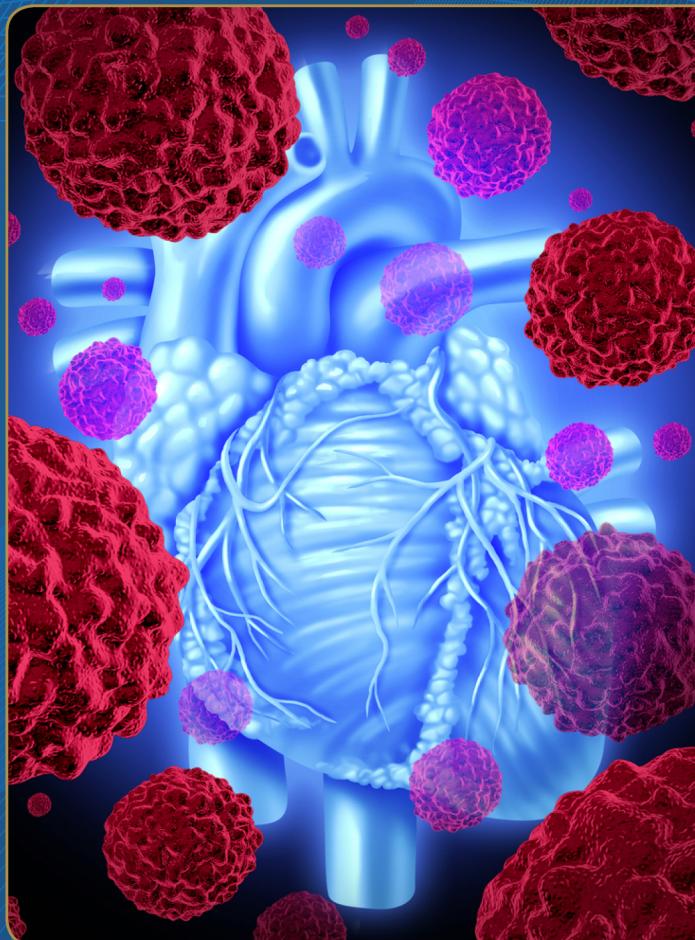


TREATING CANCER WITH IMMUNOTHERAPY AND TARGETED THERAPY

- Easy to follow, question-and-answer format
- Cites numerous in-text Web links to information at the National Institutes of Health, the National Cancer Institute, journals, and other online sources
- Up-to-date treatments and recent drug information



DAVID A. OLLE

TREATING CANCER WITH IMMUNOTHERAPY AND TARGETED THERAPY

LICENSE, DISCLAIMER OF LIABILITY, AND LIMITED WARRANTY

By purchasing or using this book and any companion files (the “Work”), you agree that this license grants permission to use the contents contained herein, including the files, but does not give you the right of ownership to any of the textual content in the book / disc or ownership to any of the information or products contained in it. *This license does not permit uploading of the Work onto the Internet or on a network (of any kind) without the written consent of the Publisher.* Duplication or dissemination of any text, code, simulations, images, etc. contained herein is limited to and subject to licensing terms for the respective products, and permission must be obtained from the Publisher or the owner of the content, etc., in order to reproduce or network any portion of the textual material (in any media) that is contained in the Work.

The information provided in this book is designed to provide helpful information on the subjects discussed. This book is not meant to be used, nor should it be used, to diagnose or treat any medical condition. Although the material in the book draws from numerous medical articles and sources written by medical professionals and physicians, the publisher does not intend nor is it authorized to offer professional medical or clinical advice. The reader should consult a physician for the diagnosis or treatment of any medical problem. The publisher, authors, and anyone involved with the preparation, production, or distribution of this book are not responsible for any specific health or medical needs that might require medical attention and they are not liable for damages or negative consequences of any kind from any treatment, action, application or preparation, to any person reading or following the information in this book or appearing on the companion disc. This includes, but is not limited to, loss of revenue or profit, or other incidental, physical, or consequential damages arising out of the use of this Work. No warranties or guarantees are expressed or implied by the publisher’s choice to include any of the content in this volume. References are provided for informational purposes only and do not constitute endorsement of any Web sites or other sources. The reader is solely responsible for any medical action or decision based on the reading of this book. Readers should be aware that the Web sites listed in this book are subject to change. The sole obligation of MERCURY LEARNING AND INFORMATION to the purchaser is to replace the book and/or disc, based on defective materials or faulty workmanship, but not based on the content, operation, or functionality of the product.

MERCURY LEARNING AND INFORMATION (“MLI” or “the Publisher”) and anyone involved in the creation, writing, or production of the companion files, accompanying algorithms, code, or computer programs (“the software”), and any accompanying Web site or software of the Work, cannot and do not warrant the performance or results that might be obtained by using the contents of the Work. The author, developers, and the Publisher have used their best efforts to insure the accuracy and functionality of the textual material and/or programs contained in this package; we, however, make no warranty of any kind, express or implied, regarding the performance of these contents or programs. The Work is sold “as is” without warranty (except for defective materials used in manufacturing the book or due to faulty workmanship).

The sole remedy in the event of a claim of any kind is expressly limited to replacement of the book and/or files, and only at the discretion of the Publisher. The use of “implied warranty” and certain “exclusions” vary from state to state, and might not apply to the purchaser of this product.

TREATING CANCER WITH IMMUNOTHERAPY AND TARGETED THERAPY

David A. Olle



MERCURY LEARNING AND INFORMATION
DULLES, VIRGINIA | BOSTON, MASSACHUSETTS | NEW DELHI

Copyright ©2020 by MERCURY LEARNING AND INFORMATION LLC.
All rights reserved.

This publication, portions of it, or any accompanying software may not be reproduced in any way, stored in a retrieval system of any type, or transmitted by any means, media, electronic display or mechanical display, including, but not limited to, photocopy, recording, Internet postings, or scanning, without prior permission in writing from the publisher.

Publisher: David Pallai
MERCURY LEARNING AND INFORMATION
22841 Quicksilver Drive
Dulles, VA 20166
info@merclearning.com
www.merclearning.com
(800) 232-0223

192021321 This book is printed on acid-free paper in the United States of America.

David A. Olle. *Treating Cancer with Immunotherapy and Targeted Therapy*.
ISBN: 9781683924500

Library of Congress Control Number: 2019940567

The publisher recognizes and respects all marks used by companies, manufacturers, and developers as a means to distinguish their products. All brand names and product names mentioned in this book are trademarks or service marks of their respective companies. Any omission or misuse (of any kind) of service marks or trademarks, etc. is not an attempt to infringe on the property of others.

Our titles are available for adoption, license, or bulk purchase by institutions, corporations, etc. For additional information, please contact the Customer Service Dept. at (800)232-0223(toll free).

All of our titles are available in digital format at academiccourseware.com and other digital vendors. The sole remedy in the event of a claim of any kind is expressly limited to replacement of the book and/or files, and only at the discretion of the Publisher.

Table of Contents

	<i>Introduction</i>	x
PART ONE		
CHAPTER 1	Cancer Basics	
	<i>Characteristics of Cancer</i>	
	1. What is cancer?	2
	2. What are the differences between cancer cells and normal cells?	3
CHAPTER 2	<i>Why Genes Are Important in Understanding Cancer</i>	
	3. What are genes?	5
	4. What causes cancer?	8
CHAPTER 3	<i>Why the Cell Cycle and Cell Signaling Are Important for Cancer Development</i>	
	5. What is cell signaling?	9
	6. What is the cell cycle?	11
CHAPTER 4	<i>The Process of Cancer Development</i>	
	7. What is the importance of cell cycle regulation for cancer development?	14
	8. What types of genes are affected during cancer development?	14
	9. How does cancer spread?	16
	10. When are tissue changes not cancer?	20
	11. When cells acquire mutations associated with cancer, do they turn into cancer?	21
	12. Why do cancers come back?	21
CHAPTER 5	<i>Diagnosis of Cancer</i>	
	13. How are laboratory tests used in cancer medicine?	22
	14. How can a biopsy of a tumor help to diagnose cancer?	23
	15. What examinations and tests does the pathologist perform on the biopsy sample?	23
	16. What imaging tests can be employed to diagnose cancer?	23
	17. How does a computed tomography scan work?	23
	18. How does magnetic resonance imaging work?....	25
	19. What are nuclear medicine scans?	25
	20. What is tumor grade?	26
	21. What is cancer stage?	26

CHAPTER 6***Classification of Cancers***

22. What is the conventional method of classifying cancers?	27
23. What is the method of classifying cancers by molecular alterations of tumor cells?.....	27
24. What are carcinomas?	28
25. What are sarcomas?.....	29
26. What are leukemias?	31
27. What is lymphoblastic leukemia?	32
28. What are lymphomas?.....	33
29. What is multiple myeloma?	34
30. What are melanomas?	34
31. What are brain and spinal cord tumors?	35
32. What are germ cell tumors?.....	35
33. What are neuroendocrine tumors?	35
References	36

PART TWO**CHAPTER 7****Standard Methods of Cancer Treatment*****Surgery***

34. When is surgery considered as part of a cancer treatment plan?	40
35. How can surgery help to prevent cancer?	40
36. How can surgery be used to diagnose or stage cancer?	41
37. How can surgery be used to remove cancer?	41
38. What is cryosurgery?	41
39. What is laser surgery?	41
40. What is hyperthermia treatment?	42
41. What is photodynamic therapy?	43
42. Can surgery occasionally increase the spread of cancer?	44

CHAPTER 8***Chemotherapy***

43. What is chemotherapy?.....	45
44. How does chemotherapy work?.....	45
45. Who receives chemotherapy?	46
46. What are the side effects of chemotherapy?	46
47. How do cancer cells develop resistance to chemotherapeutic drugs?	47

48.	Can a more modest use of chemotherapy overcome the problem of drug resistance?	48
CHAPTER 9	<i>Radiotherapy</i>	
49.	What is radiotherapy?	48
50.	What sources of radiation are used in cancer therapy?	48
51.	What are the main types of radiation therapy?	49
52.	What are the types of external beam radiation therapy?	49
53.	What is internal radiation therapy (brachytherapy)?	53
CHAPTER 10	<i>Hormone Therapy</i>	
54.	What are hormones?	54
55.	How does hormone therapy block the action of hormones?	54
56.	How is hormone therapy used in breast cancer?	55
57.	How is hormone therapy used in prostate cancer?	56
	References	57
PART THREE		
Targeted Cancer Therapy		
CHAPTER 11	<i>Development of Targeted Therapy</i>	
58.	What are targeted cancer therapies?	60
59.	How are targets for targeted cancer therapies identified?	61
60.	How are targeted therapies developed?	62
61.	What types of targeted therapies are available? ..	63
62.	Can therapies target tumors that have inactivated tumor suppressor genes?	65
63.	What targeted therapies have been approved for specific types of cancer?	66
CHAPTER 12	<i>Disadvantages of Targeted Therapies</i>	
64.	What are the limitations of targeted cancer therapies?	69
65.	What are the challenges in developing targeted therapies?	70

66. What are the side effects of targeted cancer therapies?	71
References	73

PART FOUR

CHAPTER 13

Immunotherapy

The Immune System as It Relates to Cancer

67. What is the basic function of the immune system?	76
68. What are the main components of the immune system?	76
69. What are the types of innate immune cells?	76
70. What are the types of acquired immune cells?	77
71. What are signaling molecules?	78
72. What is the role of co-stimulatory molecules for activation of the immune system?	80
73. What is the role of co-inhibitory molecules?	80
74. How can cancer cells evade detection and destruction by the immune system?	81

CHAPTER 14

Immune Checkpoint Inhibitors

75. What are immune checkpoint inhibitors?	82
76. What drugs have been developed to block PD-1?	83
77. What drugs have been developed to block PD-L1?	83
78. What drugs have been developed to block CTLA-4?	84
79. What new checkpoint inhibitor drugs are being developed?	84
80. Why do regulatory T cells need to be considered in checkpoint inhibitor therapy?	84
81. What are the side effects of immunotherapy, and how are these side effects controlled?	85
82. What is the response rate to checkpoint inhibitor drugs?	94
83. Can a combination of checkpoint inhibitor drugs enhance treatment?	98
84. Can other types of cancer treatments enhance the effectiveness of immune checkpoint therapy?	98

CHAPTER 15	Cancer Vaccines	
85.	What are vaccines?	100
86.	What are cancer vaccines?	100
87.	What are the types of cancer vaccines?	101
88.	Can virus infections cause cancer?	102
89.	Can bacterial infections cause cancer?	103
90.	How successful are therapeutic cancer vaccines?	103
CHAPTER 16	Adoptive Cell Therapy	
91.	What are the beneficial properties of adoptive T cell therapy?	104
92.	What are the general approaches to adoptive cell therapy?	104
93.	How is adoptive T-cell therapy used in cancer treatment?	107
94.	Why is it difficult to treat solid tumors with CAR-T cell therapy?	107
95.	What is the future of adoptive T cell therapy?	108
CHAPTER 17	New Developments in Cancer Immunotherapy	
96.	What approaches are being taken to overcome cancer cell resistance to immunotherapy?	108
97.	What are some specific immunotherapeutic drugs under development?	109
	References	111
	Index	114

