The Treatment Development Process: The Role of Tissue

Research Advocacy Network

Advancing Patient-Focused Research

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If you or someone you know has been treated for cancer or a serious illness you may have wondered how the drugs and treatments were developed for use in the treatment of that condition. Traditionally, cancer has been treated primarily through removing the tumor surgically, giving the patient chemotherapy, and/or giving patients radiation to stop the growth of the cancer.

Chemotherapy

Chemotherapy works by killing the fast growing cells in the body. Chemotherapy drugs interfere with the DNA synthesis by the tumor so new cells are killed. But chemotherapy also kills normal cells and the side effects of some chemotherapy agents include nausea, vomiting, hair loss, and fatigue. Delivery of the chemotherapy drug directly to the tumor is difficult too.

Radiation therapy

In radiation therapy, a certain type of high-energy beam is focused on the area of the cancer. Cells in the path of the beam are damaged. Because cancer cells are very fast growing cells and not as organized in their growth they are more easily damaged than normal cells in the radiation field. Even though damaged by the radiation normal cells repair and recover while cancer cells die.

Surgical treatment

Research has brought us a long way toward being able to remove only the diseased tissue without removing healthy tissue. For example, research has shown that removing only the "lump" (removing the tumor and a margin of surrounding tissue) in breast cancer and then following with radiation therapy can eliminate the need for a mastectomy (removal of the entire breast). Advances with surgical techniques have allowed colon cancer patients to preserve more normal body functions.

High Priorities

Finding treatments that are effective in destroying the cancerous cells without damage to normal cells is a high priority for medical research. Studying tissue and biological specimens can help us learn more about selecting the right kind of drug treatment for the specific tumor. Research using donated tissue samples is helping to understand the causes of cancer and identify new ways to target only the cancer cells by identifying "biomarkers" that can be used to measure the progress of disease or the effects of treatment. By better targeting the cancer cell itself, doctors can design the optimal treatment plan for the patient. Also we are learning how to better deliver drugs to the cancer cell itself without damage to normal cells along the way.

Drug Development

Drugs used in cancer have been found in nature often by accident. The process involves taking a plant or chemical compound that looked promising because it killed cells in the laboratory or in animal studies and then testing the effects in humans. We are now moving into an era where drugs can be designed to attack the particular part of the cancer cell that makes it divide and grow.

Cancer drugs used in the clinic today have usually been studied in a trial and error fashion through the clinical trial process that is regulated by the Food and Drug Administration. Clinical studies involving humans are closely controlled and performed very systematically according to a plan called a protocol. These studies are done in three phases (Phase I, II, and III) with each phase involving a larger number of people. Each phase examines the safety and effectiveness of the drug and how it compares to standard treatments. Each phase of testing must have a study protocol designed to answer specific questions about the treatment and the number of participants to be included in the study. Requirements (eligibility) for participation in each study are clearly defined in the study protocol. These are all factors that add to the reliability of the answers we receive about the treatment but also add costs and increase the time necessary to complete the study.

Phase I studies:

- have only a small number of patients (20-100).
- mainly study the safety of the new drug.
- are the first tests in humans.
- have physicians closely monitor and report patient's side effects.
- occur only after FDA approval to proceed through the Investigational New Drug Development (IND) process.

Phase II studies:

- involve 100-300 participants
- mainly study effectiveness of the treatment on the disease
- have physicians closely monitor patients and identify adverse (bad) reactions
- often take up to 2 years to complete

Phase III studies:

- involve a larger number of participants (1,000 – 3,000)
- have physicians closely monitor patients and identify adverse reactions
- usually take about three years to complete
- are almost always randomized (patients/physician do not get to choose their treatment they are assigned to one study treatment or the other)
- usually compare (in cancer studies) a new drug vs. a standard drug or a new drug plus standard vs. standard.

The number of participants needed to be a part of the study is pre-determined in the study design and is based on the number needed to answer the research question. The number of participants needed for each phase may vary especially in rare cancers.

