenesis (new blood vessel formation) may treat cancers and develops many important laboratory methods. Dr. Folkman originated and championed the idea that tumors may be treated by interfering with the blood supply they need to grow and proliferate. Although his ideas are now considered visionary, they were once ridiculed by other scientists. More about Dr. Folkman's work can be found at the following link:
<http://www.pbs.org/wgbh/nova/body/judah-folkman.html>

1989: A scientist at Genentech, Dr. Napoleone Ferrara, discovers and clones the VEGF protein.

1993: Dr. Ferrara and his team publish an article showing that an antibody directed against VEGF suppressed angiogenesis in laboratory animals.

1997: Clinical trial of bevacizumab begins.

2004: The FDA approves bevacizumab for the treatment of colorectal cancer.

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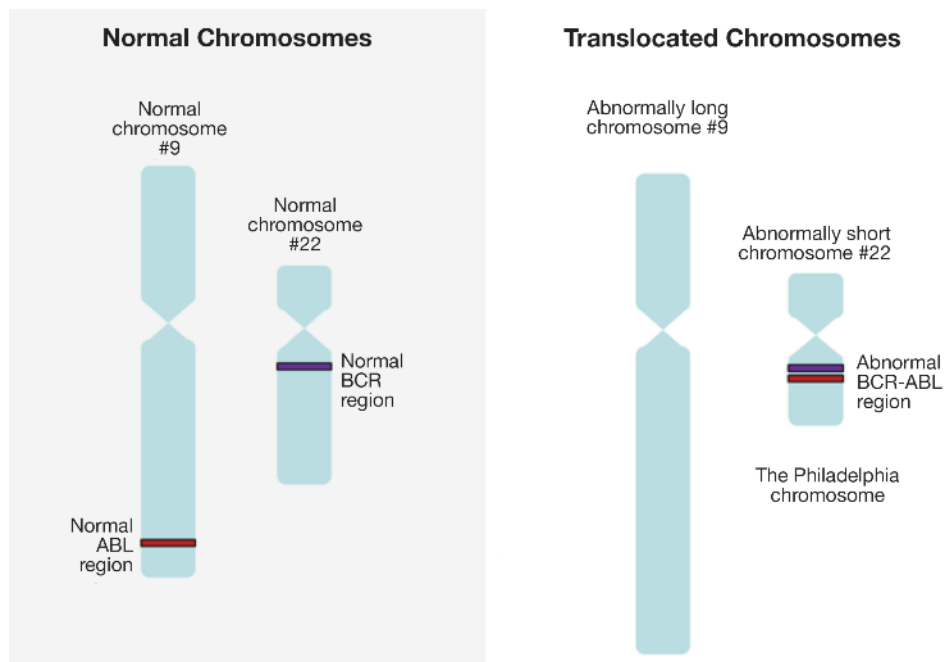
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Chapter 4: Small Molecule Inhibitors – Another Major Class of Targeted Therapies in Cancer

One of the earliest targets of targeted cancer therapy was identified in 1960 when Dr. Peter Newell and his graduate student David Hungerford were working at the University of Pennsylvania School of Medicine in Philadelphia. These researchers described a small, strange-looking chromosome in the white blood cells of patients with chronic myelogenous leukemia that was not found in normal white blood cells. This chromosomal abnormality became known as the Philadelphia chromosome.

This finding led to many questions, such as whether the abnormal chromosome causes the cancer or whether the cancer causes the abnormal chromosome. Researchers eventually discovered that the Philadelphia chromosome was caused by a translocation (changing places) of genetic material from chromosomes 9 and 22. When the genetic material from these two chromosomes combines, it creates a cancer-causing gene known as BCR-ABL. This abnormal gene provides the instructions to make an abnormal protein that that causes leukemia. This abnormal protein is similar to our normal proteins except that it cannot be turned off.

Once the overactive protein was identified, researchers began searching for a way to shut it off. These efforts eventually led to the development of a small molecule inhibitor known as imatinib (Gleevec®), which effectively inhibits the overactive protein and decreases progression of the cancer. Imatinib is a highly effective therapy, leading to a complete response in 98% of patients with chronic myelogenous leukemia. The triple discovery of the Philadelphia chromosome, the BCR-ABL gene, and imatinib represents one of the earliest and most dramatic success stories in the world of targeted therapies.



The Philadelphia Chromosome and BCR-ABL gene. Graphic representation of chromosomes 9 and 22 in their normal, non-cancerous state (left) and after the cancer-causing translocation of chromosomes 9 and 22 seen in chronic myelogenous leukemia (right). This translocation causes an abnormally long chromosome #9 and an abnormally short chromosome #22, known as the Philadelphia chromosome. The Philadelphia chromosome contains the aberrant BCR-ABL region that provides the instructions for a cancer-causing protein.

What Are Small Molecule Inhibitors?

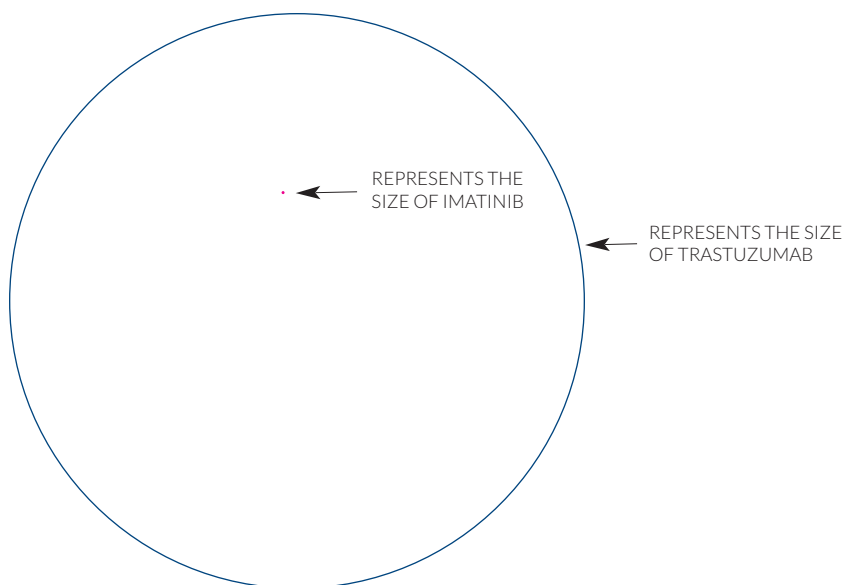
Small molecule inhibitors are drugs that interfere with important cell pathways such as replication. These pathways are essential to cancer growth. Whereas most monoclonal antibodies bind to proteins found outside of cells or on cell surfaces, small molecule inhibitors can bind to molecules or proteins inside the cells. One of the major reasons for this difference is that small molecule inhibitors are tiny compared to monoclonal antibodies. Size is one of the most important determinants of a drug's ability to cross cell membranes and access the insides of cells. Smaller molecules and drugs have a much easier time entering cells than do larger molecules and drugs.

The following table and graphic show an example of the enormous size differences between a small molecule inhibitor and a monoclonal antibody. The small molecule inhibitor shown for comparison is imatinib (Gleevec®), which is used to treat certain types of leukemias and gastrointestinal tumors. The monoclonal antibody shown for comparison is trastuzumab (Herceptin®), which is used to treat HER2+ breast cancer.

As can be seen from the table, both of these drugs are made from chemicals that are common in our bodies: C for carbon, H for hydrogen, N for nitrogen, O for oxygen, and S for sulfur. Whereas imatinib contains 29 carbon atoms, trastuzumab contains 6,470. Whereas imatinib contains 31 hydrogen atoms, trastuzumab contains 10,012. When you count up all of the atoms in these drugs, imatinib has 1,390 and trastuzumab has 20,263. When considered by their molecular weights, imatinib weighs approximately 250 times less than trastuzumab. These size and weight differences are typical for small molecule inhibitors versus monoclonal antibodies.

COMPARISON OF SIZE AND WEIGHT DIFFERENCES BETWEEN SMALL MOLECULE INHIBITORS AND MONOCLONAL ANTIBODIES: AN EXAMPLE

| | Example of Small Molecule Inhibitor | Example of Monoclonal Antibody |
|-------------------|--|---|
| Name of drug | Imatinib | Trastuzumab |
| Chemical formula | $C_{29}H_{31}N_{70} \cdot CH_4SO_3$ | $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$ |
| Number of atoms | 1,390 | 20,263 |
| Molecular weight | About 590 | About 145,000 |
| Weight comparison | About 250 times smaller than trastuzumab | About 250 times bigger than imatinib |



Comparison of size difference between imatinib (a small molecule inhibitor) and trastuzumab (a monoclonal antibody). The red dot in the center represents imatinib and the large blue circle represents trastuzumab. Trastuzumab weighs approximately 250 times more than imatinib.

What Do Small Molecule Inhibitors Inhibit?

Small molecule inhibitors interfere with or inhibit cell processes such as growth, proliferation, movement, and new blood vessel formation. Many of the small molecule inhibitors available today inhibit proteins known as kinases, or more specifically, tyrosine kinases. Kinases are enzymes that transfer chemical groups called phosphate groups from one place in the cell to another. The transfer of phosphate groups within cells acts as a cellular switch, turning off or on a variety of cellular functions. Tyrosine kinases are a type of kinase that transfers phosphate groups from important cell energy molecules known as adenosine triphosphate (ATP) to specific places on proteins.

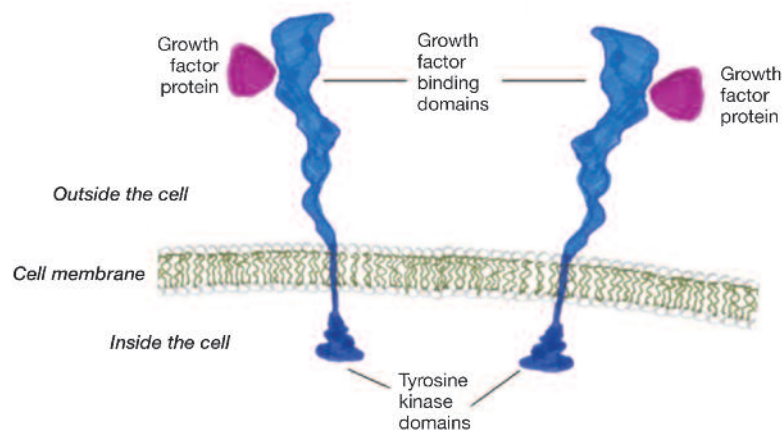
Kinase is a general term for enzymes that transfer phosphate groups from one place in the cell to another.

Tyrosine kinases are enzymes in the kinase family that transfer phosphate groups from one place in the cell to another. They transfer the phosphate groups from important cell energy molecules known as adenosine triphosphate (ATP) to specific places on proteins.

Tyrosine kinases are critical control points in cell growth and development pathways. Many growth factor receptors have a tyrosine kinase portion inside the cell. That is, these receptors are large proteins that have some of their parts or domains outside the cell, some in the cell membrane, and some inside the cell. As we saw in the monoclonal antibody chapter, trastuzumab is a monoclonal antibody that binds to the extracellular part of the HER protein. The part of the HER protein that is inside the cell is the tyrosine kinase domain.

Under normal conditions, the growth factors outside the cell bind to their receptors, leading to a change in the receptor's shape. In some cases, this causes two of the growth factor receptors to come together, which activates the tyrosine kinase portions of the two receptors. These enzymes then transfer the phosphate groups to other proteins and activate or inhibit them. The next proteins, in turn, affect the activity of other proteins, and eventually one of the proteins in the relay may access the cell's nucleus where it turns on or off gene expression. This series of events represents a cell pathway in which one event causes another to happen and, again, goes back to the analogy of a relay race. One cellular event occurs and then hands off the baton to the next, which then hands off to the next, continuing until the end of the race or, in this case, the turning on or off of a gene.

Some of the growth factor receptors that contain tyrosine kinase portions are called receptor tyrosine kinases, and this family includes the epidermal growth factor receptor (EGFR), the human epidermal growth factor receptor (HER2/neu), and the vascular endothelial growth factor (VEGF) receptor.



Example of a receptor tyrosine kinase. The growth factor binds to the portion or domain of the receptor located outside the cell. This causes a change in the shape of the receptor protein and causes two of the receptor proteins to associate. This causes activation of their tyrosine kinase domains, which are inside the cell. Activation of tyrosine kinases leads to activation or inhibition of other proteins, eventually causing cell growth or replication.

Not all small molecule inhibitors act on tyrosine kinases. Some act on other types of kinases or other proteins that are further downstream in the cell signaling pathways. Still others may act by a more general mechanism, for instance, by allowing the cancerous cells to undergo programmed cell death (apoptosis). We will discuss these pathways in more detail in the next chapter.

Naming Small Molecule Inhibitors

Like monoclonal antibodies, small molecule inhibitors available for clinical use have a non-proprietary name that is not owned by the manufacturer and a proprietary name that is owned by the manufacturer. The non-proprietary names of small molecule inhibitors generally end in -ib. Examples are imatinib and bortezomib. Some small molecule targeted therapies inhibit the immune system and end in -imus.

A good site to consult for more information on naming of targeted therapies is maintained by the Vanderbilt-Ingram Cancer Center: <http://www.mycancergenome.org/content/other/molecular-medicine/overview-on-targeted-therapies-for-cancer>. This site contains an up-to-date list of the approved targeted therapies for cancer, as well as a diagram illustrating how generic names for targeted therapies are derived.

A list of stems used in creating nonproprietary names is available at the American Medical Association Web site under Resources: <http://www.ama-assn.org/resources/doc/usan/stem-list-cumulative.pdf>

Major Differences Between Small Molecule Inhibitors and Monoclonal Antibodies

We have already discussed several ways in which small molecule inhibitors differ from monoclonal antibodies: (1) in size and (2) in their ability to access the insides of cells. However, these two classes of targeted therapies differ in other ways too.