Introduction

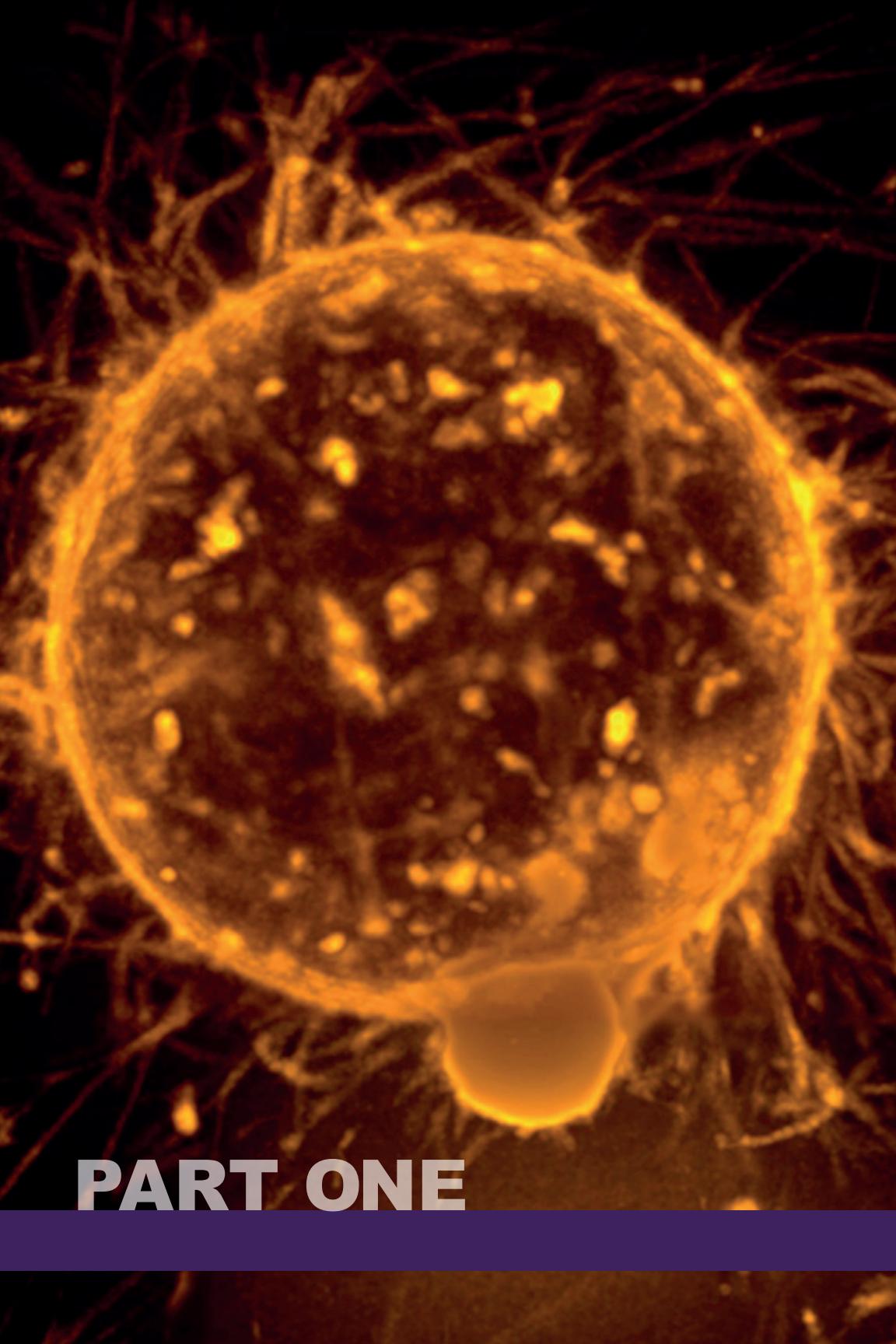
Treating cancer has always been a major challenge. Although great strides in treatment have taken place in recent years, all too often current treatments are less than effective, or patients relapse. Newer methods of cancer treatment, namely targeted therapy and immunotherapy, have generated great excitement in the scientific community. These newer methods of cancer treatment hold promise for patients who otherwise may have few options. Also, in the case of immunotherapy, responses to treatment can be maintained even after a cycle of treatments is complete.

Cancer has been called a genetic disease involving inappropriate activation or deactivation of genes and their effect on cell activities. Since cancer is a disorder of the body's cells, the author presents a considerable discussion of the normal functioning of the cells as background material. These topics include genes and their role in the synthesis of proteins, cell signaling, and the cell cycle. Cells communicate with each other using chemical signals to carry out a multitude of life processes. The cell cycle relates to the growth and development of the cell, including cell division. Cellular processes are under strict control to function properly. Cancer circumvents these processes.

Classification of cancer types is important in the diagnosis and treatment of cancers. The book illustrates improvements in classification based on genetic profiles of individual cancers. The major cancer types, such as carcinomas, sarcomas, leukemias, lymphomas, and melanomas, are discussed. This book is a general discussion of cancer; specific cancers are mentioned in relation to the treatments.

The established methods of treating cancer, including surgery, radiation, chemotherapy, and hormone therapy, are discussed, including recent advancements in these fields. The appropriate conditions of use, as well as the limitations of these methods,

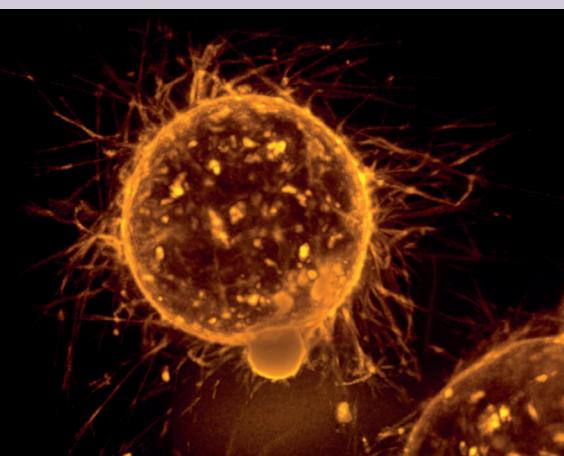
are described. In spite of the newer cancer treatments, these established methods will always have a place, and chemotherapy, in particular, will often be used in conjunction with the newer methods.



PART ONE

Cancer Basics

A basic understanding of normal cellular functioning is important to understand the nature of cancer. Part 1 describes the normal cellular processes of gene functioning, cell signaling, and the cell cycle, serving as a backdrop on how cancer arises when the checks and balances of the system break down. Beginning with a basic description of cancer, this Part then elaborates on the process by which cancer spreads. Classifying a particular cancer is used in determining treatment methods. This Part describes the standard methods of classifying cancer by organ or tissue as well as a newly emerging method of classifying by the genetic profile of cancer. Finally, the main classifications of cancer by tissue origin are discussed.



▲ FIGURE I.1

Microtentacles and metastasis.
Source: National Cancer Institute

CHAPTER 1

Characteristics of Cancer

CHAPTER 2

Why Genes are Important in Understanding Cancer

CHAPTER 3

Why the Cell Cycle and Cell Signaling Are Important for Cancer Development

CHAPTER 4

The Process of Cancer Development

CHAPTER 5

Diagnosis of Cancer

CHAPTER 6

Classification of Cancers

Characteristics of Cancer

1. What is cancer?



Cancer is a disease of uncontrolled growth and proliferation of cells that have escaped the body's normal growth control mechanisms and have gained the ability to divide indefinitely. Proliferation is the spread of cancer cells to other tissues and organs of the body. Cancer is a multistep process that requires the accumulation of many genetic changes over time.

Three primary cellular properties are changed during the development of cancer:

- Deregulation of the cell cycle resulting in lost control of cell division
- Breakdown of cell adhesion (the binding of cells to each other)
- Prevention of cell death (apoptosis)

These changes will be discussed in detail later in the chapter.

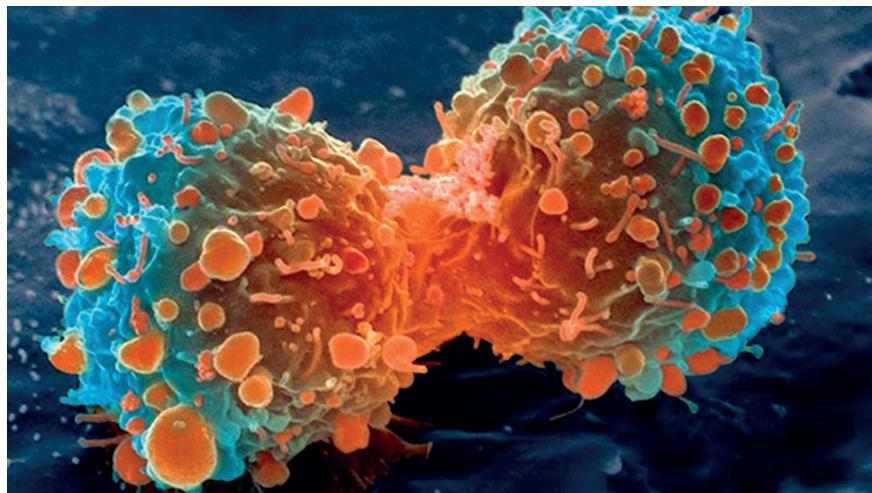
Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and divide to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. When cancer develops, however, this orderly process breaks down. As cells become more and more abnormal, old or damaged cells survive when they should die, and new cells form when they are not needed. These extra cells can divide without stopping and may form growths called tumors.

Many cancers form solid tumors, which are masses of tissue. Cancers of the blood, such as leukemias, generally do not form solid tumors.

Cancerous tumors are malignant, which means they can spread into or invade nearby tissues. Also, as these tumors grow, some cancer cells can break off and travel to distant places in the body through the blood or the lymph system and form new tumors far from the original tumor.

Unlike malignant tumors, benign tumors do not spread into or invade nearby tissues. Benign tumors can sometimes be quite

large, however. When removed, they usually don't grow back, whereas malignant tumors sometimes do. Unlike most benign tumors elsewhere in the body, benign brain tumors can be life-threatening.



▲ **FIGURE 1.1**

A dividing lung cancer cell.
<https://www.cancer.gov/about-cancer/understanding/what-is-cancer>

2. What are the differences between cancer cells and normal cells?

Cancer cells differ from normal cells in many ways that allow them to grow out of control and become invasive. One important difference is that cancer cells are less specialized than normal cells. That is, whereas normal cells mature into very distinct cell types with specific functions, cancer cells do not. This lack of specialization is one reason that, unlike normal cells, cancer cells continue to divide without stopping.

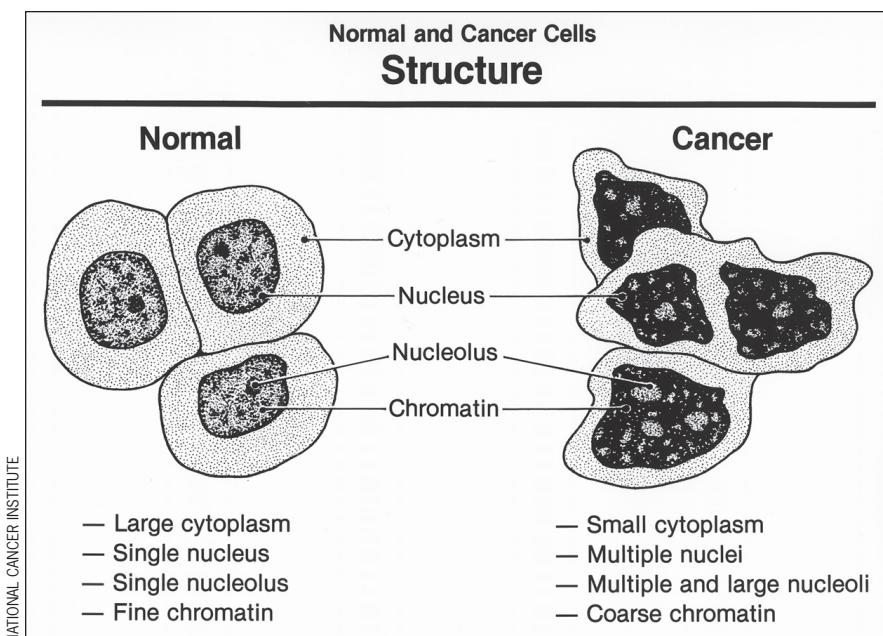
Also, cancer cells can ignore signals that normally tell cells to stop dividing or to begin a process known as programmed cell death, or apoptosis, which the body uses to get rid of unneeded cells.

Cancer cells may be able to influence the normal cells, molecules, and blood vessels that surround and feed a tumor—an area known as the microenvironment. For instance, cancer cells can induce nearby normal cells to form blood vessels that supply

tumors with oxygen and nutrients, which they need to grow. The formation of new blood vessels is known as angiogenesis. These blood vessels also remove waste products from tumors.

Cancer cells are also often able to evade the immune system, a network of organs, tissues, and specialized cells that protects the body from infections and other conditions. Although the immune system normally removes damaged or abnormal cells from the body, some cancer cells can hide from the immune system.

Tumors can also use the immune system to stay alive and grow. For example, with the help of certain immune system cells that normally prevent a runaway immune response, cancer cells can keep the immune system from killing cancer cells.



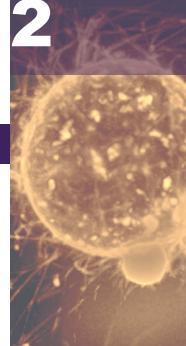
▲ FIGURE 1.2

Characteristic structures of normal and cancer cells.

Author: Pat Kenney

https://commons.wikimedia.org/wiki/File:Normal_and_cancer_cells_structure.jpg

Public Domain



Why Genes Are Important in Understanding Cancer

3. What are genes?

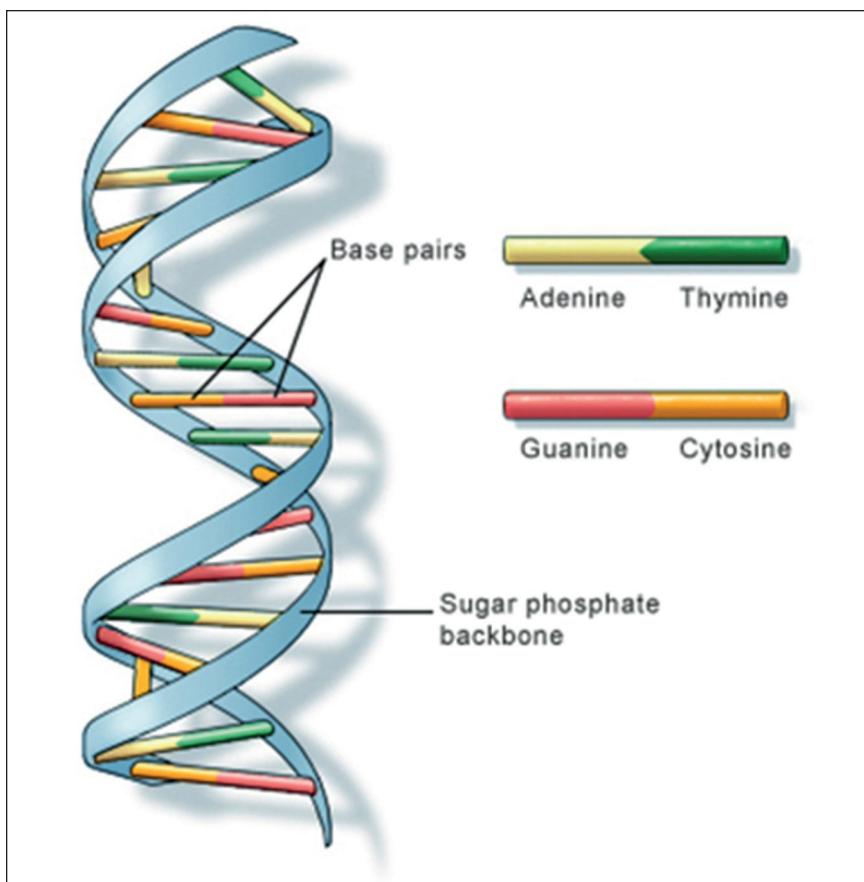
The nuclei of all cells in the body contain twenty-three pairs of structures called chromosomes. The chromosomes contain the DNA molecule surrounded by a protein coat. The DNA/protein complex is known as chromatin.