Protecting the Patient

While the FDA watches the regulatory issues of the drug development process, each study must be approved by an Institutional Review Board (IRB) which is responsible for oversight of research at the site or hospital. The IRB helps protect the participants in each study.

Studying Tissue Leads the Way to New Strategies

Studying tissues has opened up new ways to:

- identify targets for treatment;
- discover biomarkers;
- use biomarkers to identify responders to certain types of therapies; and,
- develop treatments that work differently than standard chemotherapy.

New ways of identifying treatments, often involving tissue samples are helping scientists and physicians learn how to target activity in the cancerous cell and avoid damaging the normal cells. These new therapies work by different mechanisms such as starving the tumor of the blood supply that is necessary to grow (anti-angiogenics), blocking a receptor on the cancer cells surface that is necessary to divide and grow (monoclonal antibodies, enzymes, hormonal treatments) or stimulating the body's immune system to attack the tumor.

The following table gives some examples of these types of biological drugs:

Monoclonal antibodies	**Anti-angiogenic drugs** ■Works through starving the tumor of blood supply necessary to grow ■Targets a unique tumor "fingerprint" or receptor on the cancer cell's surface	**Some examples of biological drugs:** ■Avastin® (bevacizumab) for treatment of advanced colon cancer ■Rituxan® (rituximab) attacks B cells in non-Hodgkin's lymphoma ■Herceptin® (trastuzamab) for breast cancers that over-express her2 neu
Tyrosine kinase inhibitors	**Anti-neoplastic** Intercepts enzymes that carry the message to the cancer cell to divide and grow	■Gleevec® (imatinib) for treatment of chronic myelogenous leukemia
Immunotherapy or vaccines	Boosts the ability of the entire immune system to fight off a tumor	■interferon-alpha and interleukin-2 are cytokine therapies can help boost immunity in patients with melanoma or metastatic renal cell carcinoma. These therapies may have severe side effects

New drugs/ new problems
How is new technology improving or changing the process?

While answering questions about cancer, the development of these new types of therapies brings about new problems and barriers. These include:

- lack of access to innovative therapeutics;
- lengthy approval process for these new therapies.

It is also important to continue inspiring the development of new treatments that will satisfy unmet medical needs by addressing barriers within the system.

Several legislative acts were passed in 1980's and 1990's designed to:

- encourage development of innovative products for rare, serious or life threatening diseases.
    - The Orphan Drug Act provided incentives for companies developing drugs for rare diseases or conditions.

To ensure timely access to drugs and facilitate the transfer of new technologies from government/academia to industry:

- The Bayh-Dole Act allowed NIH (National Institutes of Health) grantees and contractors to patent /license discoveries to commercial companies.
- The Hatch-Waxman Act allowed patent life extension and fostered innovation in industry. It promoted competition in markets dominated by older drugs by adding new requirements in abbreviated new drug application (ANDA).
- The Prescription Drug User Fee Act of 1992 and FDA Modernization Act of 1997 began the accelerated approval and fast-track designation mechanisms for serious or life-threatening diseases.

Some new therapies require that patients be on treatment for longer periods of time, sometimes for the rest of their life. This increases the costs of treatment and may make cancer treatment more like a treatment for a chronic disease. In order for development of these new types of therapies to continue, the pharmaceutical and biotech industry must address the associated financial issues.

By learning more about how cells work, scientists and physicians are able to be more rational in designing new therapies. The ability to not only learn how to target but to understand how the targeted therapy will affect the system is critical. In the future, we hope that the right therapy (or combination of therapies) will be matched to the right patient to control the growth of the tumor. We have made progress in the fight against cancer and are on our way to more individualized medicine, but there is still much to be learned. You can help by giving permission to study your tissue obtained after medical procedures.

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Human Genome Project http://www.ornl.gov/sci/techresources/Human_Genome/medicine/medicine.shtml
Medicines by Design publication http://www.nigms.nih.gov/publist/ or call 301-496-7301

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