- Small molecule inhibitors are manufactured by combining chemicals in a laboratory, whereas monoclonal antibodies are produced using bioengineering techniques. The latter are expensive and technically difficult; as a result, small molecule inhibitors are easier and less costly to produce than monoclonal antibodies.
- Small molecule inhibitors are usually taken orally, whereas monoclonal antibodies are usually administered intravenously (into the veins). If monoclonal antibodies were taken orally, their structure would be altered in the stomach and intestines and they would not work because their structure is critical to their activity.
- Monoclonal antibodies last in the body for days to weeks and therefore only need to be administered on a weekly or monthly basis. In contrast, small molecule inhibitors last only hours in the body and therefore need to be taken every day.
- Monoclonal antibodies are not broken down by the liver, so they do not interact with many other types of drugs. In contrast, most small molecule inhibitors are broken down in the liver by enzymes that also break down other drugs. If multiple drugs compete for the same enzyme, this can lead to drug interactions.
- Due to the specificity of interactions between antibodies and antigens, monoclonal antibodies are highly specific for their targets. In contrast, small molecule inhibitors tend to be less specific, with some of them targeting more than one molecule.
- The names of monoclonal antibodies end in “mab” for monoclonal antibody and the names of small molecule inhibitors generally end in “ib” for inhibitor, but may have other endings such as “imus” for immune system inhibitors (immunosuppressants).

The differences between small molecule inhibitors and monoclonal antibodies do not imply that one class of medications is better than the other. Instead, these differences are noted simply as a means of understanding the types of targeted therapies. Both small molecule inhibitors and monoclonal antibodies can be highly effective against certain cancers and may show less severe side effects than traditional chemotherapies.

SUMMARY OF DIFFERENCES BETWEEN SMALL MOLECULE INHIBITORS AND MONOCLONAL ANTIBODIES

| | Small Molecule Inhibitors | Monoclonal Antibodies |
|----------------------------------|-------------------------------|-----------------------|
| Size | Small | Large |
| Can access targets inside cells? | Yes | No |
| Method of manufacture | Combining chemicals | Bioengineering |
| Route of administration | Usually oral | Usually intravenous |
| Frequency of administration | Daily | Weekly to monthly |
| Drug interactions in the liver? | Possibly | No |
| Specific for single target? | Not always | Yes |
| Names end in | "ib", "imus", or other ending | "mab" |

Treatment with Small Molecule Inhibitors

A number of different small molecule inhibitors are approved by the United States Food and Drug Administration (FDA) for the treatment of cancer. These products are listed in the attached table along with their target(s), and the type(s) of cancer they are used to treat. As you can see from the table, many of these drugs inhibit the tyrosine kinase portions of growth factor receptors (GFRs) or other kinases. As you can also see from this table, some of the small molecule inhibitors act on more than one kinase.

**** SMALL MOLECULE INHIBITORS FOR THE TREATMENT OF CANCER ****

(Chart is located in back pocket)

We've already discussed the general mechanism by which small molecule inhibitors affect receptor tyrosine kinases to inhibit processes that are critical for the maintenance and propagation of cancer. Let's take a closer look at several small molecule inhibitors in more detail: imatinib, bortezomib, and everolimus.

Imatinib (Gleevec®)

We began this chapter with a description of how imatinib was developed to target the abnormal protein produced by the BCR-ABL gene on the Philadelphia chromosome. The abnormal protein is a tyrosine kinase that has lost the ability to shut itself off. It is therefore constantly active in the cell, transferring phosphate groups to specific locations that continually tell the cell to grow and replicate. Imatinib binds to a place on the protein that is crucial for its tyrosine kinase activity. By binding to this site, imatinib prevents the protein from transferring phosphate groups. In this way, imatinib inhibits the activity of the tyrosine kinase. This is the mechanism by which imatinib treats chronic myelogenous leukemia and a type of acute lymphoblastic leukemia that is also caused by the Philadelphia chromosome.

However, imatinib is not specific for the BCR-ABL tyrosine kinase. It inhibits several other tyrosine kinases in the cell: one is known as KIT and the other is the kinase portion of the platelet-derived growth factor (PDGF) receptor. The multiple kinases inhibited by imatinib make it useful for certain types of cancer besides those caused by the Philadelphia chromosome. For instance, certain types of gastrointestinal cancers known as gastrointestinal stromal tumors (GIST) that show mutations or overexpression of the KIT protein may respond to imatinib. Imatinib (Gleevec®) is also approved for the treatment of several conditions associated with problems in the PDGF receptor.

Bortezomib (Velcade®)

Bortezomib is a small molecule inhibitor that is thought to act by a somewhat different mechanism than the other drugs in this class—all of which inhibit kinases. Instead, bortezomib inhibits the activity of a large protein complex that degrades unwanted proteins in the cell. Preventing the degradation of these unwanted cellular proteins leads to cell death, although no one is exactly sure why this is the case. It is also possible that bortezomib has more than one mechanism of action. Bortezomib (Velcade®) is used to treat two types of blood cancers: multiple myeloma and mantle cell lymphoma—a subtype of non-Hodgkin lymphoma.

Everolimus (Afinitor®)

Everolimus is a small molecule inhibitor that acts on a protein known as mammalian target of rapamycin (mTOR). Everolimus is a derivative of rapamycin, a drug that acts as an antibiotic, suppresses the immune system, and inhibits a type of serine/threonine kinase known as mTOR. Everolimus also suppresses the immune system and inhibits mTOR.

Rapamycin is a drug used to keep the body from rejecting organ and bone marrow transplants. Rapamycin blocks certain white blood cells that can reject foreign tissues and organs. It also blocks a protein that is involved in cell division. It is a type of antibiotic, a type of immunosuppressant, and a type of serine/threonine kinase inhibitor. Rapamycin is now called sirolimus.

The kinase known as mTOR is an important part of key cellular signaling pathways, including those involving several growth factors. mTOR helps regulate cell growth and proliferation, metabolism, protein synthesis and apoptosis. By inhibiting mTOR, everolimus and another rapamycin derivative known as temsirolimus are thought to have a variety of different effects on tumors such as inhibiting cell division, interfering with angiogenesis, and inducing apoptosis. Studies are ongoing to determine biomarkers for response to everolimus.

Everolimus (Afinitor®) is used to treat several different types of cancers. These include advanced HER-2 negative, hormone receptor positive breast cancer in postmenopausal women (in combination with exemestane after failure of treatment with letrozole or anastrozole), progressive neuroendocrine tumors of pancreatic origin (PNET), renal cell carcinoma, renal angiomyolipoma and tuberous sclerosis complex (TSC), and nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis.

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Chapter 5: Where to Look for the Targets of Targeted Therapies?

When thinking about the different types of cancers, most of us can name at least a dozen off the tops of our heads; brain, breast, prostate, pancreatic, colorectal, stomach, lung, liver, ovarian, bone, skin, and blood cancers come to mind. Cancers that occur in each of these locations can be further categorized into multiple subgroups based on the types of cells or parts of the organ that are affected. Some of the cancers can be further subdivided based on the biomarkers present.

Targeting individual biomarkers in various cancer subtypes is an important strategy that has worked well in the past—the success of imatinib for chronic myelogenous leukemia exemplifies the potential benefits of this approach. However, attempting to develop a drug for each unique target on each subtype of cancer cell may be a daunting task. This seemingly overwhelming complexity led some scientists to wonder about the possibility of a simpler approach. What if, instead of focusing on the differences between cancers, we focused on their similarities? This was the simple but revolutionary idea put forward in a now famous paper by Drs. Hanahan and Weinberg published in the journal Cell in 2000.

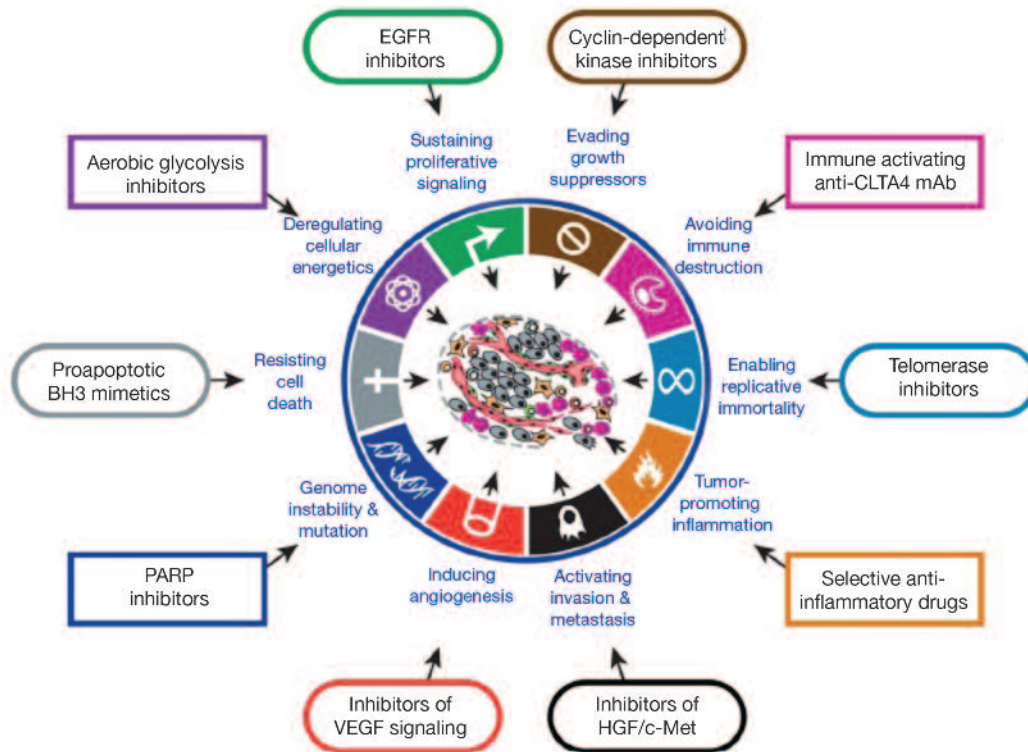
Cancer Hallmarks

Drs. Hanahan and Weinberg argued that all of our cells, cancerous or not, carry out their functions through similar mechanisms. That is, cancer cells don't all of a sudden acquire the capabilities of plant cells or begin to use completely different chemicals to grow and replicate. Instead, cancer cells use the same basic strategies and pathways as do normal cells, but they hijack one or more of these pathways to achieve their own ends.

In their original 2000 paper, Drs. Hanahan and Weinberg described six functions that all cancer cells acquire, regardless of the type of cancer, that distinguish them from normal cells. Ten years later, these authors issued an update and added two more unique abilities that cancer cells acquire. Many of these hallmarks are mediated by cell pathways or routes that transfer signals within and between cells.

The idea of similarities among cancers suggests that a drug developed against one target may treat more than one type of cancer. This idea has been borne out with the many small molecule inhibitors that are effective against multiple types of cancer that exhibit similar abnormalities such as the overactivity of certain kinases. Thus, the pathways that mediate these hallmarks of cancer are prime targets for the development of targeted therapies.

Let's discuss each of these hallmarks of cancer in more detail.



Therapeutic Targeting of the Hallmarks of Cancer. Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression have been developed and are in clinical trials or in some cases approved for clinical use in treating certain forms of human cancer. Additionally, the investigational drugs are being developed to target each of the enabling characteristics and emerging hallmarks which also holds promise as cancer therapeutics. The drugs listed are but illustrative examples, there is a deep pipeline of candidate drugs with different molecular targets and modes of action in development for most of these hallmarks.

Reprinted from *Cell*, Volume 144, Douglas Hanahan and Robert A. Weinberg, *Hallmarks of Cancer: The Next Generation*, pp. 646-674, 2011, with permission from Elsevier.

HALLMARKS OF CANCER CELLS

1. Sustained, self-sufficient growth signals
2. Insensitivity to signals that inhibit growth
3. Ability to evade programmed cell death (apoptosis)
4. Ability to replicate indefinitely
5. Ability to generate sustained blood supply (angiogenesis)
6. Ability to invade tissue and metastasize (spread to other areas)
7. Re-programming energy metabolism
8. Avoiding destruction by the immune system

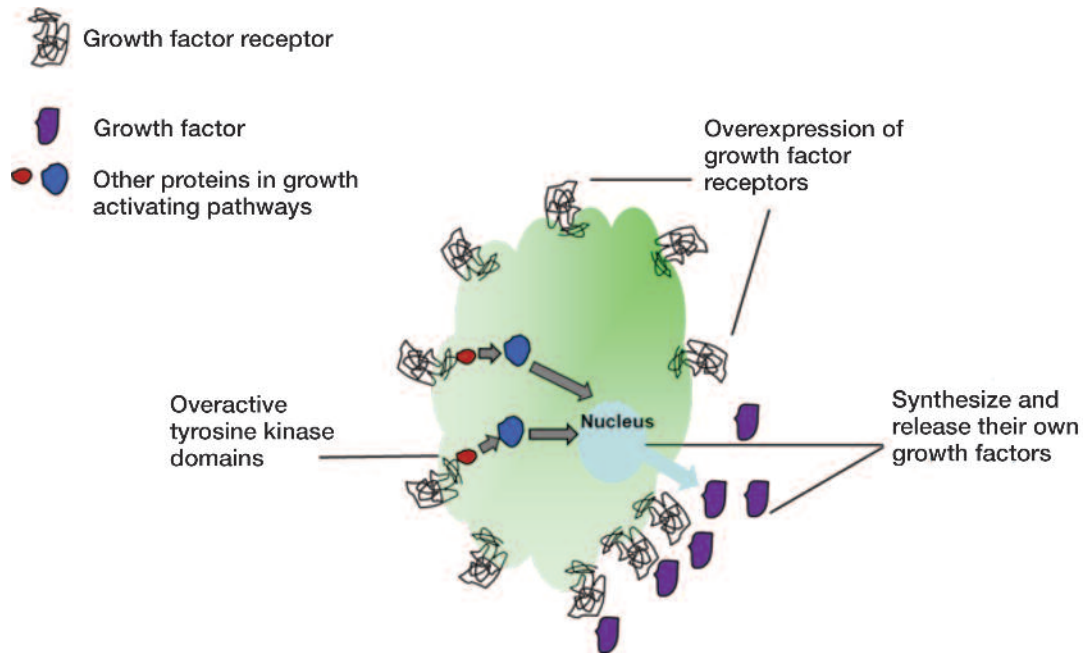
From Hanahan D, Weinberg RA. Hallmarks of cancer. *Cell*. 2000;100: 57–70; Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.