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria. Mitochondria are structures within cells that convert the energy from food into a form that cells can use.

The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about three billion bases, and more than 99% of those bases are the same in all people. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to how letters of the alphabet appear in a certain order to form words and sentences (Figure 2.1).

DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base is also attached to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.

An important property of DNA is that it can replicate or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This pattern is critical when cells divide, because each new cell needs to have an exact copy of the DNA present in the old cell.



▲ FIGURE 2.1

DNA is a double helix formed by base pairs attached to a sugar-phosphate backbone.

Genes are present as segments of the DNA molecule, either as one continuous segment or as separated segments. A DNA molecule has many genes (Figure 2.2).

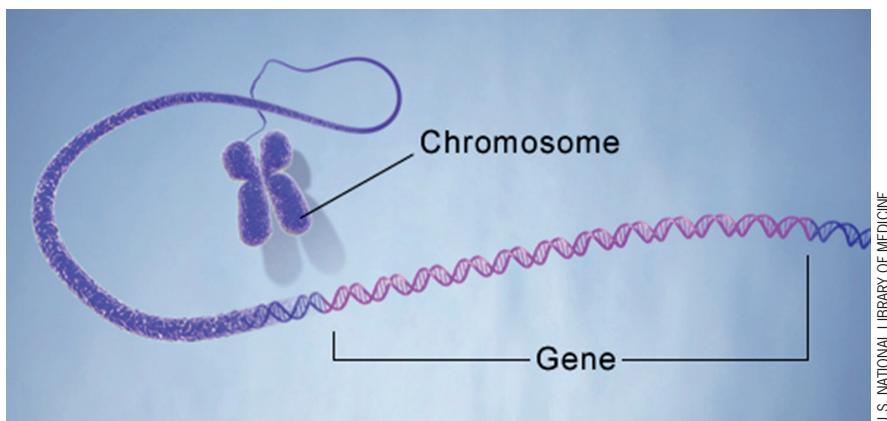
A gene is the basic physical and functional unit of heredity. Some genes act as instructions to make molecules called proteins. However, many genes do not code for proteins. In humans, genes vary in size from a few hundred DNA bases to more than two million bases. The Human Genome Project estimated that humans have between 20,000 and 25,000 genes.

Every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small

number of genes (less than 1% of the total) are slightly different between people. Alleles are forms of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features.

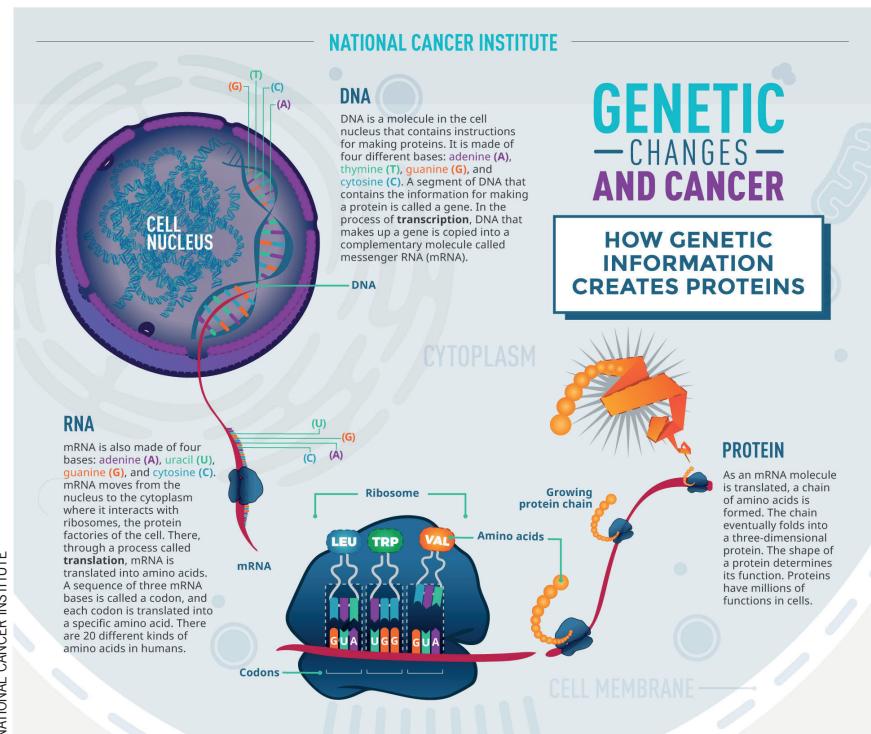
Within the nucleus is a structure known as the nucleolus (Figure 1.2). The nucleolus is a condensed region of chromatin where ribosome synthesis occurs. Ribosomes, large complexes of protein and ribonucleic acid (RNA), are the cellular organelles (specialized structures within the cell) responsible for protein synthesis. They receive their “orders” for protein synthesis from the nucleus, where the DNA is transcribed into messenger RNA (mRNA). A promoter is a region of DNA that initiates transcription of a particular gene. Promoters are located near the transcription start sites of genes, on the same strand and upstream on the DNA. This mRNA travels to the ribosomes, which translate the code provided by the sequence of the nitrogenous bases in the mRNA into a specific order of amino acids in a protein (Figure 2.3).

Abnormalities in size and shape of nucleoli are associated with cancer. These changes in nucleoli may occur either as a consequence of cancer or, in some cases, may even promote tumor formation. The changes are the consequence of the increased metabolic requirements of proliferating cells, which drive an increased synthesis of ribosomes.



▲ FIGURE 2.2

Genes are made of DNA. Each chromosome contains many genes.



▲ FIGURE 2.3

How genetic information creates proteins.

<https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-changes-infographic>

4. What causes cancer?

Cancer is a genetic disease—that is, it is caused by changes to genes that control the ways our cells function, especially how they grow and divide.

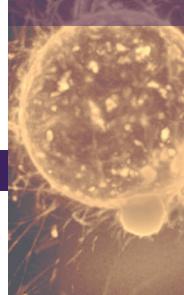
Genetic changes that cause cancer can be inherited from our parents. They can also arise during a person's lifetime as a result of errors that occur as cells divide or because of damage to DNA caused by certain environmental exposures. Cancer-causing environmental exposures include substances, such as the chemicals in tobacco smoke, and radiation, such as ultraviolet rays from the sun.

Each person's cancer has a unique combination of genetic changes. As the person's cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes.

In general, cancer cells have more genetic changes, such as mutations in DNA, than normal cells. Some of these changes may have nothing to do with cancer; they may be the result of cancer, rather than its cause.

Why the Cell Cycle and Cell Signaling Are Important for Cancer Development

CHAPTER
3

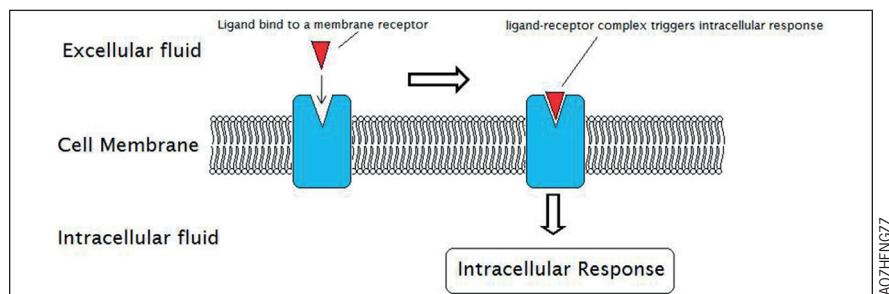


5. What is cell signaling?

Cell signaling is the process by which cells communicate with each other. Cell signaling is a very complex and integrated process which is essential for regulating a multitude of life processes, including cell division, repair of damaged DNA and, when necessary, apoptosis. One of the goals of the signaling process is to maintain a constant and balanced internal environment, called homeostasis. Cancer can result when the signaling process is disrupted and is out of control. The complexity of signaling pathways allows cancer cells to bypass drug inhibitors along one pathway by activating another pathway.

Cell signaling (also called transduction) occurs in three stages:

- Binding of the signal molecule (also called a ligand) to a receptor within the cell membrane enclosing the cell or within the cell
- Secondary transmission of the signal to a network of molecules within the cell
- Cellular response



▲ FIGURE 3.1

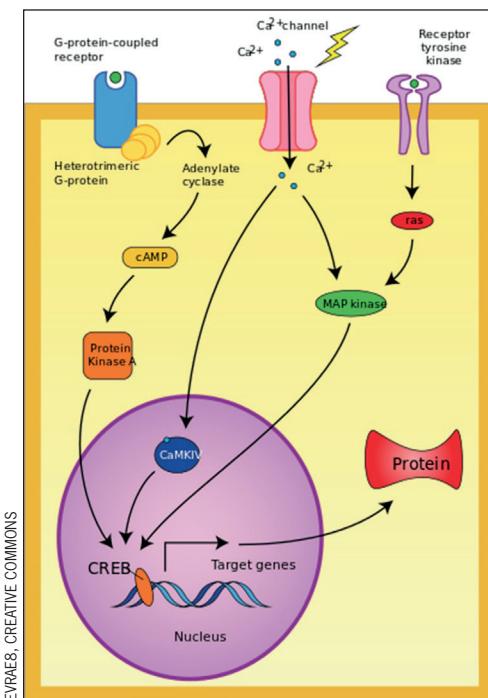
The general process of membrane receptor action. (Public Domain)

When the receptor is located within the cell (intracellular), the signaling molecule must be small enough to pass through the cell membrane to bind with it. The most important signaling molecules of this type are the steroid hormones, estrogen and testosterone. After binding takes place, the resultant complex structure enters the nucleus and binds to the DNA, stimulating the transcription of a gene.

Most receptors are located within the cell membrane enclosing the cell. These receptors span the cell membrane with one portion extending outside the cell (extracellular) and another portion extending within the cell (intracellular). The signaling molecule binds to the extracellular portion, typically causing a physical change in the intracellular portion. A secondary molecule inside the cell then binds to the intracellular portion and initiates a complex series of signaling events resulting in a cellular response (Figure 3.1).

There are three major types of extracellular receptors:

- G-protein receptors
- Receptor tyrosine kinases (growth factor receptors)
- Ion channels



◀ FIGURE 3.2
Schematic diagram illustrating the action of three major types of extracellular receptors (they do not act simultaneously).

Receptor tyrosine kinases are important in regulating growth factors. Two growth factor signals important in cancer are:

- Vascular-endothelial growth factor (VEGF) which promotes new blood vessel growth. The development of new blood vessels is essential for the growth of tumors.
- Insulin-like growth factor-1 (IGF-1) is a hormone produced in response to growth hormone.

Ion channel receptors are involved in regulating the distribution of ion charges (such as K⁺, Na⁺, and Ca⁺⁺) across the cell membrane. This charge distribution is important in many physiological processes including cell signaling and cell cycle progression (see next section). These functions are important for cancer cell proliferation.



For details on G-protein receptors visit:
[https://en.wikipedia.org/
wiki/G_protein](https://en.wikipedia.org/wiki/G_protein)

[https://courses.washington.edu/
conj/bess/gpcr/gpcr.htm](https://courses.washington.edu/conj/bess/gpcr/gpcr.htm)



For details on the action of receptor tyrosine kinases, visit:
Receptor tyrosine kinases: role in cancer progression
[www.ncbi.nlm.nih.gov/pmc/3394603/
pdf/CO13_5p191.pdf](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394603/pdf/CO13_5p191.pdf)



For details on the action of ion channel receptors, visit:
Ion channels as targets for cancer therapy
[https://www.ncbi.nlm.nih.gov/
pmc/articles/PMC3134009.pdf/
ijppp0003-0156.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3134009/pdf/ijppp0003-0156.pdf)

6. What is the cell cycle?

The cell cycle is the process by which a cell grows, develops, and eventually divides. All steps in the process are closely controlled in the normal cell. Cancer can develop when these controls break down.

The cell cycle is the series of events that take place in a cell leading to its division and duplication of its DNA (DNA replication) to produce two daughter cells. Control mechanisms known as cell cycle checkpoints ensure the proper cell division.

The cell cycle consists of: the G1 phase, S phase (synthesis), G2 phase (collectively known as interphase), and M phase (mitosis or meiosis) (Table 3.1). The cell grows during the G1 phase, and duplicates its DNA during the S phase. During the G2 phase, the cell continues to grow, accumulating nutrients needed for mitosis and cell division. The M phase is composed of two tightly

coupled processes: karyokinesis, in which the cell's chromosomes are divided, and cytokinesis, in which the cell's cytoplasm divides, forming two daughter cells. Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called the G₀ phase.

Table 3.1. States and phases of the cell cycle.