Sustained, Self-Sufficient Growth Signals

In order for cells to grow, they must be activated by a growth signal. This signal is often a growth factor that is released into the area surrounding the cell, where it binds to a receptor on the cell surface. However, cells can also receive signals from nearby cells to which they are attached and from the complex of proteins and other biochemicals that make up the so-called extracellular matrix that surrounds cells.

Extracellular matrix: A structural and functional complex of proteins and other biochemicals produced by cells and excreted to the extracellular space within the tissues, serving as a scaffolding to give tissues their structure and helping to determine their characteristics.

Cancer cells are able to subvert the need for external growth signals and/or their shut off mechanisms. They do this by one or more different mechanisms. For instance, some cancer cells make and release their own growth factors, which then bind to their own growth factor receptors. Other cells greatly increase their numbers of growth factor receptors, as is the case for HER2+ breast cancers. Still other cells have receptor tyrosine kinases that can't be shut off by the normal mechanisms, as is the case for the BCR-ABL protein that causes chronic myelogenous leukemia. Other cells may use different mechanisms such as the way cells attach to nearby cells or to the extracellular matrix, and some cancer cells use more than one mechanism.



Some ways that cancer cells achieve self-sufficient growth signals. Cancer cells may synthesize and release their own growth factors, overexpress growth factor receptors, or express overactive tyrosine kinase domains of growth factor receptors. These are only some of the possible ways by which cancer cells can achieve their own sustained growth signals.

Inensitivity to Signals that Inhibit Growth

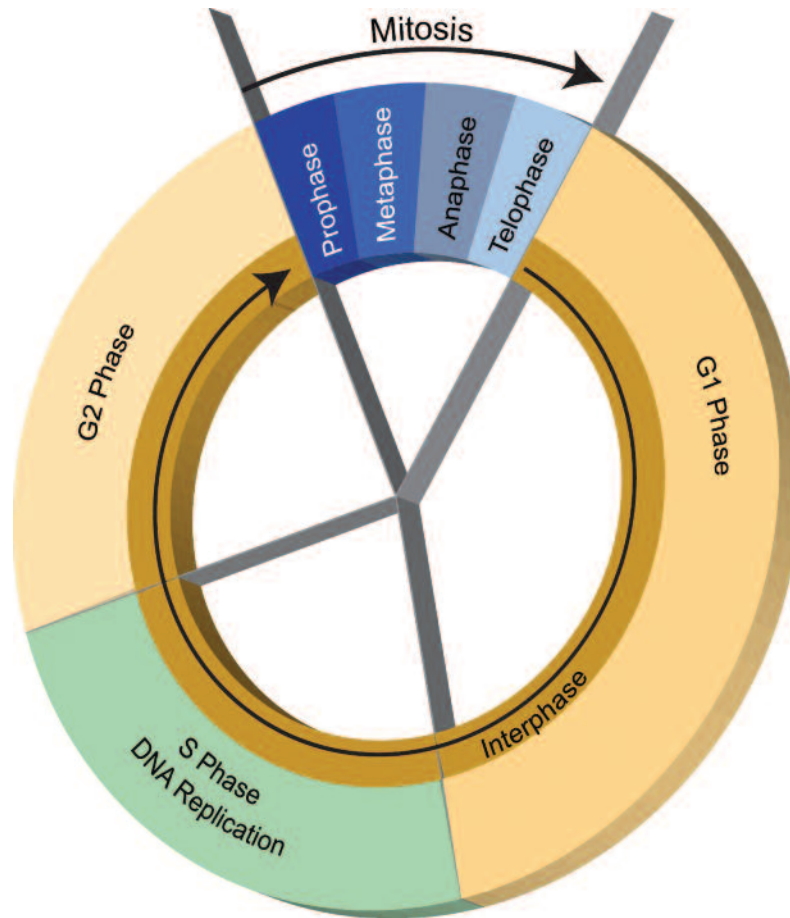
Our bodies have built in mechanisms designed to inhibit growth once the desired result is achieved. For example, when we cut our skin, the skin cells grow back to close the gap but they do not continue growing to make a large tumor. The cells know when to stop because they receive stop signals.

Cancer cells are able to ignore the signals that tell them to stop growing. The most common way that cancer cells do this is by interfering with the cell cycle clock. The cell cycle is the process by which cells replicate. It consists of a series of events during which the chromosomes and other cell materials double to make two copies. The cell then divides into two identical cells, with each receiving one copy of the doubled material.

Cell cycle: A series of steps during which the chromosomes and other cell material double to make two copies. The cell then divides into two identical cells, each receiving one copy of the doubled material. The cell cycle is complete when each cell is surrounded by its own outer membrane.

Whether or not a cell enters the cell cycle is determined by proteins that evaluate signals coming from outside and inside the cell. These proteins essentially weigh the stop and go signals, and either permit the cell to enter the cell cycle, where it replicates itself, or cause it to remain in its resting state. Many of these regulatory proteins are referred to as tumor suppressors.

Tumor suppressor: A type of gene or the protein that it encodes that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer.



The Cell Cycle. A cell cycle is a series of events that takes place in a cell as it grows and divides. A cell spends most of its time in what is called interphase, and during this time it grows, replicates its chromosomes, and prepares for cell division. The cell then leaves interphase, undergoes mitosis, and completes its division. The resulting cells, known as daughter cells, each enter their own interphase and begin a new round of the cell cycle.

Graphic credit: Darryl Leja, National Human Genome Research Institute.

For our purposes, it is not necessary to know all of the different phases of the cell cycle, but more information is available at several Web sites:

- Cells Alive: http://www.cellsalive.com/cell_cycle.htm
- National Institutes of Health and National Institute of Cancer. Cell Biology. Student Activities 2, The Cell Cycle: http://science.education.nih.gov/supplements/nih1/cancer/activities/activity2_animations.htm
- National Cancer Institute. The Cell Cycle: <http://training.seer.cancer.gov/disease/cancer/biology/cycle.html>

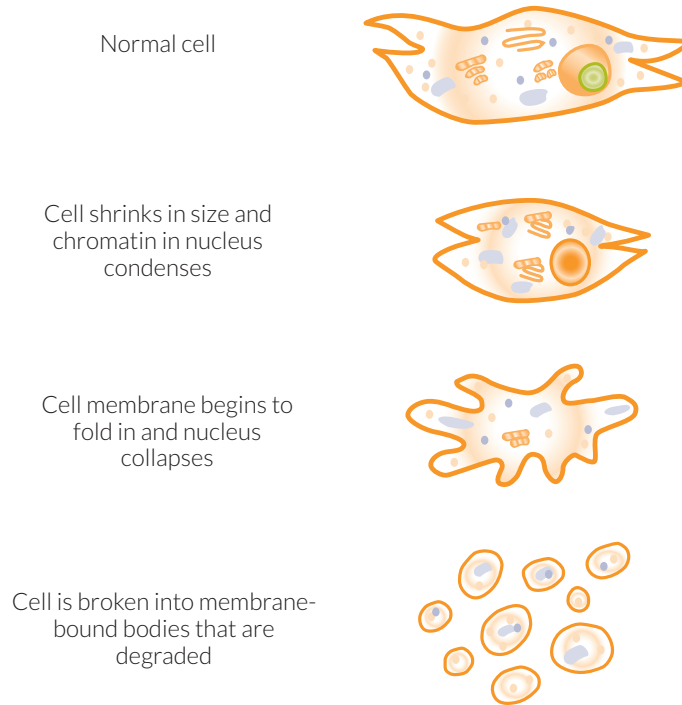
Apoptosis – Programmed Cell Death

Our cells constantly monitor their environment to determine whether conditions are normal, signaling that they should continue to live, or whether conditions are abnormal, signaling that they should self-destruct. Under normal conditions, most cells are linked to one another and to the extracellular matrix. These linkages send survival signals, telling the cells to continue to live. When cells do not receive these survival signals, they undergo a process called apoptosis or programmed cell death. Cells may also receive active self-destruct signals that tell them to undergo apoptosis.

Apoptosis refers to the process by which cells actively destroy themselves when they are unneeded in the body, at the end of their lifespan, or damaged in a critical way. Apoptosis is controlled by a genetic program. The major steps of apoptosis are well characterized and distinguish this form of cell death from necrosis, which is a more passive form of cell death caused by injury/trauma to the cell or exposure to toxic substances.

Apoptosis: A type of cell death in which a series of molecular steps in a cell lead to its death. This is one method the body uses to get rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells.

APOPTOSIS



When cells need to be removed from the body, they are typically eliminated through apoptosis – programmed cell death. The major steps of apoptosis are shown here. First the cell shrinks in size and chromatin in the cell nucleus condenses. Chromatin is the complex of DNA and proteins (histones) that condenses to form a chromosome during cell division. The membrane then begins to fold in and the nucleus collapses. The cell is then broken into membrane-bound compartments that are then degraded by other cells.

Cancer cells are able to overcome the signals that tell them to self-destruct. For example, they can detach from the extracellular matrix and continue to grow into a tumor even though they no longer receive the survival signals.

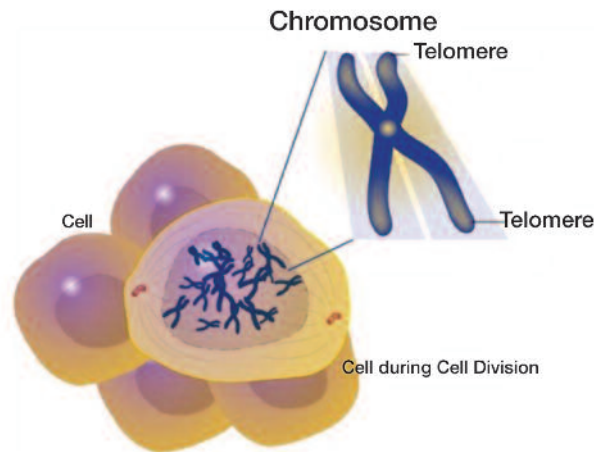
Cancer cells can get around apoptosis through several mechanisms. One way is through inactivation of a pathway known as the p53 pathway. The p53 gene functions as a tumor suppressor and, when activated, it promotes apoptosis. More than 50% of all cancers exhibit mutations in the p53 gene. Another method by which cancer cells can overcome the normal process of apoptosis is by increasing the activity of pathways that interfere with this process. One such pathway is mediated by growth factors and involves the activation of a kinase known as PI3K.

Informative slide shows and videos on apoptosis are available at the following Web site:
<http://www.researchapoptosis.com/apoptosis/multimedia/index.m>

Ability to Replicate Indefinitely

The lifespan of a cell is normally regulated by structures on the ends of our chromosomes called telomeres. Telomeres are synthesized by an enzyme known as telomerase. Each time a cell divides, the telomeres become shorter. When telomeres become too short and are not replaced by telomerase, the cell can no longer divide and eventually dies. Thus, telomeres limit the number of times a cell can divide and replicate.

Unlike normal cells, cancer cells can replicate themselves indefinitely. In order to do this, they must overcome the limitation on cell division imposed by telomeres. In cancer cells the telomeres do not get shorter as the cells divide; in fact, the telomeres may even become longer.



Telomeres on a chromosome.

Graphic credit: Adapted from Darryl Leja, National Human Genome Research Institute
<http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85248>

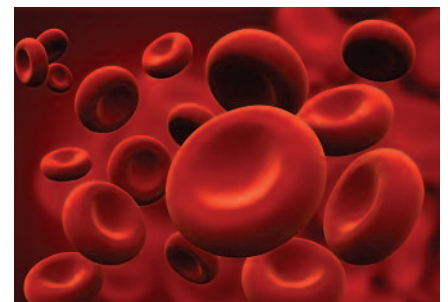
Telomere: The ends of a chromosome. Each time a cell divides, the telomeres lose a small amount of DNA and become shorter.

Telomerase: An enzyme in cells that helps keep them alive by adding DNA to telomeres.

Cancer cells maintain their telomere length in at least two different ways. The most common way is for the cells to produce more telomerase. Telomerase consists of a protein component and an RNA component. Up to 90% of all human cancer cells increase the activity of TERT, which is the protein component of telomerase. A smaller portion of cancer cells use another pathway to lengthen telomeres, although researchers don't know exactly what this mechanism is.

Ability to Generate Sustained Blood Supply (Angiogenesis)

In order to stay alive, cells must have oxygen and nutrients that are delivered via the blood. In fact, nearly all cells must have a blood vessel very near them in order to live. Cancer cells are no exception, and in fact, tumors must have the ability to generate their own blood supply or they would not be able to grow. One of the ways that cancer cells turn on angiogenesis is by shifting the balance between inhibitors and activators.



As we saw in the chapter on monoclonal antibodies, the formation of new blood vessels is called angiogenesis. In that chapter, we discussed a monoclonal antibody called bevacizumab (Avastin®) that treats cancer by interfering with angiogenesis. Angiogenesis pathways are attractive targets in cancer therapy partly because these pathways are not very active in adults. During wound healing and during menstruation in females are two of the only times that angiogenesis occurs in adults.

For more information about angiogenesis in cancer, you may want to visit the National Cancer Institute's slides on Understanding Cancer, available at:
<http://www.cancer.gov/cancertopics/understandingcancer/angiogenesis>

Ability to Invade Tissue and Metastasize (Spread to Other Areas)

A familiar hallmark of tumors is their ability to invade tissue and spread to other areas. Tumors that remain in one location are not as much of a threat to life as those that spread, and indeed, the distant spread of tumor cells is responsible for about 90% of all cancer-related deaths.

The ability of tumors to invade tissue and metastasize is related to their ability to detach from other cells and from the extracellular matrix. As noted previously, this would normally deprive cells of their survival signals, causing them to undergo apoptosis. In cancer cells, it does not.

Cancer cells are able to survive without adherence to other cells and to the extracellular matrix through one or more mechanisms that are still being studied. Cells normally contain different types of linkage molecules. Some promote tight linkages, whereas others do not. In some cancers, cells switch from the tight linkage molecules to the loose linkage molecules, which allows them to break away from their moorings. In other cases, cancer cells may increase their production of enzymes that break down tissue. This allows cancer cells to roam through the relatively empty space without encountering stop signals.

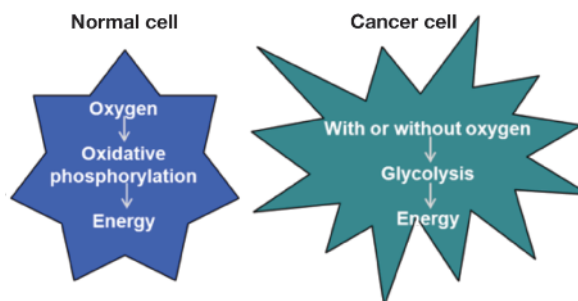
Re-Programming Energy Metabolism

In order to carry out their normal processes, all cells need energy. The way cells usually get energy is through a process that requires oxygen, known as oxidative phosphorylation. However, when there is not enough oxygen available, cells get energy through an alternative process known as glycolysis. Glycolysis is much less efficient than oxidative phosphorylation but it is useful under conditions of low oxygen.

Oxidative phosphorylation: A process by which cells get energy; enzymes in the part of the cell known as mitochondria synthesize energy molecules in the presence of oxygen.

Glycolysis: A process by which cells get energy that can occur with or without oxygen; cell enzymes break down glucose into pyruvic and lactic acids, which liberates energy.

Unlike normal cells, cancer cells prefer to get their energy through glycolysis, even under conditions where oxygen is at normal levels. They make up for the low efficiency of this pathway, at least in part, by increasing the proteins that concentrate glucose inside cells. But why would cancer cells use such an inefficient pathway in the first place? Although no one can say for sure, one reason may be that the by-products of glycolysis are used in other pathways that are important for the proliferation of cancer cells. Another possible reason is that some cancers may have mutations in the enzymes that make glycolysis more efficient—such mutations have been found in certain types of brain cancers and leukemia.



Energy metabolism in normal vs. cancer cells. Normal cells obtain energy via oxidative phosphorylation in the presence of oxygen. Cancer cells preferentially obtain energy via glycolysis, regardless of the presence of oxygen.

Avoiding Destruction by the Immune System

Under normal conditions, the activity of our immune system helps identify and eliminate potentially cancerous cells before they can grow and proliferate. The cancerous cells can be detected as dangerous if they display certain molecules on their surfaces or release biochemicals that mark them as dangerous. These cells are readily eliminated by our immune systems.

However, some of the cancer cells exhibit slight differences that allow them to hide from the immune system a bit better. These cells continue to grow and replicate even as our immune system eliminates the obvious bad cells. In this way, our immune defenses foil some of the cancer cells but not others, giving the appearance of holding the cancer in check.

The cancer cells that do survive continually adapt to the challenges of the immune system in somewhat the same way that weeds become resistant to herbicides over time. This eventually results in a set of cancer cells that are not detected as threats by the immune system and therefore are not eliminated. Researchers have identified at least two ways that cancer cells adapt to the immune system challenges and continue to survive in the body. One way is by failing to express molecules that can be detected by the immune system. The cancer cells that do express these molecules are eliminated and the cancer cells that don't survive; the latter cells then replicate, producing a population of cells that can hide from the immune system.

Another mechanism cancer cells use to evade the immune system is by the production of biochemicals that actively suppress immune function. In fact, tumors establish an environment around themselves comprising cells and biochemicals that actively inhibit the immune system, functioning like a fortress that protects the colony of tumor cells. In this way, the local area around the tumor known as the tumor microenvironment, is different from the rest of the body and Investigators are looking into several ways to help the immune system eliminate cancer cells. Strategies include the identification of new molecules on cancer cells that can be targeted with monoclonal antibodies or other drugs, increasing our overall immune function, and overcoming the immune suppression induced by the tumor. Some of these methods may involve targeted therapies and some may not. For instance, treatments designed to stimulate overall immune function may or may not qualify as targeted therapies.

Summary of Cancer Hallmarks

All of the eight hallmarks of cancer represent important ways that cancer cells differ from normal cells. Because these hallmarks are essential to the survival, growth, and proliferation of cancers, researchers are trying to better understand them in the hope that this will lead to new treatments. By understanding the specific molecular players involved, new targeted therapies can be developed against them. Alternatively, by understanding how the various pathways converge, researchers may be able to find a target that is common to multiple cancer types.

Another concept related to cancer hallmarks and the study of pathways is that one target may not be enough. Future cancer therapies, some of which are currently in development, may consist of several drugs designed to target different pathways or different parts of the same pathway. This strategy is a little like taking a cold medicine that contains an analgesic, a decongestant, and a cough suppressant. It is also clear from the eight hallmarks described here that cancers have multiple survival strategies and it is possible that future therapies will simultaneously address more than one of these essential features of cancer.

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Chapter 6: Methods In Targeted Therapy Development

Bioluminescence—the biochemical emission of light by living organisms—is something we usually associate with fireflies and exotic deep sea creatures. Most of us probably don't think about bioluminescence as a method of tracking tumors, but such uses are increasingly at the forefront of cancer imaging research. Investigators are now loading body-friendly bacteria like those in yogurt with the genes that permit them to luminesce. It turns out that bacteria have a predilection for tumors: When administered into the body, bacteria will home in on tumors for a variety of reasons that may involve low oxygen, irregular blood supply, immunosuppression, and/or availability of nutrients. If bioluminescent bacteria localize to tumors, it may enable tumor visualization and eventually, perhaps, targeted drug delivery to tumors.

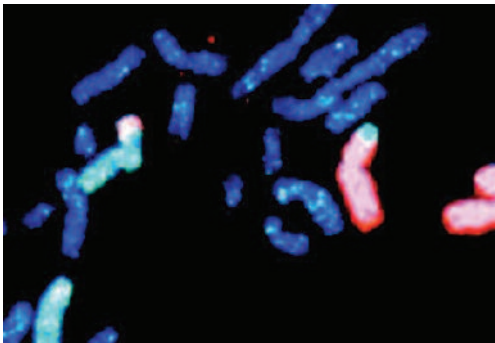
Methods for Identifying Targets for Targeted Therapies

Overall strategies for identifying new drug targets in cancer include examining chromosomes, DNA, and proteins. Let's consider each of these.

Chromosome Assessment—Cytogenetic Testing

One important strategy that scientists have used to identify cancer targets is the assessment of chromosomes, known as cytogenetic testing. In cytogenetic testing, investigators examine the number and structure of chromosomes. This is the method that was used to identify the Philadelphia chromosome—the shortened version of chromosome #22 that contains the abnormal BCR-ABL gene that causes chronic myelogenous leukemia.

Cytogenetic testing: Examining the number and structure of chromosomes.



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Human chromosomes "painted" by fluorescent dyes to detect abnormal exchange of genetic material frequently present in cancer. Chromosome paints also serve as valuable resources for other clinical and research applications.

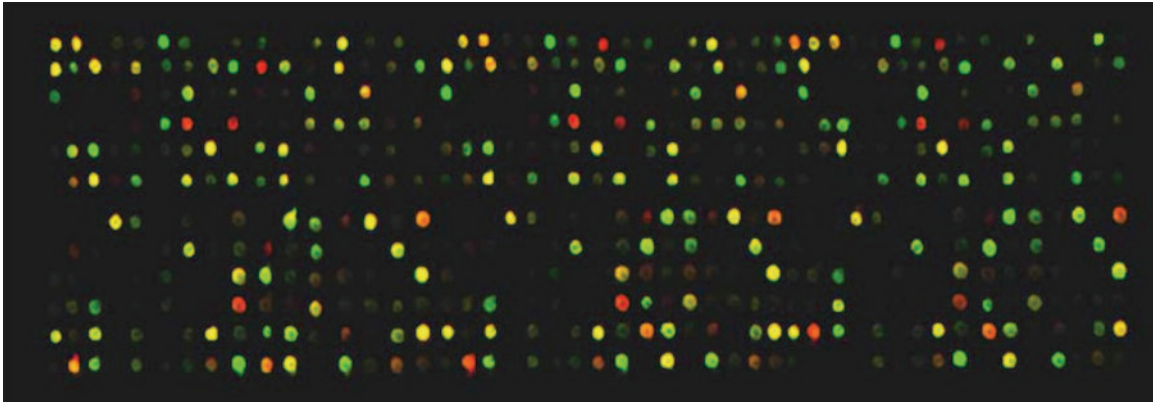
Image credit: Human Genome Program, U.S. Department of Energy, Human Genome Program Report, 1997. Web site: <http://genomicscience.energy.gov>.
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During cytogenetic testing, investigators may “freeze” cancer cells during the process of cell division. At this stage, the chromosomes are readily visible and can be compared to those of normal cells. Cancer cells often lose or gain large areas of the chromosomes or show rearrangement or exchange of chromosomal material. Once these changes are identified, they can be further analyzed using techniques designed to determine which genes are involved.

Assessment of DNA Sequences and Genes—DNA Microarrays

In addition to examining the overall chromosome structure, scientists can examine DNA at a much closer and detailed level. Gene expression using DNA microarrays is a common strategy used for determining which genes or forms of genes are present in cells. DNA microarrays were developed to allow the detection of thousands of genes at once.

DNA microarrays consist of tiny areas of glass or other materials onto which DNA probes are attached. The array actually looks like a series of colored dots arranged in columns and rows. DNA samples taken from cells are exposed to the probes. If one of the DNA probes matches the DNA present in the sample, it will bind and give off a color. Computers then analyze the pattern of colored dots to determine which genes or DNA sequences are present in the sample. Often the DNA from cancer cells is compared to that of normal cells.



DNA microarray. DNA microarray technology allows the detection of hundreds or thousands of genes at once. Each dot on the microarray contains a DNA probe that can bind to a specific sequence of DNA. If a given sequence of DNA is present in the sample, it will stick to the microarray and give off a color. Thus, the colored dots indicate the DNA sequences that are present in the sample of DNA taken from a cell. The computer knows which sequences of DNA are located at every dot.

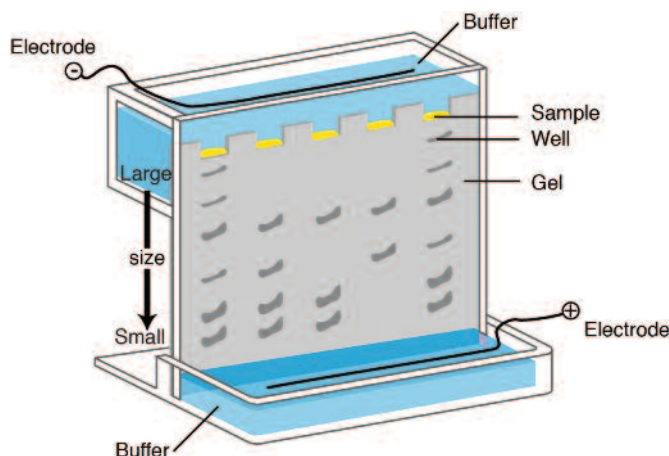
Image credit: Genomes to Life Program Roadmap, April 2001, DOE/SC-0036, U.S. Department of Energy Office of Science. Web site: <http://genomicscience.energy.gov/>.

Assessment of Proteins

Instead of looking at the genes that encode proteins, investigators can also look for the proteins themselves. Today, many of the techniques used for the assessment of proteins in cancer evaluate multiple proteins that exist in the cell at the same time. This is often referred to as proteomics, which is defined as the study of many proteins present in the cell at the same time, including their identity, biochemical properties and functional roles, and how their quantities, modifications, and structures change during development and in response to internal and external stimuli.

Proteomics: The study of proteins expressed in a cell at a given point in time.

Proteins can be identified using several different techniques. One of these is similar to a DNA microarray except that antibodies are used instead of DNA probes. As a sample is exposed to the antibodies, antigens that specifically pair with them “stick” and become visible as colored dots. Another combination of techniques used to identify proteins is gel electrophoresis combined with enzyme-linked immunosorbent assay (ELISA). Gel electrophoresis separates proteins based on their size and electrical charge. Once separated, these proteins can then be specifically identified using an ELISA procedure that also uses the antibody-antigen interaction to determine which proteins are which.



Gel Electrophoresis. Electrophoresis is a laboratory technique used to separate DNA, RNA, or protein molecules based on their size and electrical charge. An electric current is used to move molecules to be separated through a gel. Pores in the gel work like a sieve, allowing smaller molecules to move faster than larger molecules. The conditions used during electrophoresis can be adjusted to separate molecules in a desired size range.

Graphic credit: Darryl Leja, National Human Genome Research Institute.

Patterns of proteins can be assessed using methods known as mass spectrometry or surface-enhanced laser desorption and ionization (SELDI). These techniques permit the assessment of many different proteins at once and the pattern can be compared between cancerous and non-cancerous cells.

A number of other methods are available for detecting proteins, DNA, and RNA. Some of these methods are described in the booklet entitled *Genomics in Cancer*, available on the Research Advocacy Network Web site: www.researchadvocacy.org.