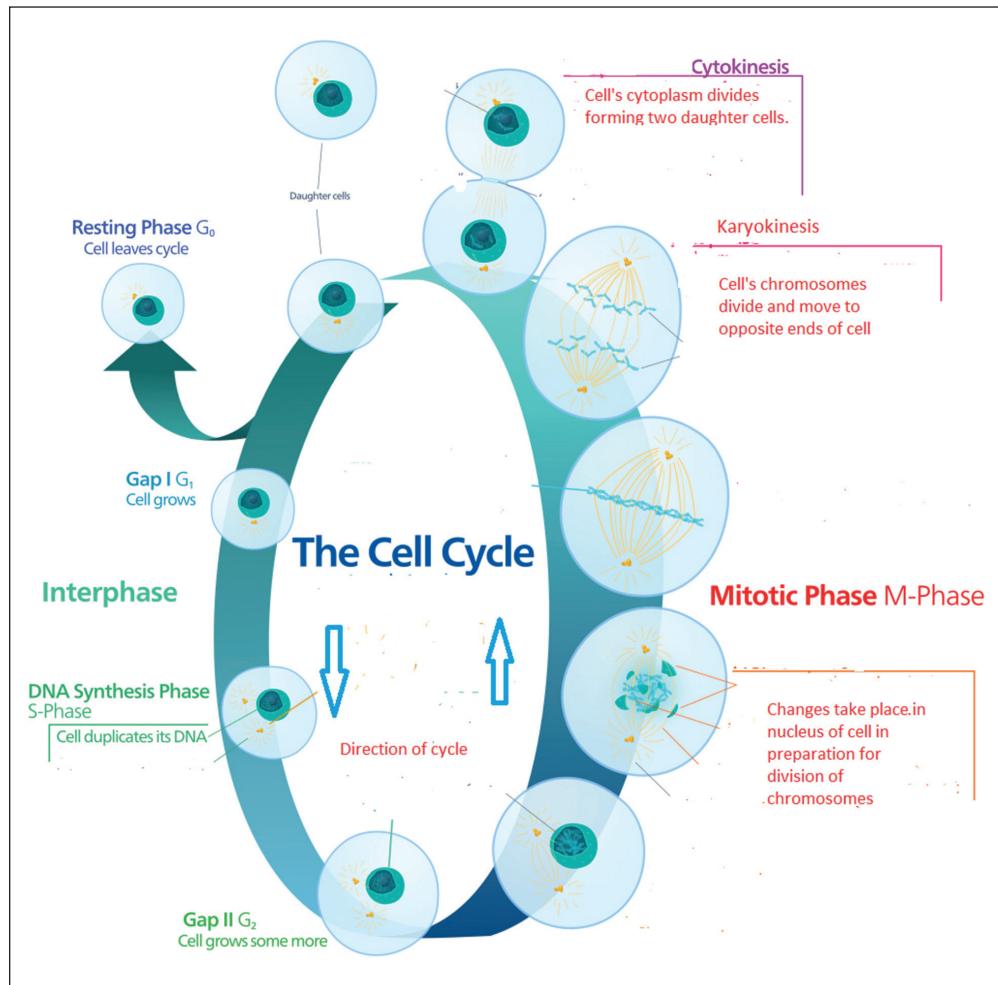
State	Phase	Abbre-viation	Description
Resting	Gap 0	G ₀	A phase where the cell has left the cycle and has stopped dividing.
Interphase	Gap 1	G ₁	Cells increase in size in Gap 1. The G₁ checkpoint control mechanism ensures that everything is ready for DNA synthesis. (See Question 7 relating to the importance of the G₁ phase during cancer development.)
	Synthesis	S	DNA replication occurs during this phase.
	Gap 2	G ₂	During the gap between DNA synthesis and mitosis, the cell will continue to grow. The G₂ checkpoint control mechanism ensures that everything is ready to enter the M (mitosis) phase and divide.
	Mitosis	M	Cell growth stops at this stage, and cellular energy is focused on the orderly division into two daughter cells. A checkpoint in the middle of mitosis (Metaphase Checkpoint) ensures that the cell is ready to complete cell division.

Author: Kelvingsong

https://commons.wikimedia.org/wiki/File:Animal_cell_cycle-en.svg

Public Domain

After cell division, each of the daughter cells begins the interphase of a new cycle. Although the various stages of interphase are not usually morphologically (the form or structure of the cell) distinguishable, each phase of the cell cycle has a distinct set of specialized biochemical processes that prepare the cell for initiation of cell division.



▲ FIGURE 3.3

The cell cycle.

Author: Kelvinsong

Wikimedia Commons – Creative Commons CC BY-SA 3.0 Unported License

The Process of Cancer Development

7. What is the importance of cell cycle regulation for cancer development?

At the G₁ phase of the cell cycle, a decision is made whether a cell will enter the resting phase G₀ or be committed to cell division beginning with the S-phase. Enzymes called cyclin-dependent kinases (CDKs) are essential to drive progression through the cell cycle when activated. CDKs are activated or inactivated by binding (or not) to proteins called cyclins. Cancer cells develop their own signals to activate the S-phase contrary to normal conditions. The importance of cell signaling in regulating biological processes was discussed in Question 5.

8. What types of genes are affected during cancer development?

Three main types of genes—proto-oncogenes, tumor suppressor genes, and DNA repair genes—are present in normal cells to balance cell proliferation and cell loss. When the activity of these genes goes awry, the result could be cancer.

Proto-oncogenes are involved in normal cell growth and division, but are so named because they have the potential to become cancer-causing genes (oncogenes). When proto-oncogenes become oncogenes, cells are allowed to grow and survive when they should not. Only one allele of a proto-oncogene needs to be mutated to become an oncogene.

Some proto-oncogene mutations are inherited, but most mutations are acquired. Oncogenes are generally activated by:

- Chromosome rearrangements that put a growth-regulatory gene under the control of a different promoter (see Question 3), leading to overexpression of a gene.
- Duplication of a DNA segment that contains a proto-oncogene, leading to overexpression of an encoded protein.

Tumor suppressor genes are activated when genes involved in cell growth and division are damaged. When the damaged genes cannot be repaired, tumor suppressor genes promote apoptosis

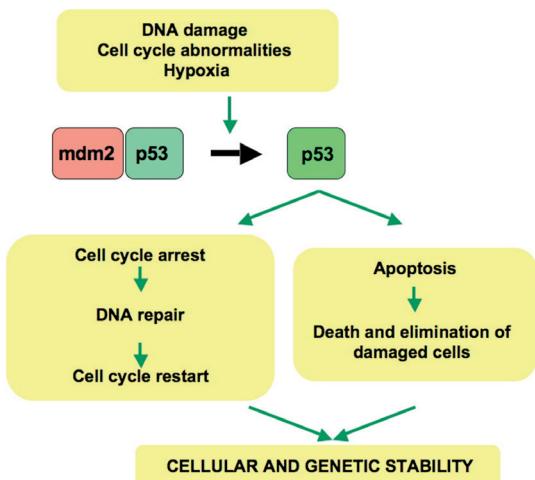
of the genes. Tumor suppressor genes can be deactivated when both alleles are inactivated either by mutation or by deletion. The resultant deactivated tumor suppressor genes suffer a “loss of function” and can no longer control cell growth and division. The following are the most common tumor suppressor genes:

<u>Gene</u>	<u>Resultant cancers from loss of function</u>
p53	Carcinoma of lung and breast, sarcoma
Retinoblastoma (Rb)	Retinoblastoma, sarcoma, some carcinomas
NF1	Neurofibromas, malignant peripheral nerve tumors
APC	Colonic carcinoma
WT1	Wilms' Tumor, bladder cancer

p53 deserves special attention, as it is present in a large percentage of cancers. p53 is known as the “guardian of the genome” due to its role in monitoring all the genes in the genome. In the cell, p53 protein binds to DNA to control activity through the cell cycle. When p53 is mutated, it can no longer bind to DNA, so there is no longer a “stop” signal for cell division.

p53 plays a role in regulation or progression through the cell cycle through several mechanisms.

- It can activate DNA repair proteins when DNA has sustained damage.
- It can arrest growth by holding the cell cycle at the G1/S regulation point on DNA damage recognition. If it holds the cell at this point long enough, the DNA repair proteins will have time to fix the damage, and the cell will be allowed to continue through the cell cycle.
- It can initiate apoptosis if the DNA damage proves to be irreparable.



▲ FIGURE 4.1

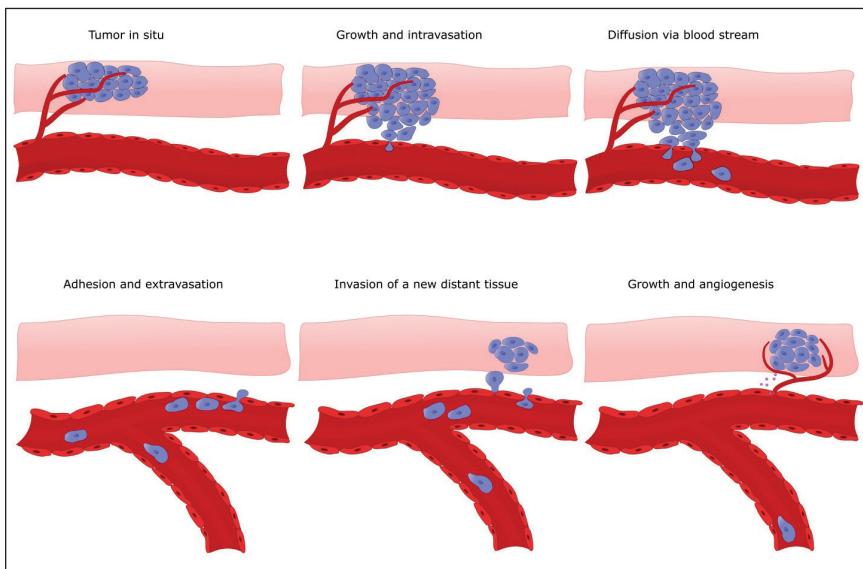
p53 pathway.

In a normal cell, p53 is inactivated by its negative regulator, mdm2. Upon DNA damage or other stresses, various pathways will lead to the dissociation of the p53 and mdm2 complex. Once activated, p53 will induce a cell cycle arrest to allow either repair or survival of the cell or apoptosis to discard the damaged cell.

Author: Thierry Soussi
Public Domain

9. How does cancer spread?

In metastasis, cancer cells break away from where they first formed (primary cancer), travel through the blood or lymph system, and form new tumors (metastatic tumors) in other parts of the body. The metastatic tumor is the same type of cancer as the primary tumor.



▲ FIGURE 4.2

Mechanism of cancer diffusion: metastasis.

Author: ellepigrafica

Shutterstock common license

Figure 4.2 illustrates the challenges tumor cells need to overcome to accomplish metastasis. They must be able to migrate from the primary tumor, pass through epithelial tissue, enter a blood vessel, survive transit within the blood vessel, exit the blood vessel at a distant site, and finally establish a new colony in a new tissue site.

Cancer in situ. Early-stage cancer in which the cancerous growth or tumor is still confined to the site from which it started, and has not spread to surrounding tissue or other organs in the body.



Studies have shown that cancer cells must progressively acquire traits necessary to achieve metastasis. Indeed, before acquiring these traits, millions of cancer cells could be released into circulation without establishing colonies at distant sites.

The hallmark of cancer cells is genetic instability, which can facilitate some cells to acquire the traits necessary for metastasis. Tumors develop when cell cycle inhibitors and DNA-repair genes are blocked. Telomeres are sections of DNA found at the ends of chromosomes that protect the chromosomes. As part of the aging process, telomeres shorten, damaging the chromosomes. The enzyme telomerase protects and maintains telomere length. Cancer cells are notable for having high levels of telomerase, making them “immortal.” Tumors can grow rapidly without accompanying blood vessels. This situation can result in a lack of oxygen, called hypoxia, to the cells. The cancer cell must first break free of the tumor *in situ* and begin migrating through tissues. This process is described in the following paragraph. The cancer cell must promote angiogenesis. When the cell enters the blood vessel, it must survive in transit. Survival is often accomplished by adhering to blood platelets.

Tissues in the body are composed of two types of cells: epithelial and mesenchymal cells. Epithelial cells maintain their location in an organ or tissue by cell-to-cell adherence and by physical barriers. A protein known as E-cadherin binds cells together with the release of antigrowth signals. This contact results in contact inhibition and hindering of further growth. Epithelial cells are further bound to molecules in a space known as the extracellular matrix. The extracellular matrix, in turn, is bound together by transmembrane receptors known as integrins. Mesenchymal cells, on the other hand, are solitary and capable of migrating.

A cytoskeleton is present in the cytoplasm of all cells. It is a complex, dynamic network of interlinking protein filaments that extends from the cell nucleus to the cell membrane.



DEFINITION

The extracellular matrix is a three-dimensional network of extracellular macromolecules, such as collagen, enzymes, and glycoproteins, that provide structural and biochemical support of surrounding cells.



NOTE

Integrins are transmembrane receptors that bind components of the extracellular matrix (ECM). Upon ligand binding, integrins activate signal transduction pathways that mediate cellular signals such as regulation of the cell cycle, organization of the intracellular cytoskeleton, and movement of new receptors to the cell membrane. Integrins work alongside other receptors such as cadherins to mediate cell-cell and cell-matrix interaction. Integrins have a profound influence on tumor cells in which they regulate tumor cell survival and malignancy.

During normal body processes associated with embryonic development and responses to inflammation, epithelial cells can develop the capability to migrate. Epithelial cells can transform into mesenchymal cells. In the process, E-cadherin breaks down as well as the binding of cells to the extracellular matrix. The cells can then migrate to specific sites to form new epithelial tissues. Tumor cells are able to take control of these normal processes for their own purposes to invade and migrate through tissues. Tumor cells are also able to send signals to regulate the activity of E-cadherin and integrin adhesions.

Cancer cells change their appearance from a neat, ordered shape to spindly and long. These changes in physical shape allow the cancer cells to squeeze around and through epithelial cells. When the cancer cells encounter the rigid outer layer known as the basal lamina, they secrete enzymes known as matrix metalloproteases that can break down the physical barrier to allow passage of the cells. The cancer cells can then squeeze through the cells of the blood vessels and enter the bloodstream.