Here are some other resources that may be useful in understanding the types of techniques available for identifying protein, DNA, and RNA targets:

- Cold Spring Harbor Laboratory DNA Learning Center: <http://www.dnalc.org/> (click on the Resources tab and then on the 3-D animation library. Near the bottom is a group of animations related to many several different techniques.
- National Cancer Institute Proteomics Fact Sheet: http://www.cancer.gov/cancertopics/factsheet/detection/Fs5_38.pdf

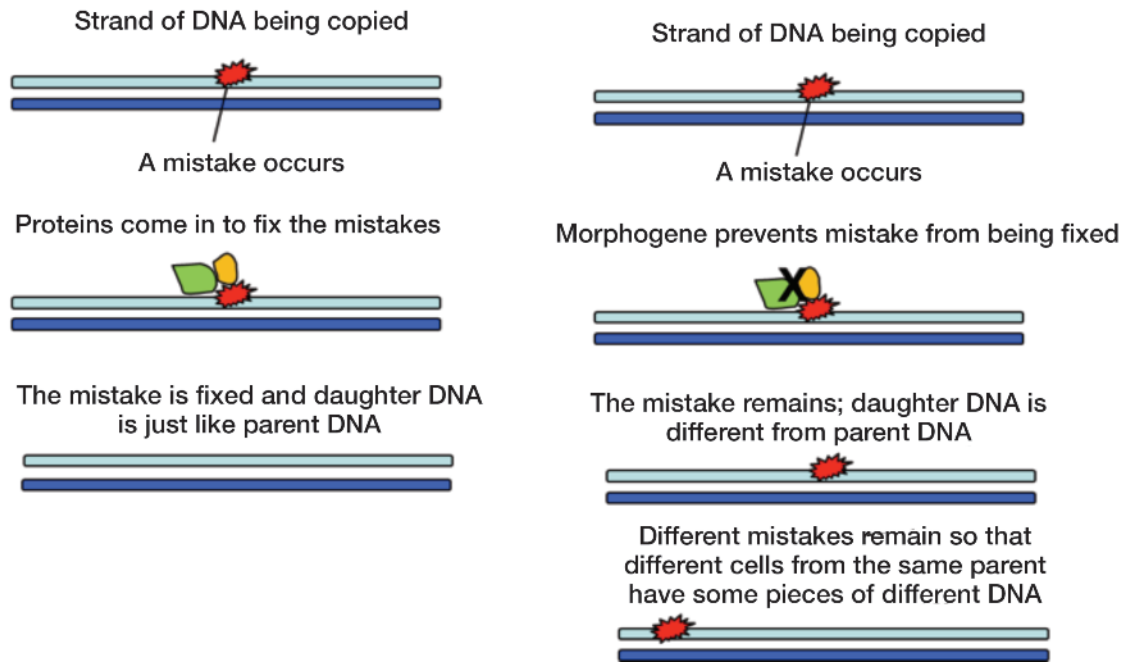
Platform Technologies: The Morphogenics Example

In addition to specific techniques that help researchers identify new targets for cancer therapies, a host of underlying technologies make it easier to do so. These so-called platform technologies provide an underlying base that can be used for a variety of different studies; that is, they enable discoveries by providing a foundation on which to work. DNA microarrays are platform technologies.

Another example of a platform technology that is enabling the identification of targets—and drugs to target them—is known as morphogenics. Morphogenics capitalizes on the ability of our cells to correct mistakes in the DNA copying process. Whenever our cells replicate, they first need to copy their DNA that will be passed onto the new cell. Mistakes inevitably occur during this process that entails the copying of three billion units contained within each human cell's genome. To ensure accurate heritability, cells have developed a variety of mechanisms designed to correct mistakes that occur during the copying process. If these mistakes were not corrected, some of the DNA sequences in the copied cells would be different from those in the parent cells, thus resulting in different traits, and in some instances, disease such as cancer.

Although we do want the genetic mistakes corrected when they occur in our bodies, the genetic mistakes can be useful when used in the laboratory to look for molecular targets or designing drugs. This is because a single parent cell can generate daughter cells whose DNA is slightly different, potentially exhibiting new traits. In the context of antibody-producing cells, these genetically different cells may produce better antibodies, whereas cells used for disease target discovery may show a molecular target that the parent cell did not.

In the morphogenics platform technology, proprietary agents are used to prevent cells from fixing their DNA copying mistakes. When the cells do replicate, they generate some cells whose DNA sequences are different from those of the parent cells—essentially increasing the diversity of the cell population. These cells can then be studied to identify new molecular targets or be used to screen for those producing biological agents with enhanced therapeutic potential.



Graphic depiction of morphogenetics. The left side of the figure shows a normal strand of DNA being copied when a mistake occurs (shown in red). Under normal conditions, proteins come in to fix the mistake in the newly replicated genome so the daughter cells are genetically identical to the parent cell. The right side of the figure shows a normal strand of DNA being copied when a mistake occurs (shown in red). The use of morphogenetics prevents the mistake from being fixed and the mistake remains, making the daughter cell genetically different from the parental cell. Different mistakes occur as the cells continue to replicate, generating a population of cells whose DNA is diverse. These cells can be used to study a variety of questions related to targeted therapies, including cell pathways that are involved in disease and in cells producing biological medicines that may have enhanced activity.

Drug Discovery—High-Throughput Screening

Once a target molecule has been identified, the next step is to find a drug to affect it. As we have seen in previous chapters, this often means finding a drug that will block the target's activity. As a starting point, investigators frequently use what is known as high-throughput screening. In high-throughput screening, millions of chemical compounds are examined for their ability to bind to the molecular target. In some cases, compounds are screened "virtually" on the computer. Compounds that bind are investigated further. Scientists may try to alter these compounds using computer modeling to try to optimize their activity. They may also physically or chemically alter the compounds in an attempt to arrive at a drug that is highly active against the target.

Preclinical Testing

Once a candidate drug has been identified, it undergoes preclinical testing. This is done in cell lines in the laboratory to make sure that the drug has a measurable action on cancer cells. The drug is then tested in animals to determine whether it slows down cancer without being too toxic. Researchers also monitor how the animal's body gets rid of the drug to study its metabolism.

Clinical Trials

A drug that has passed preclinical tests may be a candidate for clinical trials in humans. These trials are designed to determine whether the drug is safe and effective for the condition it is designed to treat. If a drug successfully passes through these trials, it gets approved by the United States Food and Drug Administration (FDA).

First, patients whose cells have the right target are identified; in some cases this may involve all patients with a certain type of cancer, whereas in others it may involve only a subgroup of patients such as those with the Philadelphia chromosome. The clinical trials are then conducted in stages or phases:

- **Phase 0: Exploratory Investigational New Drugs (IND) Trials**

Phase 0 studies are designed to determine whether the new drug actually affects its intended target. In these studies, people are given small doses of the drug and the drug's effects on the target are measured. These studies do not provide information about whether the drug is safe and effective.

- **Phase I – Safety Testing**

Phase I studies involve a small number of people and are designed to determine whether the drug is safe. Often the dose of a drug is gradually increased until problematic side effects occur. Participants in Phase I trials may be cancer patients whose disease has not responded to other therapies.

- **Phase II – Efficacy Testing**

If the drug passes Phase I trials, it is eligible for Phase II studies in which the effectiveness of the drug is examined. These studies often involve between 40 and 100 people—usually those whose cancers have not responded to other treatments. With targeted therapies, we may be seeing more phase II studies conducted earlier in the course of the disease.

- **Phase III – Efficacy Testing in Larger Populations**

Phase III trials are the primary safety and efficacy studies that determine whether a drug will be approved by the FDA to treat a given condition. In Phase III trials, hundreds or thousands of people are treated with the drug and their responses are compared to a group who receives a current standard treatment. The goal of these trials is to determine whether a drug's benefits outweigh its risks for the disease in question.

- **Phase IV – Studying Long-Term Effects or Safety in Larger Populations**

After a drug receives FDA approval, it may be required to undergo further studies to evaluate its long-term effects and/or safety when used in actual clinical practice as opposed to a controlled clinical trial. These studies may also involve hundreds or thousands of patients.

For more information on clinical trials and targeted therapies, you may want to read the National Cancer Institute's tutorial:

<http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies/htmlcourse/page5>

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Chapter 7: Challenges with Targeted Therapies

If you knew that swallowing a pill once or twice daily would greatly reduce the risk that your cancer would grow, you'd be sure to take your medicine as prescribed, right? Although most of us would answer this question with a resounding affirmative, the reality is a bit different. Even though cancer is a serious, potentially deadly disease, many people do not take their cancer medicine every day, compromising the effectiveness of treatment.

Taking medication as prescribed, known as medication adherence, is not an issue with traditional chemotherapies or monoclonal antibodies, both of which are typically infused into the veins. However, medication adherence is an issue with drugs that are taken orally such as hormone therapies for breast cancer. Most of the small molecule inhibitors are oral therapies as well.

Medication adherence is only one of many challenges posed by targeted therapies. In this chapter we will discuss some of these challenges, including medication adherence, acquired resistance, the lack of correlation between biomarkers and treatment effectiveness, how to determine effectiveness and dosing, and cost.

Medication Adherence

Traditional chemotherapies are administered via infusion into the veins and therefore require that patients come into a physician's office or cancer center to receive treatment. This is also the case for monoclonal antibodies. Adherence to infusion treatments is not typically an issue because patients schedule the appointments at specified times and re-schedule if they cannot keep them. Healthcare providers know whether patients show up for their infusions and can be sure they are getting the right amount of medication at the correct intervals.

In contrast, many of the small molecule inhibitors are pills that patients must swallow every day for months or even years. Patients may forget to take their pills or decide to skip a couple of days or weeks here and there. Often it is difficult to determine exactly how many days patients did take their medication as prescribed and not all doctors and patients attempt to keep track of this.

Medication adherence refers to the extent to which patients take medications as prescribed by their healthcare providers. For instance, if you are prescribed a medication to take once daily for two months and you do follow this schedule, you are adhering to treatment. If you take the medication daily for the first month, then forget for a week, and begin again for a few days, then forget again, you are not adhering well to treatment.

A number of studies have sought to determine adherence rates, or the percentage of prescribed medication doses that are actually taken by cancer patients. Findings show that cancer patients may take about 50% to 90% of their medication doses as prescribed when not participating in clinical trials. Adherence rates during clinical trials are higher.

Many factors influence medication adherence, including the patient's ability to follow the prescribed regimen (ability to understand the regimen, frequency of dosing, amount of behavioral change required, duration of therapy); communication with health care providers; patient satisfaction; patient health beliefs (eg, belief that the regimen will be beneficial or is worth the risks/costs); family stability; and social support. Some but not all studies find that older individuals may show lower adherence than younger ones, but the reason(s) for this is not known (eg, ability to understand directions, attitudes, comorbidities, etc). Cost to the patient, or higher copayments for the medication, can also negatively affect adherence. Other factors may also be important determinants of adherence and, overall, it is difficult to predict in advance which patients will adhere and which will not.

FACTORS THAT AFFECT MEDICATION ADHERENCE

Factors that reduce adherence

- Duration on medication: patients who have been on medication for years tend to show less adherence than those taking medication for weeks or months
- Regimen complexity: more frequent dosing is associated with less adherence
- Higher copayments
- Patient perceptions and motivations

Factors that can improve adherence

- Education about the importance of taking the meds as prescribed
- Improved dosing (eg, ease of taking medication, once daily vs. twice daily dosing)
- Reduced medication toxicities
- Good communication between patients and healthcare providers

Many of the small molecule inhibitor drugs act to prevent progression of the tumor or to keep cancer cells from replicating. They do not actually cure the cancer. When treated in this way, cancer can be viewed as a chronic disease that has much in common with several other serious chronic diseases such as diabetes and multiple sclerosis. That is, in all of these diseases, individuals must take medication regularly to prevent disease progression and, in all of these diseases, medication adherence is an issue. Many of the strategies developed to improve medication adherence in these and other chronic diseases may be applied to cancer, and this may be an area in which advocates can help. We discuss more about this in the final chapter of this booklet, which is devoted to a discussion of how advocates can use the information presented here.

For more information on medication adherence, you may want to read the following articles:

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Acquired Resistance

Although many cancers respond to targeted therapies, response by the cancer to the drug may be lost over time—a phenomenon known as acquired resistance. Acquired resistance can be contrasted with intrinsic or primary resistance, in which the cancer does not ever respond to the therapy.

Acquired resistance refers to a situation in which the cancer initially responds to the therapy but then stops responding; **intrinsic or primary resistance** means that the cancer does not respond to the therapy in the first place.



Illustration of drug resistance

Scientists are still attempting to determine what causes acquired resistance. For some drugs and cancers, the mechanisms are known, whereas for others they are still uncertain. For a given type of cancer and a given drug, there can be more than one mechanism of acquired resistance. To make things even more complex, different people can have different mechanisms and the same person may have more than one mechanism. This variability makes it extremely hard to characterize the reasons for acquired resistance.

One mechanism that has been well characterized is acquired resistance to imatinib in individuals with the BCR-ABL gene. You may remember that most cases of chronic myelogenous leukemia are caused by a translocation of chromosomal material that results in a kinase with no off switch. Imatinib binds to the active site on the kinase, preventing it from exerting its action—essentially turning it off. After treatment with imatinib, some individuals begin to show a mutation that causes the kinase protein to take on a slightly different shape. Imatinib does not bind to this new protein as well and thus the drug does not shut off the kinase activity as effectively—acquired resistance. Although other drugs that inhibit kinase proteins may work for a while in these individuals, mutations also develop to these drugs and they too become ineffective.

Researchers are investigating not only mechanisms of acquired resistance, but several other features as well. One important observation is that targeted therapies are often combined with traditional chemotherapies in clinical practice, whereas in the laboratory they are often studied in isolation. It is possible that mechanisms of acquired resistance may differ between the two situations and, in the future, we are likely to see more laboratory studies that pair targeted therapies with traditional chemotherapies.

Another observation is that acquired resistance may not always be passive, characterized only by lack of response. Some investigators believe that, in attempting to thwart the drug, the cancer can actually become more aggressive. This point is debated in the scientific literature and the safest conclusion right now is probably that acquired resistance may affect the pattern of cancer growth rather than increasing its aggressiveness overall. In order for targeted therapies, or any drugs, to get approved for clinical use, they must undergo rigorous testing. Studies have shown the approved targeted therapies do benefit cancer patients or they would not have been approved. Nevertheless, it is important to continue studies in this area so that better drugs can be developed and the best drugs possible can be given to patients.

Presence of Target Does Not Always Predict Response

Another challenge with targeted therapies is that the presence of the “target” as determined by a test (usually a gene- or protein-based test) does not always predict response. Some people with the target will fail to respond, a situation we briefly discussed in the last section as primary resistance. Conversely, some people without the target will respond. This situation is not as odd as it sounds because the targets are usually proteins such as growth factor receptors that all of us have in our bodies. It is possible that blocking the growth factor receptors could help benefit certain cancers even if the cancer is not overexpressing them.

A related finding is that the effects of the targeted therapy are not always related to the amount of the target. That is, you might think that a monoclonal antibody against a growth factor receptor would work better for people whose cancer cells have more of the receptor. This is not always the case. For instance, the effects of cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), are not related to the amount of EGFR protein expressed in the tumor. These observations make it difficult to devise a test to separate people for whom the treatment will work from those for whom it will not.

It is worth noting that the overall level of protein expression can be used as a predictor of response in some cases. For example, HER2 status, based on percentage of tumor cells staining positive for the HER2 protein, is used to determine whether a breast cancer will respond to the monoclonal antibody trastuzumab. HER2 status can be determined using a test that evaluates number of copies of the gene or the amount of HER2 protein. Higher scores on either test are an indication for treatment with trastuzumab. In rare cases, however, an increase in the number of copies of the HER2 gene (gene amplification) is not associated with an increase in protein expression—despite the use of validated tests in both cases. Additionally, among tumors that have a confirmed HER2 gene amplification and are HER2 positive, it is not known whether higher levels of gene amplification lead to different (eg, better or worse) response to therapy than those with lower levels of gene amplification. The quality of the test for any biomarker such as HER2 is a critical consideration. For more information about biomarker test validation, you may want to consult Research Advocacy Network’s booklet on *Biomarkers in Cancer*, available at our Web site (www.researchadvocacy.org). This booklet also contains a description of the tests used to determine HER2 biomarker status.

Gene amplification refers to an increase in the number of copies of a gene.

Determining Optimal Dosing and Effectiveness

With traditional chemotherapies, determining optimal dosing and effectiveness is relatively straightforward. Doses that cause tumors to shrink are effective and doses that cause prolonged decreases in white blood cells or other prolonged or severe effects are too high. Tumor size can be monitored using imaging techniques, and the status of blood cancers and white blood cell levels can be monitored by drawing blood.

With targeted therapies, determining optimal dosing and effectiveness is not as easy. For one thing, some targeted therapies cause tumor size to remain in check, or stabilize, without actually shrinking. When tumor size remains the same it is hard to tell whether the drug is really working. Conversely, most targeted therapies are less toxic to normal tissues than traditional chemotherapies. With traditional chemotherapies, one typically sees increased toxicity to normal tissues as the dose is pushed higher. This acts as a kind of thermometer to tell researchers and clinicians when doses are getting too high. With targeted therapies, optimal effectiveness may be reached before toxicities become severe, so there is no obvious criterion for concluding that a dose is too high.

These difficulties pose challenges in clinical trials, such that investigators and drug companies are often unsure about what doses to study. If the doses tested are too low, investigators may falsely conclude that the drug has no benefit. However, researchers are cautious not to push doses too high because unknown side effects may occur.

Monitoring Cancer During and After Treatment

Another challenge is how to monitor patients during or after therapy. As part of the monitoring procedures, clinicians typically take a careful history and perform periodic physical examinations. In some cases, patients without metastatic cancer who do not have symptoms and appear free of detectable disease after treatment may be monitored with annual screenings. Patients with metastatic disease are typically monitored to determine the effects of the therapy and whether an alternative regimen should be initiated. Again, periodic histories and physical examinations are performed, but clinicians also monitor routine blood tests that give an indication of how a patient’s bone marrow (a complete blood test) and liver (liver function tests) are functioning.

Metastatic refers to the spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a “metastatic tumor” or a “metastasis.” The metastatic tumor contains cells that are like those in the original (primary) tumor.

Additionally, many clinicians take periodic blood tests to examine levels of biomarkers in the blood, often referred to as tumor markers. Tumor markers are proteins made by cells; although normal cells also make these proteins, cancer cells often make higher amounts and release them into the bloodstream. In breast cancer, the most commonly followed tumor marker is a protein called MUC1. Several different tests evaluate the levels of MUC1: CA15-3 and CA2729. Because both of these tests measure the same thing (MUC1), clinicians order one or the other but not both. Another commonly used tumor marker is carcinoembryonic antigen (CEA). Although these tumor markers are not absolutely accurate, increasing levels in the blood generally suggest that the tumor is growing, whereas declining tumor marker levels generally suggest that the therapy is working.

In addition, most clinicians perform periodic imaging tests or tests that give a picture of what is going on in the body. Imaging tests can be based on x-rays, such as standard radiographs (what we normally think of as X-rays) or computerized tomography (CT) scans. Magnetic resonance imaging (MRI) can provide an indication of the location and size of the primary cancer and metastases. Imaging may also be done using radioactive agents that localize to a person's cancer deposits. The most frequently used test of this type is a bone scan. A second technique measures the activity level of the tumor using activity imaging scans, called positron emission tomography (PET).

In monitoring the effects of therapy, it would be ideal if physicians could evaluate the levels of certain target molecules in tumor tissue over time. This method is hampered by the need to take repeated samples of the tumor. In such cases, people with tumors would need to undergo periodic sampling procedures to obtain tumor tissue that can then be tested for proteins or genes of interest. Because obtaining tumor samples is generally invasive, it is not practical for patients—particularly when performed repeatedly. Studies that include repeated tumor sampling procedures may also be time consuming and expensive. However, repeated tumor sampling may provide important information about the types of tumors that respond best to a given therapy, leading to more accurate individualized treatments and helping others to avoid treatments unlikely to help them.

Another monitoring method that is being intensively studied is the measurement of tumor cells in the blood, known as circulating tumor cells. Circulating tumor cells break off from tumors and travel through the blood circulation. Several studies have demonstrated that circulating tumor cells levels can provide important information about breast, colon, and prostate cancers. Circulating tumor cells can be used to complement history and physical examination and tumor marker blood tests to monitor patients with metastatic breast cancer.

Recent evidence also suggests that certain cancer biomarkers can be evaluated in circulating tumor cells. As a result, researchers are also working on the possibility that circulating tumor cells may be an alternative to biopsies of the tumor itself. If this proves to be the case, it may be possible to determine molecular features of the tumor by sampling tumor cells in the blood circulation. Characterization of such biomarkers in circulating tumor cells, such as estrogen receptor, HER2, or other new targets of therapy, could be extremely useful in selecting specific therapies for patients and for tracking tumor activity. However, circulating tumor cells occur at extremely low levels, and at present no clinical trials have demonstrated that using circulating tumor cells to monitor biomarkers provides clinically useful information.

Researchers are also working on the possibility that circulating tumor cells discussed in the previous paragraph may be an alternative to cells localized to the tumor itself. If this proves to be the case, it may be possible to determine molecular features of the tumor by sampling tumor cells in the blood circulation. However, as mentioned previously, circulating tumor cells occur at extremely low levels and are not yet measured routinely in clinical practice. Another alternative being investigated is measuring the blood for circulating tumor DNA and this will be an interesting area of research to watch in the coming years.

Developing new methods for evaluating the effectiveness of therapies is a time consuming process because the methods need to be tested in the laboratory, optimized, validated in clinical studies, and made accessible for clinical use. However, these methods may ultimately lead to a better matching of patients with treatments, enabling each patient to begin on the therapy most likely to benefit him or her without wasting time on ineffective therapies and being unnecessarily subjected to their side effects.

Cost

The cost of targeted therapies is a critical consideration, particularly given their cost differential compared to traditional chemotherapies. Traditional chemotherapies have been around for years and, in medical terms, are relatively inexpensive. For example, an 8-week treatment regimen with a common chemotherapy may cost less than \$100. In contrast, targeted therapies are generally expensive, with some costing more than \$30,000 for 8 weeks of treatment. The reasons for the high price tag with targeted therapies are multi-faceted, including the costs of drug discovery and clinical trials, biotechnology costs for monoclonal antibodies, insurance and reimbursement issues, and the need for drug companies to re-coup development costs and make a profit.

As patents expire on name-brand targeted therapies, companies are allowed to develop drug products that are generic copies or biosimilars. Drugs that are chemically synthesized can be copied exactly and are referred to as generics. Drug products derived from living cells or organisms cannot be copied exactly and are referred to as biosimilars. The availability of these products is expected to decrease the prices of targeted therapies.

Biosimilar: A copy of a biological product that is highly similar to an already-approved biological product.

Biological product: A drug or other product used for medical purposes that is derived from living cells or organisms. Monoclonal antibodies are biological products. Many of the small molecule inhibitors are not biological products—they are chemically synthesized.

Some argue that the availability of competition for targeted therapies will reduce prices and make these drugs affordable for patients. However, others argue that the price reductions will be modest, particularly with biological products, because of the complexity of manufacturing methods. The cost of targeted therapies is an issue that our nation will increasingly face as more of these products are developed for what may be a decreasing number of select patients whose cancer profile matches that of the targeted therapy.

For an interesting article on the cost-benefit of targeted therapies, you may want to read the following article on the Economist Web site: <http://www.economist.com/node/18743951>

Another interesting article on the economics of targeted therapies is available from the Deloitte Center for Health Solutions and Deloitte Consulting LLP. This article discusses the economic challenges with developing targeted therapies for fewer individuals as opposed to the old model of developing a blockbuster drug for many individuals. The article considers the roles of multiple stakeholders in making the targeted therapies model work and considers these roles within the larger healthcare system. This article is available on the Web at: [http://www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_chs_targeted_Therapies_012307\(1\).pdf](http://www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_chs_targeted_Therapies_012307(1).pdf)

Drug Shortages

Another issue that has affected targeted therapies is the shortage of medication supply. Drug shortages are not unique to cancer therapies—different areas of medicine have been experiencing these problems—but cancer has been particularly affected in the area of “sterile injectable therapies” such as monoclonal antibodies. Drug shortages have caused problems in obtaining enough drug to treat patients, lack of drugs for clinical trials, borrowing and hoarding drugs in pharmacies and hospitals, and illegal activities such as counterfeit copies of the drugs.

Many different reasons have been proposed for these shortages, including manufacturing problems, quality issues, insurance and regulatory problems, and the fluctuating economics of producing “sterile injectables,” which tend to be biological products like monoclonal antibodies. According to the United States Department of Health and Human Services (HHS), the shortage in sterile injectables has been caused by an increase in the number and amount of products over a short period of time without an expansion in manufacturing capacity. The expiration of patents for name brand drugs and the entry of biosimilars may also have played a role.

The United States Food and Drug Administration (FDA) maintains information about drug shortages. Although manufacturers are not required to report drug shortages, many do and these are freely available on the FDA's Web site: <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>. The HHS stresses that, although drug shortages can be a significant problem, they affected about 10% of the injectable cancer procedures in 2008 meaning that most drugs were available for most patients.

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Chapter 8: Future of Targeted Therapies – Toward Tailored Therapy

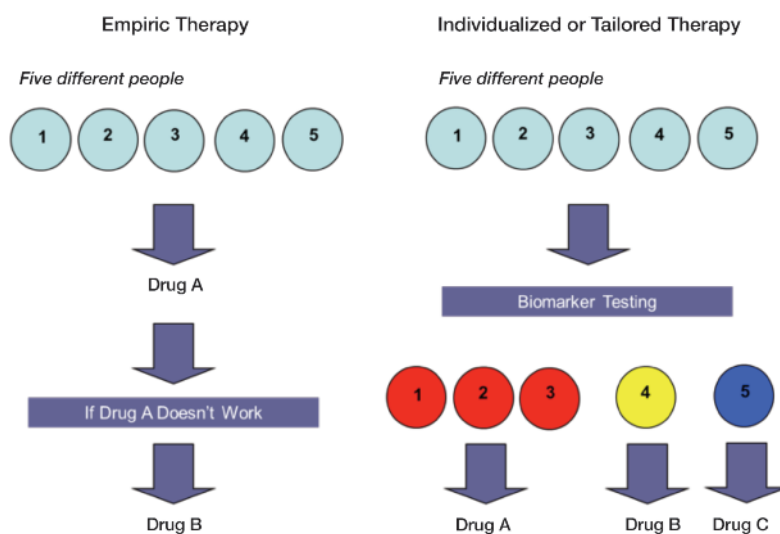
Stella owns an internet-based business that designs and prints pamphlets, business cards, and posters. Over the past few years revenues have declined, with fewer new clients approaching her for business and existing clients placing fewer and smaller orders. In thinking about the reasons for her reduced business, Stella evaluates many possible influences. She considers the dip in the economy, the trend toward electronic as opposed to print communication, her advertising strategies, and the quality of her materials. After analysis, Stella concludes that all of these factors are negatively impacting her business and she initiates a strategy designed to address the problems.