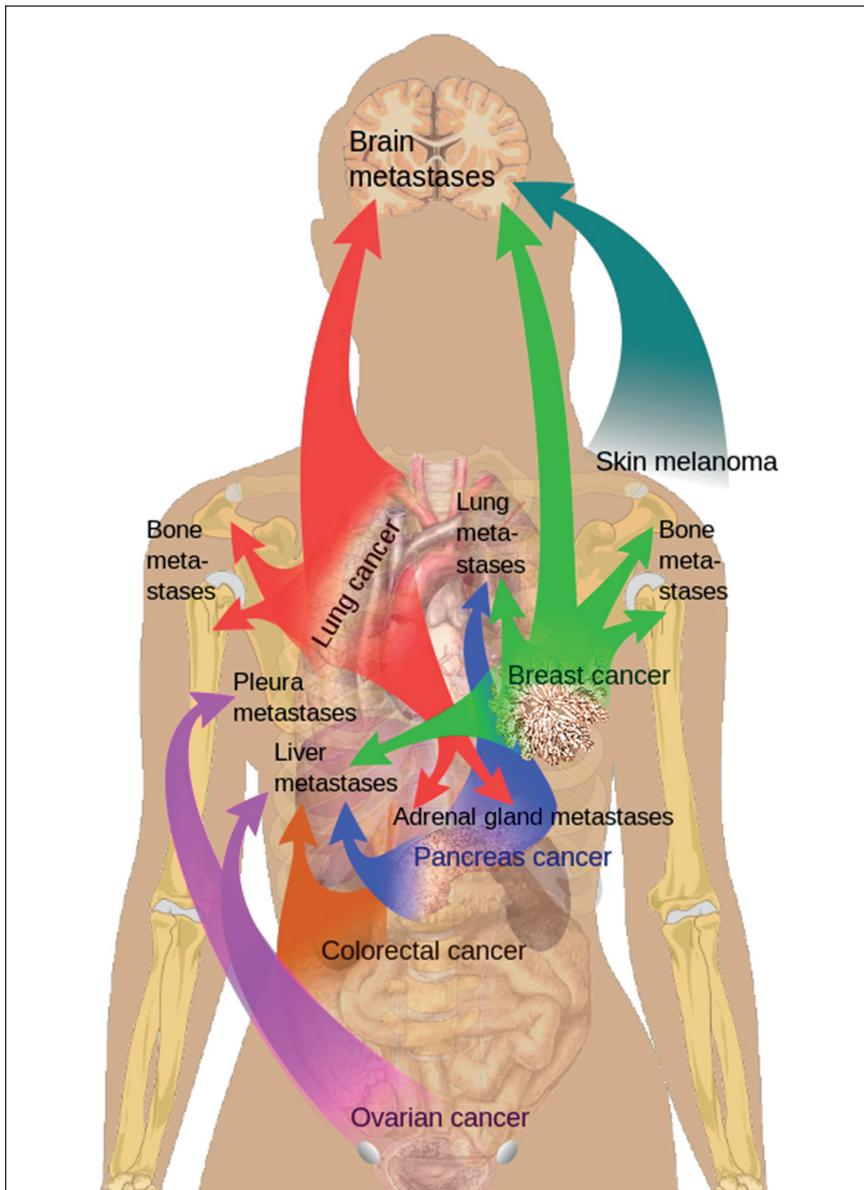
What determines the likely first metastasis site for a given cancer type, as shown in Figure 4.2? To successfully establish a colony depends on the interaction of the metastasizing tumor cells with the cells of the target organ. The tumor cells must produce factors that alter the target organ cells in such a manner as to promote the survival and growth of the tumor. Recent studies have indicated that these factors are related to the genetic profile of the tumor.

Metastatic cancer has the same name and the same type of cancer cells as the original, or primary, cancer. For example, breast cancer that spreads to and forms a metastatic tumor in the lung is metastatic breast cancer, not lung cancer.

Under a microscope, metastatic cancer cells generally look the same as cells of the original cancer. Moreover, metastatic cancer cells and cells of the original cancer usually have some molecular features in common, such as the presence of specific chromosome changes.

Treatment may help prolong the lives of some people with metastatic cancer. In general, though, the primary goal of treatments for metastatic cancer is to control the growth of

cancer or to relieve symptoms caused by it. Metastatic tumors can cause severe damage to how the body functions and most people who die of cancer die of metastatic disease.



▲ FIGURE 4.3

Metastasis sites for common cancers.

https://commons.wikimedia.org/wiki/File:Metastasis_sites_for_common_cancers.svg

Author: Mikael Haggström

Public Domain

Primary cancers are denoted by “...cancer” (except for skin melanoma) and their main metastasis sites are denoted by “...metastases.”

The metastasis sites for common cancer types (causing most death as per data from the U.S. in 2008) are as follows:

- Lung cancer is mainly spread to the adrenal glands, brain, and bone.
- Breast cancer is mainly spread to the bone, liver, lung, and brain.
- Colon cancer is mainly spread to the liver.
- Pancreatic cancer is mainly spread to the liver and lungs.
- Melanoma is mainly spread to the brain.
- Ovarian cancer is mainly spread to the pleural cavity and liver.

Also of major importance (not shown in the illustration):

- Prostate cancer (in males) usually metastasizes to the bones.

10. When are tissue changes not cancer?

Not every change in the body’s tissues is cancer. Some tissue changes may develop into cancer if they are not treated, however. Here are some examples of tissue changes that are not cancer but, in some cases, are closely watched:

Hyperplasia occurs when cells within a tissue divide faster than normal, and extra cells build up or proliferate. However, the cells and the way the tissue is organized look normal under a microscope. Hyperplasia can be caused by several factors or conditions, including chronic irritation.

Dysplasia is a more serious condition than hyperplasia. In dysplasia, there is also a buildup of extra cells. But the cells look abnormal, and there are changes in how the tissue is organized. In general, the more abnormal the cells and tissue look, the greater the chance that cancer will form.

Some types of dysplasia may need to be monitored or treated. An example of dysplasia is an abnormal mole (called a dysplastic nevus) that forms on the skin. A dysplastic nevus can turn into melanoma, although most do not.

An even more serious condition is carcinoma in situ. Although it is sometimes called cancer, carcinoma in situ is not cancer, because the abnormal cells do not spread beyond the original tissue. That is, they do not invade nearby tissue the way that cancer cells do. But, because some carcinomas in situ may become cancer, they are usually treated.

11. When cells acquire mutations associated with cancer, do they turn into cancer?

The answer is, not necessarily. Scientists estimate that it takes five to ten cancer-related mutations in a healthy cell to become cancerous. A study was conducted to determine the number of mutations found in esophageal cells of healthy people. A large portion of cells contained far more mutations than expected. Some of the cells with mutations multiplied faster than normal esophageal cells, eventually spreading throughout the esophagus, forming colonies of mutant cells known as clones. However, cancer did not result. It appears that much of this abnormal growth is age-related with a gradual accumulation over time.

12. Why do cancers come back?

After cancer is successfully treated, the patient lives with the uncertainty that cancer could recur. Physicians are hesitant to say to the patient when he or she is effectively “cured.” The longer the patient remains cancer-free after treatment, the more likely he or she will indeed be considered cured. For most cancers, if recurrence occurs, it will happen within the first two years after treatment. For some cancers, the wait time may be as long as ten years.

Two primary reasons for cancer recurrence are:

- A few cancer cells remained after treatment
- The cancer had already spread to other parts of the body, but the cancer cells were too small to detect (micrometastases)

Doctors describe recurrent cancer by where it develops and how far it has spread. The different types of recurrence are:

- **Local recurrence** means that the cancer is in the same place as the original cancer or very close to it.
- **Regional recurrence** means that the tumor has grown into lymph nodes or tissues near the original cancer.

Diagnosis of Cancer

13. How are laboratory tests used in cancer medicine?



After a physician has taken the medical history of a patient, noted symptoms, and performed a physical exam, he or she may order laboratory tests.

A laboratory test is a procedure in which a sample of blood, urine, other bodily fluid, or tissue is examined to get information about a person's health. Some laboratory tests provide precise and reliable information about specific health problems. Other tests provide more general information that helps doctors identify or rule out possible health problems. Doctors often use other types of tests, such as imaging tests, in addition to laboratory tests to learn more about a person's health. Laboratory tests are used in cancer medicine in many ways:

- To screen for cancer or precancerous conditions before a person has any symptoms of the disease
- To help diagnose cancer
- To provide information about the stage of a cancer (that is, its severity); for malignant tumors, this includes the size and extent (reach) of the original (primary) tumor and whether or not the tumor has spread (metastasized) to other parts of the body
- To plan treatment
- To monitor a patient's general health during treatment and to check for potential side effects of the treatment
- To determine whether a cancer is responding to treatment
- To find out whether cancer has recurred (come back)

14. How can a biopsy of a tumor help to diagnose cancer?

When a suspicious growth is discovered in a patient's body, it may or may not indicate cancer. A sample of the tissue must be collected (called a biopsy) and examined by a pathologist (a doctor who identifies diseases by studying cells and tissues under a microscope). A diagnosis of cancer is based upon observations of physical abnormalities of the cells in the sample. If the tumor is indeed cancerous, various tests are conducted to characterize the cancer.

15. What examinations and tests does the pathologist perform on the biopsy sample?

The pathologist's examination of the sample includes the following:

- Microscopic description: How the sample looks under the microscope and how it compares with normal cells
- Diagnosis: Type of tumor/cancer and grade (how abnormal the cells look under the microscope and how quickly the tumor is likely to grow and spread)
- Tumor size

After identifying the tissue as cancerous, the pathologist may perform additional tests to get more information about the tumor that cannot be determined by looking at the tissue with routine stains.

16. What imaging tests can be employed to diagnose cancer?

Imaging tests are advancements in diagnosing cancer, since they are noninvasive and avoid the disadvantages of biopsies. Imaging tests are ultrasound (sonography), computed tomography (CT scans), magnetic resonance imaging (MRI scans), and positron emission tomography (PET scans).

17. How does a computed tomography scan work?

Computed tomography (CT) is an imaging procedure that uses special x-ray equipment to create detailed pictures, or scans, of areas inside the body. It is also called computerized tomography and computerized axial tomography (CAT).

Each picture created during a CT procedure shows the organs, bones, and other tissues in a thin “slice” of the body. A series

of pictures are produced and can be combined into a three-dimensional picture. The technician and physician can look at individual slices or the three-dimensional picture.



▲ FIGURE 5.1

Patient undergoing a CT scan of the thorax.

Author: Ptrump16

CC BY-SA 4.0

https://en.wikipedia.org/wiki/CT_scan#/media/File:CT_Scan_Siemens_Somatom_Sensation_64.jpg

CT is used in cancer treatment in many different ways:

- To detect abnormal growths
- To help diagnose the presence of a tumor
- To provide information about the stage of a cancer
- To determine exactly where to perform (i.e., guide) a biopsy procedure
- To guide certain local treatments, such as cryotherapy, radiofrequency ablation, and the implantation of radioactive seeds

- To help plan external-beam radiation therapy or surgery
- To determine whether a cancer is responding to treatment
- To detect recurrence of a tumor

Studies have shown that CT can be effective in both colorectal cancer screening (including screening for large polyps) and lung cancer screening.

18. How does magnetic resonance imaging work?

MRI is a noninvasive imaging technology that produces three-dimensional detailed anatomical images without the use of damaging radiation. It is often used for disease detection, diagnosis, and treatment monitoring. It is based on sophisticated technology that excites and detects the change in the direction of the rotational axis of protons found in the water that makes up living tissues. An MRI scan takes cross-sectional views of your body from many angles.

MRI scanners are particularly well suited to image the non-bony parts or soft tissues of the body. They differ from computed tomography (CT), in that they do not use the damaging ionizing radiation of x-rays. The brain, spinal cord, and nerves, as well as muscles, ligaments, and tendons, are seen much more clearly with MRI than with regular x-rays and CT.

In the brain, MRI can differentiate between white matter and gray matter and can also be used to diagnose aneurysms and tumors. Because MRI does not use x-rays or other radiation, it is the imaging modality of choice when frequent imaging is required for diagnosis or therapy, especially in the brain. However, MRI is more expensive than x-ray imaging or CT scanning.

19. What are nuclear medicine scans?

Nuclear medicine uses small amounts of radioactive substances to find tumors and to determine the extent that cancer has spread in the body. While MCI and CT scans provide anatomic pictures of internal organs and tissues, nuclear medicine finds differences in physiological functions of the body, such as metabolism. This ability of nuclear medicine to make molecular processes in the body visible has made the field increasingly prominent in cancer diagnosis.

Examples of nuclear medicine scans are:

- PET (positron emission tomography) scans. The most common radiotracer used in PET is F-18 fluroglucose, a molecule similar to glucose. Cancer cells are more metabolically active than normal cells, so they absorb this radioactive glucose at a greater rate. PET scans may be combined with CT scans with the images superimposed on each other. These combined images allow for more precise information and accurate diagnosis.
- SPECT (single-photon emission computed tomography) scans. The radiotracer used in a SPECT scan remains in the bloodstream rather than being absorbed in the tissues. Rapidly growing tumors are noted for being blood deprived (ischemic), since the growth of cells exceeds the growth of blood vessels. SPECT scans can identify tumors by detecting areas of reduced blood flow. SPECT scans are also cheaper and more readily available than PET scans.

20. What is tumor grade?

Tumor grade is the description of a tumor based on how abnormal the tumor cells and the tumor tissue look under a microscope. It is an indicator of how quickly a tumor is likely to grow and spread. If the cells of the tumor and the organization of the tumor's tissue are close to those of normal cells and tissue, the tumor is called "well-differentiated." These tumors tend to grow and spread at a slower rate than tumors that are "undifferentiated" or "poorly differentiated," which have abnormal-looking cells and may lack normal tissue structures. Based on these and other differences in microscopic appearance, doctors assign a numerical "grade" to most cancers. The factors used to determine tumor grade can vary between different types of cancer.

21. What is cancer stage?

Cancer stage refers to the size and extent (reach) of the original (primary) tumor and whether or not cancer cells have spread in the body. Cancer stage is based on factors such as the location of the primary tumor, tumor size, regional lymph node involvement (the spread of cancer to nearby lymph nodes), and the number of tumors present.

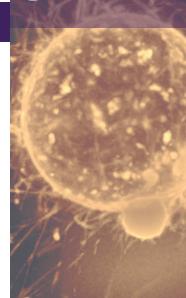
Knowing the stage of your cancer helps your doctor:

- Understand how serious your cancer is and your chances of survival

- Plan the best treatment for you
- Identify clinical trials that may be treatment options for you

Cancer is always referred to by the stage it was given at diagnosis, even if it gets worse or spreads. New information about how cancer has changed over time gets added on to the original stage. So, the stage doesn't change, even though the cancer might.

CHAPTER 6



Classification of Cancers

22. What is the conventional method of classifying cancers?

There are around 200 hundred different types of cancer. Types of cancer are usually named for the organs or tissues where the cancers form. For example, lung cancer starts in cells of the lung, and brain cancer starts in cells of the brain. Cancers also may be described by the type of cell that formed them, such as an epithelial cell or a squamous cell. With this method of classification, oncologists tend to treat cancers in isolation, with breast cancer treatment being distinctive from stomach cancer treatment, for example.

A recent article in *Science* described the remarkable tissue specificity of cancer types, which is likely related to the underlying biology of tissues (Haigis 2019). Oncogenes and tumor suppressor genes can only exert their effects if the conditions within a particular tissue allow the expression of these genes.

23. What is the method of classifying cancers by molecular alterations of tumor cells?

An NIH program called “The Cancer Genome Atlas” was launched in 2006 to create a dataset of genomic changes across an array of cancers. The researchers discovered that some DNA changes, gene expression, and chromosome numbers were similar for tumors across different organs. These findings indicate that the traditional system of anatomic cancer classification could be supplemented by a classification system based on molecular alterations shared by tumors across different tissue types.