Like the decline in Stella’s business, cancer is determined by multiple problems. Fixing one of these problems may help improve the situation, but ideally all the problems would be addressed to give the best chance of success. Today we have biomarker tests for a few cancer types that can determine whether our cancer is likely to respond to a given drug. However, we would like to have a test that tells us all of the factors that are contributing to the cancer. We would further like to be able to target all of these problems with drugs that are effective and safe. We would like to predict who will respond to which drug combination and who will and will not be able to tolerate the treatment.

In this chapter, we discuss the future of targeted therapies for cancer. We discuss how multiple gene changes that cause cancer can be characterized and targeted with treatment. We also consider strategies of testing and drug development that are leading us further along the road toward tailored or individualized therapy for cancer.

What Is Tailored or Individualized Therapy?

Tailored or individualized therapy refers to treatment that takes into account individual differences such as the gene- or protein-based differences in tumors. Tailored or individualized therapy differs from the traditional trial-and-error method known as empiric therapy. In empiric therapy, everyone is given the treatment that works the best for most people. If this treatment doesn’t work for someone, he or she then receives a different treatment. In tailored therapy, everyone undergoes a test to determine one or more specific features of the disease. In cancer, this usually means a test that is designed to detect a specific gene- or protein-based alteration in the cancer. Based on the outcome of the test, each person is treated with a drug that best matches his or her cancer profile.



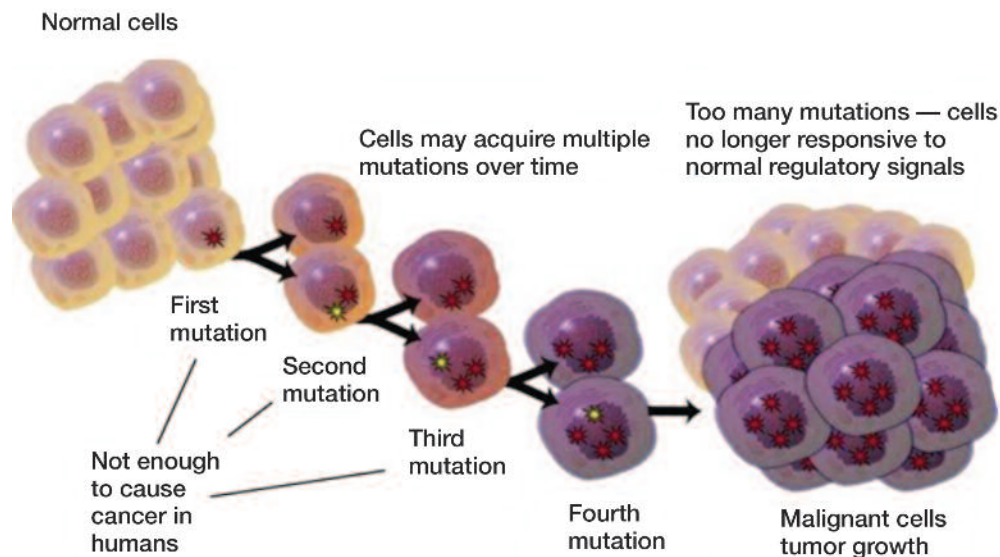
Empiric therapy compared to tailored or individualized therapy. In empiric therapy, each individual (labeled #1 through #5) receives the treatment that works best for most patients. This is Drug A. If Drug A doesn't work for a particular individual, Drug B is tried. In tailored or individualized therapy, each individual (labeled #1 through #5) is tested for the presence of a biomarker. In this example, biomarker testing shows that patients #1 through #3 are best matched with Drug A, patient #4 is best matched with Drug B, and patient #5 is best matched with Drug C.

As we've discussed in past chapters, we already have targeted therapies that can treat certain types of cancers based on the presence of a certain feature such as HER2 overexpression. However, many experts believe that in the not-too-distant future, targeted therapies will become part of a more comprehensive individualized approach to cancer treatment. Instead of looking at a single gene or protein that may differ among people, tests will be designed to detect many different features of the cancer. Drug combinations that target multiple alterations in cancer cells can then be given to maximize the chances of stopping cancer progression.

Multi-Hit Theory of Cancer

One of the reasons that scientists are striving to find treatments that target multiple features of cancer is because cancer is caused and/or maintained by alterations in more than one gene. A single alteration in one gene is not typically enough to cause cancer in humans. Instead, cancer is believed to occur when we accumulate multiple alterations in genes that are part of pathways critical to cell growth and the regulation of normal cell behavior.

When a cell accumulates 4 to 6 such mutations, it may begin to replicate out of control, eventually resulting in cancer. These cells lose their shape and become unable to perform their normal functions. Because cancerous cells are very good at replicating and growing, they crowd out normal cells in the tissue, preventing them from performing their functions. Some cells can escape into the blood and be transported to distant locations where they may begin to replicate uncontrollably; for example, cells from a lung tumor may break off and travel to the spine. In this case, the tumor is said to be metastatic.



Multiple Gene Alterations in Critical Cell Pathways Can Lead to Cancer. This graphic shows how multiple mutations can lead to cancer. The left cells show that a single mutation is not enough to cause cancer in humans; similarly, in the second cell, two mutations are still not enough to cause cancer. As cells accumulate multiple critical mutations over time – typically 4 to 6 – the cell may begin to transform into a cancerous cell. In this example, after a fourth mutation, the cell has accumulated a critical number of mutations in pathways important to cell behavior or fate and has become cancerous. The cell in this example has lost its normal shape and the nucleus, depicted as the dark purple circle in the middle, has become enlarged to take up more and more space in the cell. If this cancerous cell continues to replicate or make more copies of itself, cancer will result as shown on the right.

Graphic credit: Darryl Leja, National Human Genome Research Institute

In cancer treatment today, many people do receive multiple drugs. These drug combinations may include different types of traditional chemotherapies with or without a targeted therapy. For example, the combination of two monoclonal antibodies that target different parts of the human epidermal growth factor receptor, pertuzumab (Perjeta™) and trastuzumab (Herceptin®), is approved for the treatment of HER2 positive breast cancer when taken along with docetaxel. In the future, we are likely to see drug combinations that include multiple different targeted therapies without traditional chemotherapies.

Pharmacokinetics or Predicting Drug Doses

Predicting efficacy is not the only important aspect of tailored therapy. Some people have genetic alterations that make them unable to readily metabolize or break down certain drugs. Decreased metabolism of certain drugs causes high levels of the drug to accumulate in the body. This may cause the drug's effects to be more intense and prolonged than expected, and may lead to more toxic side effects. Tests that can detect the genetic alterations in drug metabolism would greatly improve treatment because doses could be adjusted in advance to minimize the side effects.

This aspect of tailored therapy is known as pharmacokinetics. Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and eliminated by the body. In cancer research, this typically means studying how levels of the drug vary based on variations in metabolism.

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and eliminated by the body.

Tests are already available for several genetic alterations that make it difficult to metabolize certain drugs. A biomarker known as UGT1A1*28 can be detected by analyzing samples of blood or cells from a cheek swab. Approximately 10% of people in the United States have a genetic variation that leads them to metabolize the drug irinotecan more slowly. Irinotecan is used to treat certain types of colorectal cancers. Doses of irinotecan can be adjusted for people with this genetic variation so that their side effects are less severe.

Another example of how therapy is being tailored based on pharmacokinetic information relates to a gene that codes for an enzyme called thiopurine methyl-transferase (TPMT). Some individuals have mutations in this gene that prevent them from metabolizing and clearing the drug mercaptopurine. Mercaptopurine is often used to treat a type of childhood leukemia. Peoples with certain mutations in the TPMT gene who are given mercaptopurine cannot adequately metabolize the drug, leading to a sustained reduction in the number of white blood cells. White blood cells fight infections and their prolonged decrease can be life threatening. If it is determined that someone has a mutation in this gene, he or she can be given a lower dose of mercaptopurine that may be safer and more tolerable.

Both of these examples show how gene-based tests are being used to predict the pharmacokinetics of traditional chemotherapies. Gene-based alterations that affect pharmacokinetics are not yet a major issue for targeted therapies, but these may become important as new targeted therapies are developed.

Companion Diagnostics

The utility of many targeted therapies in cancer is determined by a test. If a drug acts on a specific target that is only present in some cancers, then each person's cancer cells will need to be tested to see if they contain that target. Today, a different test is used for each therapy that targets a molecule present in some cancers but not others.

Some targeted therapies act by a mechanism that is common to all tumors such as drugs that inhibit angiogenesis (new blood vessel formation). In such cases, tumors do not have to be tested to see if they contain the target—all tumors require generation of a blood supply to sustain their activity. In the future, we are likely to see other targeted therapies that act on mechanisms common to all tumors such as energy metabolism, indefinite replication, or other crucial functions listed in the cancer hallmark section of Chapter 5.

In many cases, the targeted therapies were developed separately from the tests. However, there is a growing trend for companies to develop companion diagnostics that are tested alongside the drug. Companion diagnostics are medical tests that provide information essential to the safe and effective use of the product. The government agency in charge of approving new drugs, the Food and Drug Administration (FDA), recommends that if a companion diagnostic is essential for the safe and effective use of a drug, the device and the drug should be approved together. According to the FDA, a companion diagnostic could be essential for the following reasons:

- To identify patients who are most likely to benefit from a particular therapeutic product
- To identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- To monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

Companion diagnostics are medical tests that provide information essential to the safe and effective use of the product.



It should be noted that the FDA refers to these tests as in vitro companion diagnostic devices. This does not include clinical laboratory tests that provide information useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product. Examples of companion diagnostics are kits designed to determine HER2 status in breast cancer patients such as HercepTest™ (Dako Denmark A/S) and Inform™ HER2/neu (Ventana Medical Systems, Inc.). Examples of clinical laboratory tests that are not companion diagnostics include prostate-specific antigen for prostate cancer, cancer antigen 125 (CA 125) for ovarian cancer.

The FDA maintains a list of companion in vitro diagnostic devices approved for use, available at the following Web site:
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>

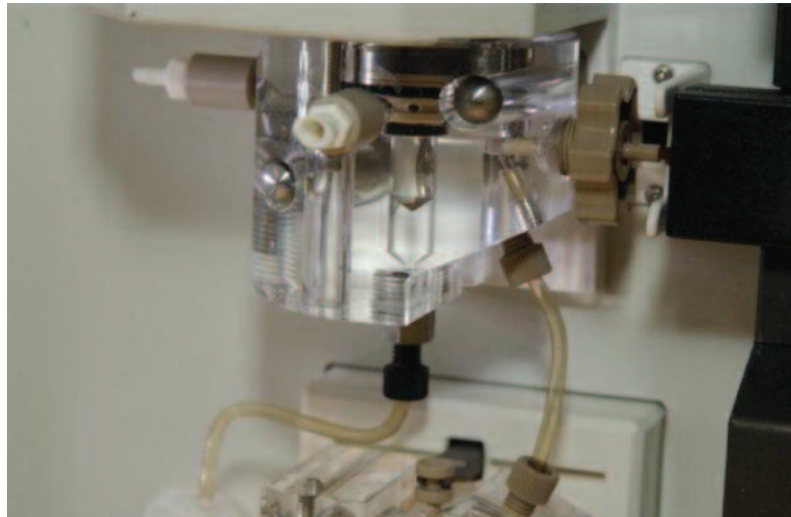
Whole Genome Sequencing

Some experts believe that a technique known as whole genome sequencing will be an important part of tailored therapy in the future. In whole genome sequencing, an individual's entire genome—all of person's DNA—is sequenced or decoded.

Genome: All of an organism's DNA

This method is, in one way, the opposite of a companion diagnostic. Whereas a companion diagnostic typically gives information about a single gene or protein, whole genome sequencing gives information about all of our DNA at once.

Whole genome sequencing is clearly a powerful technique, but serious hurdles still remain before it would be useful as a healthcare tool. Although costs are falling rapidly, sequencing a person's entire genome is an expensive undertaking. Some experts believe that costs will not be a limitation as more streamlined methods are developed and more genomes are sequenced. A second issue relates to the ethics of having your entire genome sequenced in order to determine your cancer-causing mutations. Whole genome sequencing will provide a huge amount of extraneous information about your DNA that healthcare providers do not need to make cancer-related decisions. The fate of this information is critical to consider as more and more people agree to have their genomes sequenced. Moreover, there is the issue of interpreting changes for each patient—trying to determine what the findings mean for every individual. As the whole genome sequencing becomes more cost effective over time, we will have to address the attendant ethical, legal, and social issues.



DNA Sequencer

Photo credit: Maggie Bartlett, National Human Genome Research Institute, National Institutes of Health Intramural Sequencing Center, Rockville, MD

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Chapter 9: How Can Advocates Use This Information?

As advocates, we want to understand the basic language of targeted therapies because of their current and growing importance in cancer. The information in the preceding chapters can help us gain a working knowledge of targeted therapies that will allow us to more easily communicate with physicians and researchers. It will give us added credibility for our viewpoints and permit us to better understand developments in the field.

Within the realm of targeted therapies, advocates are in a position to help address a number of important challenges, some of which are considered in Chapter 7 (Challenges With Targeted Therapies). Following is a description of several issues that advocates may be interested in pursuing.

Medication Adherence

As described in Chapter 7, medication adherence is an important issue with small molecule inhibitors—an issue that many patients with breast cancer have already experienced with hormone therapies, most of which are available as oral tablets. Despite the importance of taking these drugs as prescribed, patients often skip doses, potentially compromising treatment efficacy. Education and communication are two factors that have been found to improve medication adherence. Advocates may wish to participate in these efforts through developing educational materials or suggesting/participating in initiatives to emphasize the value of the prescribed regimen, institute medication-taking systems, enlist help from caregivers, and reward medication-taking behavior. Advocates may also be able to influence physicians, urging them to ask patients if they are taking their medications and stress the importance of medication adherence. Directions from physicians carry weight with patients. This seems to be an area in which advocate participation in the creation and/or dissemination of materials and patient education may be valuable in helping maximize adherence.