The motive behind these new classification schemes is to provide improvements in diagnosis and treatments of cancers. The unique molecular profile of each person's cancer permits more personalized treatment methods that can be more effective than generalized treatments that are organ-based. However, there are potential pitfalls in any classification scheme. Cancer, by its very nature, is genetically heterogeneous and changes over time, so the classification

Cancers can be classified by:

- Organ or tissue of origin (conventional method)
- Molecular alterations of cancer cells (new method)



For discussions on various categories of cancers, visit:
https://en.wikipedia.org/wiki/Cancer_cell

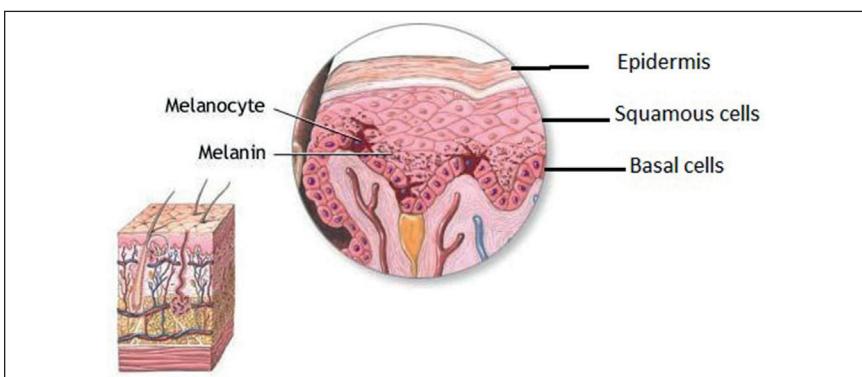


of a patient's tumor may depend on the stage at which the tumor is sampled. Current treatment methods tend to treat cancers as homogenous and unvarying.

As we shall see, an understanding of the molecular alterations of a specific patient's cancer can be particularly important when using the newer immunotherapy or targeted therapies.

24. What are carcinomas?

Carcinomas are the most common type of cancer. They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body. There are many types of epithelial cells, which often have a column-like shape when viewed under a microscope.



▲ FIGURE 6.1

Anatomy of the epithelium.

The left image is a cross-section of the entire skin, while the right image illustrates cells of the epithelium.

Source: https://commons.wikimedia.org/wiki/File:Illu_skin02.jpg
Public Domain

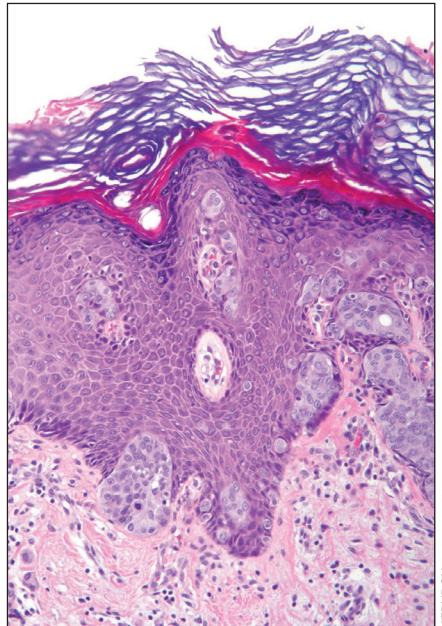
Carcinomas that begin in different epithelial cell types have specific names:

Adenocarcinoma is cancer that forms in epithelial cells that produce fluids or mucus. Tissues with this type of epithelial cell are sometimes called glandular tissues. Most cancers of the breast, colon, and prostate are adenocarcinomas.

Basal cell carcinoma is the most common type of skin cancer. This cancer begins in the lower or basal (base) layer of the epidermis, which is a person's outer layer of skin. Basal cells produce new skin cells as older cells die off.

Squamous cell carcinoma is cancer that forms in squamous cells, which are epithelial cells that lie just beneath the outer surface of the skin (epidermis). Squamous cells also line many other organs, including the stomach, intestines, lungs, bladder, and kidneys. Squamous cells look flat, like fish scales, when viewed under a microscope. Squamous cell carcinomas are sometimes called epidermoid carcinomas.

Transitional cell carcinoma is cancer that forms in a type of epithelial tissue called transitional epithelium, or urothelium. This tissue, which is made up of many layers of epithelial cells that can get bigger and smaller, is found in the linings of the bladder, ureters, and part of the kidneys (renal pelvis), as well as a few other organs. Some cancers of the bladder, ureters, and kidneys are transitional cell carcinomas.



NEPHRON

▲ FIGURE 6.2

Apocrine breast carcinoma.

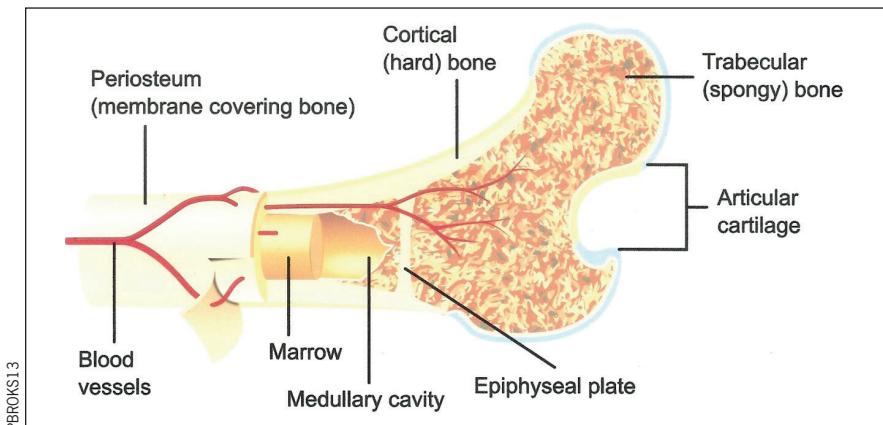
https://commons.wikimedia.org/wiki/File:Apocrine_carcinoma_-_high_mag.jpg

License: Creative Commons Attribution-Share Alike 3.0 Unported

25. What are sarcomas?

Sarcomas are cancers that form in connective tissues, including muscle, fat, blood vessels, nerves, bones, lymph vessels, and fibrous tissue (such as tendons and ligaments). Sarcomas are classified into two main groups: bone sarcomas and soft tissue sarcomas. It is important to realize that sarcomas as primary

cancers are very rare and should be distinguished from cancers found in these tissues that derive as metastases from other tissues.



▲ FIGURE 6.3

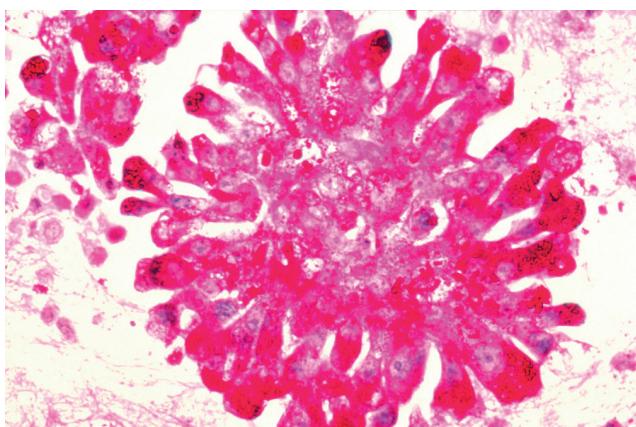
Cross-section of bone.

https://commons.wikimedia.org/wiki/File:Bone_cross-section.svg

License: Creative Commons Attribution 3.0 Unported

The most common primary bone cancer is osteosarcoma. Since it occurs in growing tissues, it is most commonly found in children. Chondrosarcoma is found in the cartilage and occurs more often in adults. Ewing's sarcoma can occur in either bone or soft tissue.

The most common types of soft tissue sarcoma are leiomyosarcoma, Kaposi sarcoma, malignant fibrous histiocytoma, liposarcoma, and dermatofibrosarcoma protuberans.



◀ FIGURE 6.4

Ewing sarcoma cells.

Source: PLoS Biology

Vol. 3/8/2005, e276

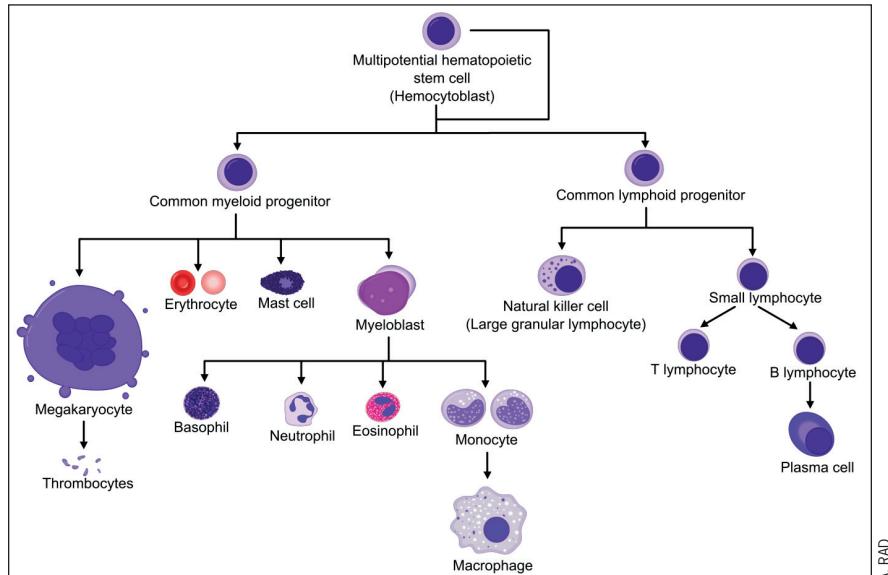
License: CC BY 2.5

26. What are leukemias?

Normally, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell. A lymphoid stem cell becomes a white blood cell known as a lymphocyte.

A myeloid stem cell becomes one of three types of mature blood cells:

- Red blood cells that carry oxygen and other substances to all tissues of the body.
- White blood cells (except for lymphocytes) that fight infection and disease.
- Platelets that form blood clots to stop bleeding.



A.RAD

▲ FIGURE 6.5

Blood cell formation.

https://www.wikilectures.eu/w/Blood_cell_formation#/media/File:Hematopoiesis_simple.png
License: CC BY-SA 3.0

The diagram illustrates that all blood cells are derived from “multipotential hematopoietic stem cells,” which means that stem cells have the potential to



DEFINITION

hematopoietic – formation and development of blood cells
blast cell – immature stages of a blood cell

progenitor cells – immature blood cells derived from stem cells that can further differentiate into specific mature blood cells

form many types of blood cells. The first differentiation leads to other types of immature cells known as myeloid or lymphoid progenitor cells. Myeloid progenitor cells further differentiate into mature thrombocytes (platelets), erythrocytes, and several types of white blood cells (basophils, neutrophils, eosinophils, and monocytes). Lymphoid progenitor cells further differentiate into mature lymphocytes.

When the blood-forming cells do not mature correctly, they can become leukemia cells. The exact causes of leukemia cell formation are not known with certainty, but it is widely believed that mutations in stem cells or progenitor cells may contributing factors. Leukemia cells also may not undergo apoptosis when they should. As a result, leukemia cells build up in the bone marrow and begin to spill into the blood. The presence of large numbers of immature blast cells in the blood can be a positive diagnosis of leukemia.

Leukemias are classified into four main types:

- Acute – when the condition is severe and sudden in onset
- Chronic – when the condition is slow-developing
- Lymphoblastic or lymphocytic
- Myeloid

27. What is lymphoblastic leukemia?

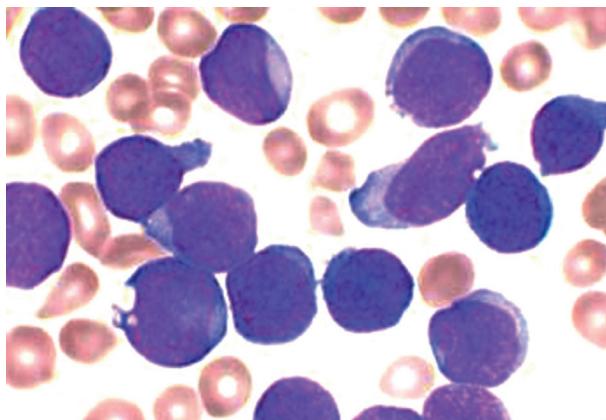
Lymphoblastic leukemia, also called lymphocytic leukemia, develops from lymphoid progenitor cells. The acute form is more common in children, and if untreated can be fatal within a few months.

Acute conditions are severe and sudden in onset, whereas chronic conditions are long-lasting.



Chronic lymphoblastic leukemia (CLL) is more common in adults than in children. In CLL, the lymphocytes look quite normal but do not perform their role in fighting infection as well as

normal white blood cells. CLL develops more slowly than the acute form but is more difficult to treat.



◀ FIGURE 6.6

Acute lymphoblastic leukemia.

Author: James Grellier

[https://en.wikipedia.org/
wiki/Cancer_cell#/media/
File:Acute_lymphoblastic_](https://en.wikipedia.org/wiki/Cancer_cell#/media/File:Acute_lymphoblastic_leukaemia_smear.jpg)
[leukaemia_smear.jpg](https://en.wikipedia.org/wiki/Cancer_cell#/media/File:Acute_lymphoblastic_leukaemia_smear.jpg)

License: CC BY-SA 3.0

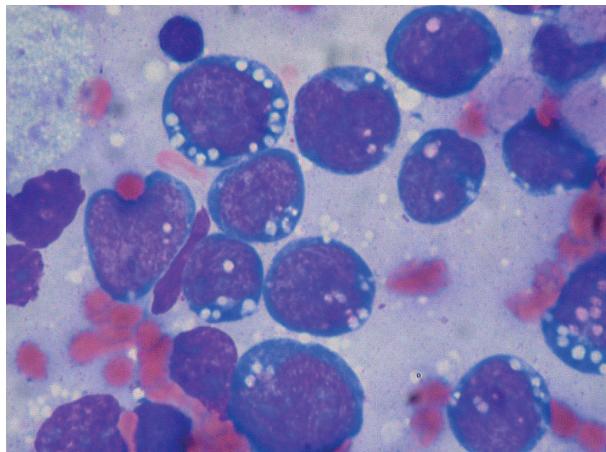
28. What are lymphomas?

In lymphoma, abnormal lymphocytes (T cells or B cells) build up in lymph nodes and lymph vessels, as well as in other organs of the body, such as the spleen and liver. Lymphoma develops in the lymphatic system, in contrast to leukemia, which develops in the bone marrow.

There are two main types of lymphoma:

Hodgkin lymphoma – People with this disease have abnormal lymphocytes that are called Reed-Sternberg cells. These cells usually form from B cells.

Non-Hodgkin lymphoma – This is a large group of cancers that start in lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells.



◀ FIGURE 6.7

Burkitt lymphoma.

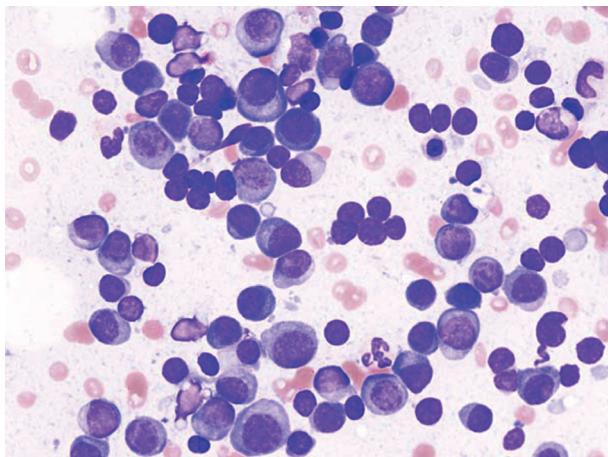
Source: [https://www.
flickr.com/photos/
euthman/144136197/in/
set-72057594114099781/](https://www.flickr.com/photos/euthman/144136197/in/set-72057594114099781/)

Author: Ed Uthman, MD

Public Domain

29. What is multiple myeloma?

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell (see Figure 6.5). The abnormal plasma cells, called myeloma cells, build up in the bone marrow and form tumors in bones all through the body. Kidney function can eventually be affected. Multiple myeloma is also called plasma cell myeloma and Kahler disease.



◀ FIGURE 6.8

Multiple myeloma.
[https://commons.wikimedia.org/wiki/File:Multiple_myeloma_\(1\)_MG_stain.jpg](https://commons.wikimedia.org/wiki/File:Multiple_myeloma_(1)_MG_stain.jpg)
GNU Free Documentation License

30. What are melanomas?

Question 24 discussed two types of skin cancer: squamous cell carcinoma and basal cell carcinoma. The basal layer of the epidermis also contains specialized cells called melanocytes that make melanin (the pigment that gives skin its color) (Figure 6.1). Genetic damage to melanocytes (often caused

by ultraviolet radiation from the sun or tanning lamps) can lead to a dangerous type of skin cancer called melanoma. Most melanomas form on the skin, but melanomas can also form in other pigmented tissues, such as the eye. Early signs of melanoma are changes to the shape or color of existing **moles** or, in the case of **nodular melanoma**, the appearance of a new lump anywhere on the skin.



▲ FIGURE 6.9

Melanoma on skin.
Public Domain

31. What are brain and spinal cord tumors?

There are different types of brain and spinal cord tumors. These tumors are named based on the type of cell in which they formed and where the tumor first formed in the central nervous system. For example, an astrocytic tumor begins in star-shaped brain cells called astrocytes, which help keep nerve cells healthy. Brain tumors can be benign (not cancer) or malignant (cancer).

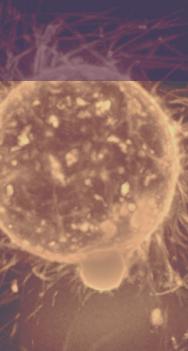
32. What are germ cell tumors?

Germ cell tumors are a type of tumor that begins in the cells that give rise to sperm or eggs. These tumors can occur almost anywhere in the body and can be either benign or malignant.

33. What are neuroendocrine tumors?

Neuroendocrine tumors form from cells that release hormones into the blood in response to a signal from the nervous system. These tumors, which may make higher-than-normal amounts of hormones, can cause many different symptoms. Neuroendocrine tumors may be benign or malignant.

Carcinoid tumors are a type of neuroendocrine tumor. They are slow-growing tumors that are usually found in the gastrointestinal system (most often in the rectum and small intestine). Carcinoid tumors may spread to the liver or other sites in the body, and they may secrete substances such as serotonin or prostaglandins, causing carcinoid syndrome.



References

CHAPTER 1

1. Canel, Marta, Alan Serrels, Margaret Frame, and Valerie Brunton. “E-cadherin-integrin Crosstalk in Cancer Invasion and Metastasis.” *J Cell Sci* 126 (2013): 393–401, <https://jcs.biologists.org/content/126/2/393.long>.
2. National Cancer Institute. “What Is Cancer?” February 9, 2015, <https://www.cancer.gov/about-cancer/understanding/what-is-cancer>.

CHAPTER 2

3. Cancer.net. “The Genetics of Cancer.” March 2018, <https://www.cancer.net/navigating-cancer-care/cancer-basics/genetics/genetics-cancer>.
4. Genetics Home Reference. “What Is a Gene?” and “What Is DNA?” U.S. National Library of Medicine, August 6, 2019, <https://ghr.nlm.nih.gov/primer/basics/gene>.
5. National Cancer Institute. “The Genetics of Cancer.” October 12, 2017, <https://www.cancer.gov/about-cancer/causes-prevention/genetics>.
6. National Human Genome Research Institute. “Deoxyribonucleic Acid (DNA) Fact Sheet.” National Institutes of Health, June 16, 2015, <https://www.genome.gov/about-genomics/fact-sheets/Deoxyribonucleic-Acid-Fact-Sheet>.

CHAPTER 3

7. Biology Dictionary. “Cell Signaling.” 2019, <https://biologydictionary.net/cell-signaling/>.
8. Sever, Richard, and Joan Brugge. “Signal Transduction in Cancer.” *Cold Spring Harbor Perspectives in Medicine*, 2015, <http://perspectivesinmedicine.cship.org/content/5/4/a006098.full.pdf+html>.
9. Wikipedia. “Cell surface receptor.” July 11, 2019, https://en.wikipedia.org/wiki/Cell_surface_receptor.

CHAPTER 4

10. Bommer, Ulrich-Axel, and Kara Perrow. “Cancer Biology: Molecular and Genetic Basis.” Cancer Council Australia, September 24, 2014, https://wiki.cancer.org.au/oncologyformedicalstudents/Cancer_biology:_Molecular_and_genetic_basis.
11. CancerQuest.org. “Cancer Development.” Emory Winship Cancer Institute. (2019) <https://www.cancerquest.org/cancer-biology/cancer-development>
12. Cancer Research UK. “Cancer Cells.” October 28, 2014, <https://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancer-starts/cancer-cells>.
13. Cancer Research UK. “How Cancer Can Spread.” December 5, 2017, <https://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancer-can-spread>.

14. Cancer Research UK. "Why Some Cancers Come Back." December 8, 2017,
<https://www.cancerresearchuk.org/about-cancer/what-is-cancer/why-some-cancers-come-back>.
15. Canel, Marta, Alan Serrels, Margaret Frame and Valerie Brunton. "E-cadherin-integrin crosstalk in cancer invasion and metastasis." *J Cell Sci.* 126. (2013): 393–401.
16. Cooper, Goeffrey. "The Development and Causes of Cancer." *The Cell: A Molecular Approach*, 2nd ed. Sinauer Associates, Inc., 2000,
<https://www.ncbi.nlm.nih.gov/books/NBK9963/>.
17. "Tumor Cells and the Onset of Cancer." Sec. 24.1 in *Molecular Cell Biology*, 4th ed. W. H. Freeman, 2000,
<https://www.ncbi.nlm.nih.gov/books/NBK21590/>.
18. Samarasinghe, B. "The Hallmarks of Cancer 6: Tissue Invasion and Metastasis." *Scientific American*. Oct. 30, 2013.
<https://blogs.scientificamerican.com/guest-blog/the-hallmarks-of-cancer-6-tissue-invasion-and-metastasis/>

CHAPTER 5

19. National Cancer Institute. "Understanding Laboratory Tests." December 11, 2013,
<https://www.cancer.gov/about-cancer/diagnosis-staging/understanding-lab-tests-fact-sheet>.
20. National Cancer Institute. "Cancer Staging." March 9, 2015,
<https://www.cancer.gov/about-cancer/diagnosis-staging/staging>.
21. National Cancer Institute. "Computed Tomography (CT) Scans and Cancer." July 16, 2013,
<https://www.cancer.gov/about-cancer/diagnosis-staging/ct-scans-fact-sheet>.
22. NIH-National Institute of Biomedical Imaging and Bioengineering. "Magnetic Resonance Imaging (MRI)." <https://www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri>.
23. RadiologyInfo.org. "Positron Emission Tomography-Computed Tomography (PET/CT)." January 23, 2017,
<https://www.radiologyinfo.org/en/info.cfm?pg=pet>.

CHAPTER 6

24. Haigis, Kevin, Karen Cichowski, and Stephen Elledge. "Tissue Specificity in Cancer: The Rule, not the Exception." *Science* 363, no. 6432 (2019): 1150–1151.
<https://science.sciencemag.org/content/363/6432/1150>.
25. Song, Qingxuan, Sofia Merajver, and Jun Li. "Cancer Classification in the Genomic Era: Five Contemporary Problems." *Human Genomics* 9, no. 27 (2015): 1–8.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4612488/pdf/40246_2015_Article_49.pdf.
26. Wikipedia. "Cancer cell."
https://en.wikipedia.org/wiki/Cancer_cell.



PART TWO

Standard Methods of Cancer Treatment

The standard methods of cancer treatment include surgery, radiation, chemotherapy and, to a more limited extent, hormone therapy. This Part discusses the situations that determine which method would be chosen for treatment and their limitations. As discussed throughout the book, a combination of treatment methods is commonly employed for the treatment of a given cancer.



Surgery
Image by David Mark
Pixabay License

CHAPTER 7

Surgery

CHAPTER 8

Chemotherapy

CHAPTER 9

Radiotherapy

CHAPTER 10

Hormone Therapy

Surgery



▲ FIGURE 7.1

Performing surgery to treat cancer.

Source: National Cancer Institute

Creator: John Crawford (Photographer)

<https://visualsonline.cancer.gov/details.cfm?imageid=4179>

Public Domain

34. When is surgery considered as part of a cancer treatment plan?

Surgery is the oldest form of cancer treatment and can still perform vital roles in a cancer treatment plan. Surgery can be used to help prevent cancer, diagnose cancer, remove cancer, and support other treatments.

35. How can surgery help to prevent cancer?

In preventive or prophylactic surgery, the surgeon removes tissue that is not yet cancer but has an increased risk of becoming cancer. An example is polyps discovered in the large intestine during colonoscopy.

People who have a genetic susceptibility for certain cancers may undergo surgery to remove tissues or organs that may not even show precancerous lesions. Examples include removal of the breast (mastectomy) or ovaries.

36. How can surgery be used to diagnose or stage cancer?

The use of a tumor biopsy to diagnosis or stage cancer was discussed in Question 14, Chapter 5. During a biopsy, the surgeon marks the track along which the biopsy was done. It is important to identify the track, because if the tumor is cancerous, some cancer cells may be deposited along the track as the needle is withdrawn.

37. How can surgery be used to remove cancer?

The goal of surgery is to completely remove the tumor or cancerous tissue from a specific place in the body. If cancer has already spread, surgery is still useful for some applications.

It may not be possible for surgery to remove the entire tumor if:

- the tumor is too large
- the location of the tumor is inaccessible, or the surgery could damage vital organs
- the cancer is too small to be seen by the surgeon
- the patient's general health is not good enough to withstand surgery

38. What is cryosurgery?

Cryosurgery (also called cryotherapy) is the use of extreme cold produced by liquid nitrogen (or argon gas) to destroy abnormal tissue. Cryosurgery is used to treat external tumors, such as those on the skin. For external tumors, liquid nitrogen is applied directly to the cancer cells with a cotton swab or spraying device. To treat tumors inside the body, liquid nitrogen or argon gas is circulated through a hollow instrument called a cryoprobe, which is placed in contact with the tumor.

39. What is laser surgery?

The term “laser” stands for light amplification by stimulated emission of radiation. Lasers focus a very high-intensity light in a narrow beam. Because lasers can focus very accurately on tiny areas, they can also be used for very precise surgical work or for cutting through tissue (in place of a scalpel).

Lasers can be used to shrink or destroy tumors or precancerous growths. Lasers are most commonly used to treat superficial cancers (cancers on the surface of the body or the lining of



▲ FIGURE 7.2

A 40-watt CO₂ laser used for soft-tissue laser surgery.

Source: National Cancer Institute

Creator: Etan J. Tal

Public Domain

internal organs) such as basal cell skin cancer and the very early stages of some cancers, such as cervical, penile, vaginal, vulvar, and non-small cell lung cancer.

Lasers also may be used to relieve certain symptoms of cancer, such as bleeding or obstruction. For example, lasers can be used to shrink or destroy a tumor that is blocking a patient's trachea (windpipe) or esophagus. Lasers also can be used to remove colon polyps or tumors that are blocking the colon or stomach.

Laser therapy can be used alone, but most often it is combined with other treatments, such as surgery, chemotherapy, or radiation therapy. Also, lasers can seal nerve endings to reduce pain after surgery and seal lymph vessels to reduce swelling and limit the spread of tumor cells.

40. What is hyperthermia treatment?

Hyperthermia (also called thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 113°F). Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. By killing cancer cells and damaging proteins and structures within cells, hyperthermia may shrink tumors.

Hyperthermia is under study in clinical trials (research studies with people) and is not widely available.

Hyperthermia is almost always used with other forms of cancer therapy, such as radiation therapy and chemotherapy. Hyperthermia may make some cancer cells more sensitive to radiation or harm other cancer cells that radiation cannot damage. When hyperthermia and radiation therapy are combined, they are often given within an hour of each other. Hyperthermia can also enhance the effects of certain anticancer drugs.

Numerous clinical trials have studied hyperthermia in combination with radiation therapy and chemotherapy. These studies have focused on the treatment of many types of cancer, including sarcoma, melanoma, and cancers of the head and neck, brain, lung, esophagus, breast, bladder, rectum, liver, appendix, cervix, and peritoneal lining (mesothelioma). Many of these studies, but not all, have shown a significant reduction in tumor size when hyperthermia is combined with other treatments. However, not all of these studies have shown increased survival in patients receiving the combined treatments.



▲ FIGURE 7.3

Whole-body hyperthermia to treat advanced cancer.