An interesting and accessible article on medication adherence and cancer is available at the following Web site: Hohnaker J, Shah-Mehta S, Brandt PS. Perspectives on adherence and persistence with oral medications for cancer treatment. *J Oncol Pract.* 2011; 7: 65-67. Available at: <http://www.jop.ascopubs.org/content/7/1/65.full>. Accessed December 17, 2012.

Cost

The cost of targeted therapies is often exorbitant and difficult or nearly impossible for patients to afford. Advocates may have experience with and knowledge of reimbursement processes that help patients obtain these drugs.

One type of program that is available for certain patients is compassionate use. Compassionate use programs allow seriously ill patients who meet specific criteria to use new, unapproved drugs if no other treatments are available. Compassionate use of these investigational drugs is available through two mechanisms: expanded access programs or single patient access. Expanded access programs are often available for investigational drugs in late-stage development if the drug has shown at least some benefit for the treatment of a given cancer in clinical trials. In such cases, the drug manufacturer may make the investigational treatment available for patients who are not able to enroll in the clinical trials. The other compassionate use program is single patient access. Physicians may contact the pharmaceutical company to see if they will supply the drug for a specific patient. Once the company approves, the FDA must approve, which requires the physician to send information about the patient and specifics of the request along with a signed informed consent from the patient.

It is undeniable that targeted therapies can be expensive for pharmaceutical companies if one considers the drug development process, manufacturing issues, extensive safety and efficacy testing, and the need to make a profit. If targeted therapies are only useful in a small portion of patients, demand for the drug will be limited, further impacting costs. Advocates need to take every opportunity to address cost issues.

The questions of cost get even more complicated for targeted therapies that provide a statistically significant but relatively small improvement in survival outcomes. As a society, it is difficult for us to address the value of such therapies and, in these types of discussions, the input of advocates is absolutely essential. Advocates who are cancer survivors provide a unique perspective that is inherently important and can help inform patient as well as policy decisions.

Of course, some targeted therapies have revolutionized treatment of selected cancers and the high costs are easier to weigh against the large benefits of the drugs. However, in cases where dramatic benefits are less likely, many have doubts about the utility of routine treatment with targeted therapies. In the future, such arguments may be avoided when patients who stand to truly benefit from the drugs can be distinguished from those who do not. However, currently, the predictive variables are not known for some types of targeted therapies in some types of cancers. In these instances, costs for the targeted therapy remain high and the potential benefit for most patients low.

In our discussion of challenges with targeted therapies, we mentioned an article from the Deloitte Center for Health Solutions and Deloitte Consulting LLP that discusses the economic challenges with developing targeted therapies for fewer individuals as opposed to the old model of developing a blockbuster drug for many individuals. It is worth repeating the link to this article here because it provides an excellent overview of the economic and social topics. This article is available on the Web at: [http://www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_chs_targeted_Therapies_012307\(1\).pdf](http://www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_chs_targeted_Therapies_012307(1).pdf)

Encouraging Research Participation

Only a small percentage of the patients who would be inclined to participate in cancer research studies actually do. According to the National Cancer Institute, one reason for this is because patients are not always informed about the studies by their healthcare providers.

Some of the most pressing challenges with targeted therapies are likely to be answered through research, including primary and acquired resistance, optimal dosing, effectiveness testing, and prediction of treatment response/identification of patients who will respond. Moreover, the benefit of combining different targeted therapies that act on different key pathways is predicted by nearly everyone—but this prediction can only be adequately studied in clinical trials.

The answers to these questions depend on conducting the right type of research and having enough patients participate in clinical trials to provide meaningful results. Advocates can help attain these ends by encouraging physicians to tell their patients about research studies, providing educational materials, and elaborating the advocate point of view regarding the urgency of such research. Research advocates can also help ensure that the clinical trials are designed in such a way that patients understand them, are willing to do what is needed by the trial, and are willing to stay in the study. This typically involves working with the research team developing study protocols.

Biomarkers and Tissue Specimens

Advances in targeted therapies for cancer depend on the identification of novel biomarkers to target, and this requires the use of tissue specimens. Tissue specimens or biospecimens are samples of biological tissue for research or testing. Tissue samples are often blood samples or samples of tumor tissue.

Because of the many studies being conducted in the United States and worldwide, tissue specimens are needed continuously. Unfortunately, many areas of cancer research do not have adequate amounts of tissue. Several professional groups have identified the lack of access to pathological tissue specimens as a primary barrier to the development of cancer diagnostics and therapies.

A related issue is that large numbers of tissue samples are needed in order to conduct robust studies that support strong conclusions. This research depends on large numbers of biospecimens for analysis because of the variability associated with any human study. That is, humans do not live in a controlled environment and many factors can affect clinical outcome. The best way to combat variability is to have a large sample size.

Given the importance of tissue to targeted therapy research, why isn't there enough tissue to go around? There are many possible reasons for this. First, some individuals simply lack knowledge about providing tissue for research. They may not understand the importance of donating tissue or even that there is an option to do so. They may also lack knowledge about what the tissue will be used for or may fear that their tissue may be misused. Often they are not asked by their physicians so the opportunity is missed. Characteristics of the cancer may also influence whether there is enough tissue for study. Some tumors may be small or the cancer may be rare. Facility issues are also important in that some medical institutions may lack the capabilities needed to collect, store, and/or ship the tissue to the

appropriate locations. Finally, in some instances, tissue is needed from diverse populations. This is particularly true for studies related to drug metabolism, as it is known that people of different races and ethnicities metabolize some drugs differently.

Advocates can play an important role in helping patients and the general public understand the need for tissue in biomedical research. Many advocates have themselves donated tissue and are aware of the issues involved. Additionally, advocates often have the motivation and contacts to help design and implement tissue collection programs. Some advocates have formed their own tissue banks in order to protect the rights of those who provide tissue for research and to ensure that they have a say in what is done with that tissue. An example is the Inflammatory Breast Cancer Research Foundation's Biobank (<http://www.ibcresearch.org/diagnosed/biobank/>). Other advocates are working with the National Cancer Institute to develop best practice standards for tissue banks. For more information on tissue banks, you may want to read Research Advocacy Network's booklet entitled *Understanding Pathology and Tissue Research*, available at the Research Advocacy Network Web site: www.researchadvocacy.org. This booklet also considers ethical issues related to tissue samples such as ownership that are important considerations for many advocates.

Genomic Tests

Although whole genome sequencing is not a routine part of today's cancer treatment, it is certainly on the horizon. As more information about gene function becomes available, allowing others to decode our entire genomes will become even more of a dicey proposition than it is today. Do we want our cancer treatment team to know that we are at risk for Alzheimer's disease? Do we even want to know that information ourselves given that there is no current preventive treatment? How can we be sure that insurance companies don't get this information and deny us coverage based on our genes? As patients are asked to provide consent for sequencing their entire genome, it will be essential to ensure that they are aware of the potential benefits and drawbacks.

Although laws protect the confidentiality of genetic information, it will be critical to make sure that safeguards are in place to ensure that the confidentiality is maintained. This might include a secure room where the computers containing the information are kept, routine password changes, destruction of the information once it has been used to inform cancer treatment, etc.

The availability of information about one's entire genome brings up a plethora of considerations that do not apply to tests for a single biomarker. Many of these considerations are outlined in several other publications available through Research Advocacy Network: *Genomics in Cancer – An Advocate's Guide and Training Manual* and *Biomarkers in Cancer – An Introductory Guide for Advocates*. Both of these publications are available through the Research Advocacy Network Web site: www.researchadvocacy.org

Advocates are well poised to champion issues that are important to patients—even if patients may not be aware of them, as is likely the case with whole genome sequencing. The passion and personal experience that advocates bring to the discussion of targeted therapies are powerful forces that can move barriers that may otherwise be insurmountable.

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Glossary

Acquired resistance: a situation in which the cancer initially responds to the therapy but then stops responding

Adherence: the extent to which patients take medications as prescribed by their healthcare providers

Antibody: a protein made by plasma cells (a type of white blood cell) in response to an antigen (a substance that causes the body to make a specific immune response)

Antigen: a substance that causes the immune system to develop antibodies; substance to which antibodies bind

Apoptosis: a type of cell death in which a series of molecular steps in a cell lead to its death. This is one method the body uses to get rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells

BCR-ABL fusion gene: A gene formed when pieces of chromosomes 9 and 22 break off and trade places. The ABL gene from chromosome 9 joins to the BCR gene on chromosome 22, to form the BCR-ABL fusion gene. The changed chromosome 22 with the fusion gene on it is called the Philadelphia chromosome. The BCR-ABL fusion gene is found in most patients with chronic myelogenous leukemia (CML), and in some patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML)

Biological product: a drug or other medical product that is derived from living cells or organisms. Monoclonal antibodies are biological products, but many of the small molecule inhibitors are not biological products—they are chemically synthesized

Biomarkers: anatomic, physiologic, biochemical, or molecular parameters associated with the presence and severity of specific disease states

Biosimilar: a copy of a biological product that is highly similar to an already-approved biological product

Cell cycle: A series of steps during which the chromosomes and other cell material double to make two copies. The cell then divides into two identical cells, each receiving one copy of the doubled material. The cell cycle is complete when each cell is surrounded by its own outer membrane

Cell proliferation: an increase in the number of cells as a result of cell growth and cell division

Chemotherapy: treatment with drugs that kill cancer cells

Chimeric monoclonal antibody: an antibody made in the laboratory by combining human antibody parts (approximately 65%) with mouse antibody parts (approximately 35%) in an attempt to reduce the immune response to the mouse antibody

Companion diagnostics: medical tests that provide information essential to the safe and effective use of the product

Cytogenetic testing: tests examining the number and structure of chromosomes

Extracellular matrix: A structural and functional complex of proteins and other biochemicals produced by cells and excreted to the extracellular space within the tissues, serving as a scaffolding to hold tissues together and helping to determine their characteristics

Gene amplification: an increase in the number of copies of a gene

Genome: all of an organism's DNA

Genomics: the study of genomes, especially multiple genes within cells

Humanized monoclonal antibody: an antibody made in the laboratory by combining a human antibody with a small part of a mouse or rat monoclonal antibody; the mouse or rat part of the antibody binds to the target antigen, and the human part makes it less likely to be destroyed by the body's immune system

Intravenous: into the veins

Intrinsic resistance (also known as primary resistance): the cancer does not respond to the therapy in the first place

Kinase: an enzyme that transfers phosphate groups from one place in the cell to another

Mechanism of action: the mechanism by which a pharmacologically active substance produces an effect on a living organism or in a biochemical system

Medication adherence: see adherence

Metastatic: the spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a "metastatic tumor" or a "metastasis." The metastatic tumor contains cells that are like those in the original (primary) tumor

Molecule: the smallest particle of a substance that has all of the physical and chemical properties of that substance

Monoclonal antibodies: antibodies that are identical because they are produced by one type of immune cell, all clones of a single parent cell

Overexpression: to make too many copies of a protein or other substance

Pharmacokinetics: the study of how drugs are absorbed, distributed, metabolized, and eliminated by the body

Phosphate groups: a functional group of atoms comprised of the element phosphorus (P) attached to four oxygen atoms (O) that carries a net negative charge, represented as PO_4^{3-}

Polyclonal antibodies: antibodies derived from different cell lines

Proliferation: (see cell proliferation)

Proteomics: the study of proteins expressed in a cell at a given point in time

Radiation therapy: the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors

Rapamycin: a drug used to keep the body from rejecting organ and bone marrow transplants. Rapamycin blocks certain white blood cells that can reject foreign tissues and organs. It also blocks a protein that is involved in cell division. It is a type of antibiotic, a type of immunosuppressant, and a type of serine/threonine kinase inhibitor. Rapamycin is now called sirolimus.

Receptors: molecules inside or on the surface of a cell that bind to specific substances and cause specific effects in the cell

Telomerase: An enzyme in cells that helps keep them alive by adding DNA to telomeres

Telomere: The ends of a chromosome. Each time a cell divides, the telomeres lose a small amount of DNA and become shorter

Tumor suppressor: A type of gene or the protein that it encodes that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer. Also called antioncogene

Tyrosine kinases: enzymes that transfer phosphate groups from one place in the cell to another. They transfer the phosphate groups from important cell energy molecules known as adenosine triphosphate (ATP) to specific places on proteins known as tyrosine amino acid residues

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Why Was this Guide Developed?

As advocates try to work within the system to advance research it is important to understand the basic tenets of the science. By gaining a better understanding, advocates can identify and illustrate the issues and problem-solve to support solutions. Targeted therapies and personalized medicine are areas important for patients and advocates and represent advancements in patient care through scientific discoveries. We hope that this information will be helpful to advocates and others interested in advancing the science and improving care for cancer patients.

About Research Advocacy Network

Research Advocacy Network is committed to improving patient care through research. Our goals are to get results of research studies for new treatments and improved methods of detection of cancer to patients more quickly, to give those touched by the disease an opportunity to give back and to help the medical community improve the design of its research to be more attractive to potential participants. Because research holds the hope for improvements in treatment, diagnostics and prevention, we are dedicated to patient focused research. We believe dissemination of research results to the medical community and patients can have a major impact on clinical practice.

The Research Advocacy Network (RAN) is a not for profit (501 c 3 tax exempt) organization that was formed in 2003 to bring together participants in the research process with the focus on educating, supporting, and connecting patient advocates with the medical research community. While there are many organizations addressing the needs of patients with specific diseases, political advocacy, cancer education and fundraising, no organization has focused on advancing research through advocacy. RAN works with advocates and organizations to effectively integrate advocates into research activities. Please learn more about us at our website at www.researchadvocacy.org or contact us about our work by e-mailing us at info@researchadvocacy.org or by phone 877-276-2187 or FAX at 888-466-8803.

Funding

Funding for the development and printing of this material was obtained through an unrestricted educational grant from Morphotek, Inc.

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