Creator: Mike Mitchell

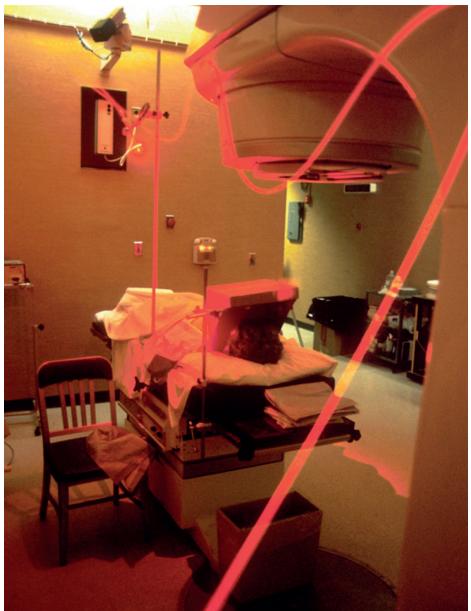
Source: National Cancer Institute

Public Domain

<https://visualsonline.cancer.gov/details.cfm?imageid=1954>

41. What is photodynamic therapy?

Photodynamic therapy (PDT) is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells. Each photosensitizer is activated by light of a specific wavelength. This wavelength determines how far the light can travel into the body. Thus, doctors use specific photosensitizers and wavelengths of light to treat different areas of the body with PDT.



▲ FIGURE 7.4

Photodynamic therapy.

Source: National Cancer Institute

Creator: John Crawford

Public Domain

<https://visualsonline.cancer.gov/details.cfm?imageid=2339>

To date, the FDA has approved the photosensitizing agent called porfimer sodium, or Photofrin®, for use in PDT to treat or relieve the symptoms of esophageal cancer and non-small cell lung cancer. Porfimer sodium is approved to relieve symptoms of esophageal cancer when cancer obstructs the esophagus or when cancer cannot be satisfactorily treated with laser therapy alone. Porfimer sodium is used to treat non-small cell lung cancer in patients for whom the usual treatments are not appropriate, and to relieve symptoms in patients with non-small cell lung cancer that obstructs the airways. In 2003, the FDA approved porfimer sodium for the treatment of precancerous lesions in patients with Barrett esophagus, a condition that can lead to esophageal cancer.

42. Can surgery occasionally increase the spread of cancer?

At times it has been observed that cancer has spread after the removal of a primary tumor by surgery. Recent studies have confirmed this phenomenon, which was previously largely based on anecdotal observations. Surgery could promote the spread of cancer by two means:

- Surgical trauma can facilitate the spread of cancer from the local site
- Micrometastases that were dormant can be activated to grow

The surgeon takes great care in removing the tumor, including removing some healthy tissue surrounding the tumor. However, surgery is traumatic, and handling the tumor results in disruption of its vasculature and the shedding of cancer cells into the blood and lymphatic systems. Additionally, some studies have shown a diminished activity of immune system components that are responsible for attacking and destroying cancer cells.

If cancer has already spread, micrometastases at distant sites may be in a dormant state with a balance between cellular growth and apoptosis. The primary tumor secretes both proangiogenic factors and inhibitors of angiogenesis into the bloodstream. The proangiogenic factors are less stable than the angiogenesis inhibitors, so the angiogenesis inhibitors have a greater influence on the micrometastases preventing new blood vessel growth. Upon removal of the primary tumor, the inhibitor levels fall, allowing the proangiogenic factors to exert greater influence on the micrometastases, resulting in renewed growth of the micrometastases.

CHAPTER

8



Chemotherapy

43. What is chemotherapy?

Chemotherapy (often abbreviated to chemo) is a type of cancer treatment that uses one or more anticancer drugs (chemotherapeutic agents) as part of a prescribed course of cancer treatment (called regimen). Chemotherapy may be given with a curative intent (which almost always involves combinations of drugs), or it may aim to prolong life or to reduce symptoms (palliative chemotherapy).

44. How does chemotherapy work?

Chemotherapy is the use of drugs that act upon rapidly dividing cancer cells by inhibiting mitosis (cell division). However, cancer cells vary widely in their susceptibility to these agents. To a large extent, chemotherapy can be thought of as a way to damage or stress cells, which may then lead to cell death if apoptosis is initiated. Many of the side effects of chemotherapy can be traced to damage to normal cells that divide rapidly and are thus sensitive to anti-mitotic drugs (see Question 46).

Chemotherapy is an example of systemic therapy in that the drug is introduced into the bloodstream and could act upon cancer at any anatomic location in the body. Systemic therapy is often used in conjunction with other types of treatment that constitute local therapy (i.e., treatments whose efficacy is confined to the anatomic area where they are applied) for cancer such as radiation therapy, surgery, or hyperthermia therapy.

Chemotherapy is the nonspecific use of drugs against cancer. This usage is distinct from selective agents that block extracellular signals (signal transduction). Drugs that block extracellular signals act on specific extracellular receptors (discussed in Question 5). The uses of selective therapeutic drugs are discussed in the sections on hormonal and targeted therapies.

45. Who receives chemotherapy?

Chemotherapy is used to treat many types of cancer. For some people, chemotherapy may be the only treatment you receive. But most often, you will have chemotherapy and other cancer treatments. The types of treatment that you need depends on the type of cancer you have, if it has spread and where, and if you have other health problems.



▲ FIGURE 8.1

Pediatric patients receiving chemotherapy.

Two girls with acute lymphoblastic leukemia receiving chemotherapy. The girl at left has a central venous catheter inserted in her neck. The girl at right has a peripheral venous catheter. The arm board stabilizes the arm during needle insertion. An anticancer IV drip is seen at top right.

National Cancer Institute – Public Domain

https://en.wikipedia.org/wiki/Chemotherapy#/media/File:Pediatric_patients_receiving_chemotherapy.jpg

46. What are the side effects of chemotherapy?

Chemotherapy can have a wide range of side effects related to its function as systemic drugs that act on fast-dividing cells. Although chemotherapeutic drugs are targeting cancer cells, other fast-dividing cells of the body, such as blood cells and the cells lining the mouth, stomach, and intestines, are also affected. The most common chemotherapy-related toxicities can occur acutely after administration, within hours or days, or chronically, from weeks to years.

The following are the primary chemotherapy-related toxicities:

- Immunosuppression and myelosuppression (blood-forming components in the bone marrow) – virtually all chemotherapeutic regimens can cause depression of the immune system, often by deactivating the bone marrow and leading to a decrease of white blood cells, red blood cells, and platelets.
- Gastrointestinal distress such as nausea, vomiting, anorexia, diarrhea, abdominal cramps, and constipation are common side effects of chemotherapeutic medications that kill fast-dividing cells.
- Anemia can be caused by a variety of body dysfunctions.
- Fatigue.
- Nausea and vomiting.
- Hair loss (alopecia) can be caused by chemotherapy that kills rapidly dividing cells.
- Development of secondary neoplasia (abnormal growth of tissue) after successful chemotherapy or radiotherapy treatment.



For an extensive discussion of chemotherapy, including the actions of chemotherapeutic drugs, a listing of common drug regimens, and the adverse effects of chemotherapy, visit:
<https://en.wikipedia.org/wiki/Chemotherapy>

47. How do cancer cells develop resistance to chemotherapeutic drugs?

Resistance is a major cause of treatment failure in chemotherapeutic drugs. Here are a few possible causes:

- Cancer cells produce high amounts of pumps, known as p-glycoprotein, to protect themselves from chemotherapeutics. These pumps actively move chemotherapeutics from inside the cell to the outside.
- Gene amplification, a process in which multiple copies of a gene are produced by cancer cells. This process overcomes the effect of drugs that reduce the expression of genes involved in replication.
- Cancer cells can also cause defects in the cellular pathways of apoptosis (programmed cell death). As most chemotherapy drugs kill cancer cells in this manner, defective apoptosis allows survival of these cells, making them resistant.
- Increased production of DNA repair genes in cancer cells overcoming the effect of DNA damage caused by chemotherapeutic drugs.

- The vascular system of tumors is noted for being poorly developed and poorly functioning. As a result, chemotherapeutic drugs may have difficulty in reaching the tumor.

48. Can a more modest use of chemotherapy overcome the problem of drug resistance?

In an attempt to destroy all cancer cells, oncologists typically administer the “maximum tolerated dose” of a chemotherapeutic drug to a patient. As pointed out by some researchers, however, a given tumor may contain a mixture of cells that are either sensitive or resistant to the drug. When a high dose of the drug is administered, only the resistant cancer cells remain, which then grow and proliferate. A more effective strategy may be to administer a “maximum effective dose” of drug that permits some drug-sensitive cancer cells to remain. These drug-sensitive cells can then outcompete the resistant cells, keeping their numbers in check. The continued presence of drug-sensitive cells allows for more effective subsequent chemotherapy treatments.

CHAPTER 9

Radiotherapy

49. What is radiotherapy?



Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors. At low doses, radiation is used in x-rays to see inside your body, as with x-rays of your teeth or broken bones.

50. What sources of radiation are used in cancer therapy?

Three sources of radiation are used in cancer therapy:

- x-rays (photons). Most radiation therapy machines use x-rays beams. X-rays are used at higher doses for therapy than doses for diagnosis. X-ray beams can reach tumors deep in the body. As they travel through the body, photon beams scatter little bits of radiation along their path. These beams do not stop once they reach the tumor but go into normal tissue past it.

- Protons are particles with a positive charge. Proton beams can also reach tumors deep in the body. However, proton beams do not scatter radiation on their path through the body, and they stop once they reach the tumor. Doctors think that proton beams might reduce the amount of normal tissue that is exposed to radiation. Clinical trials are underway to compare radiation therapy using proton beams with therapy using photon beams. Some cancer centers are using proton beams in radiation therapy, but the high cost and size of the machines are limiting their use.
- Electrons are particles with a negative charge. Electron beams cannot travel very far through body tissues. Therefore, their use is limited to tumors on the skin or near the surface of the body.



What are x-rays? X-rays can be described as the radiation of massless particles called photons. Each photon of x-rays contains a certain amount of energy that is different from the photons of other types of energetic particles.

51. What are the main types of radiation therapy?

There are two main types of radiation therapy, external beam and internal (National Cancer Institute 2019).

The type of radiation therapy that you may have depends on many factors, including:

- The type of cancer
- The size of the tumor
- The tumor's location in the body
- How close the tumor is to normal tissues that are sensitive to radiation
- Your general health and medical history
- Whether you will have other types of cancer treatment
- Other factors, such as your age and other medical conditions

52. What are the types of external beam radiation therapy?

There are many types of external beam radiation therapy, all of which share the goal of delivering the highest prescribed dose of radiation to the tumor while sparing the normal tissue around it. Each type relies on a computer to analyze images of the tumor to calculate the most precise dose and treatment path possible.

Types of external beam radiation therapy include:

a. 3-D conformal radiation therapy

What It Is

3-D conformal radiation therapy is a common type of external beam radiation therapy. It uses images from CT, MRI, and PET scans to precisely plan the treatment area, a process called simulation. A computer program is used to analyze the images and to design radiation beams that conform to the shape of the tumor.

How It Works

3-D conformal radiation conforms to the shape of the tumor by delivering beams from many directions. The precise shaping makes it possible to use higher doses of radiation on the tumor while sparing normal tissue.

Treatment Schedule

Most people have treatment once a day, Monday through Friday. The number of treatments varies from person to person based on details about your cancer, such as the type and stage of the cancer and the size and location of the tumor.

b. Intensity-modulated radiation therapy (IMRT)

What It Is

IMRT is a type of 3-D conformal radiation therapy.

How It Works

Like 3-D conformal radiation, radiation beams are aimed at the tumor from several directions.

IMRT uses beams that are smaller and of larger number than 3-D conformal radiation. The strength of the beams in some areas can be changed to give higher doses to certain parts of the tumor.

Treatment Schedule

Most people have treatment once a day, Monday through Friday. The number of treatments varies from person to person based on details about your cancer, such as the type and stage of the cancer and the size and location of the tumor.

c. Image-guided radiation therapy (IGRT)

What It Is

IGRT is a type of IMRT. However, it uses imaging scans not only for treatment planning before radiation therapy sessions but also during radiation therapy sessions.

How It Works

During treatment, you will have repeated scans, such as CT, MRI, or PET scans. These scans are processed by computers to detect changes in the tumor's size and location. The repeated imaging allows for your position or the radiation dose to be adjusted during treatment if needed. These adjustments can improve the accuracy of treatment and help spare normal tissue.

Treatment Schedule

Most people have treatment once a day, Monday through Friday. The number of treatments varies from person to person based on details about your cancer, such as the type and stage of the cancer and the size and location of the tumor.

d. Tomotherapy®

What It Is

Tomotherapy® is a type of IMRT that uses a machine that is a combination of a CT scanner and an external-beam radiation machine.

How It Works

Tomotherapy® machines take images of the tumor right before treatment sessions to allow for very precise tumor targeting and sparing of normal tissue. It rotates around you during treatment, delivering radiation in a spiral pattern, slice by slice. Tomotherapy® might be better at sparing normal tissue than 3-D conformal radiation therapy, but it has not been tested in clinical trials to be sure.

Treatment Schedule

Most people have treatment once a day, Monday through Friday. The number of treatments varies from person to person based on details about your cancer, such as the type and stage of the cancer and the size and location of the tumor.

e. Stereotactic radiosurgery

What It Is

Stereotactic radiosurgery is the use of focused, high-energy beams to treat small tumors with well-defined edges in the brain and central nervous system. It may be an option if surgery is too risky due to your age or other health problems or if the tumor cannot safely be reached with surgery. GammaKnife is a type of stereotactic radiosurgery.

How It Works

You will be placed in a head frame or some other device to make sure you do not move during treatment. In stereotactic radiosurgery, many small beams of radiation are aimed at the tumor from different directions. Each beam has very little effect on the tissue it passes through, but a precisely targeted dose of radiation is delivered to the site where all the beams come together.

Treatment Schedule

Treatment schedules can vary, but treatment is usually given in one dose. In some cases, you may receive up to five doses, given once per day.

f. Stereotactic body radiation therapy

What It Is

Stereotactic body radiation therapy is similar to stereotactic radiosurgery, but it is used for small, isolated tumors outside the brain and spinal cord, often in the liver or lung. It may be an option when you cannot have surgery due to age, health problems, or the location of the tumor.

How It Works

As in stereotactic radiosurgery, stereotactic body radiation therapy uses special equipment to hold you still during treatment. It delivers a highly precise beam to a limited area.

Treatment Schedule

Tumors outside of the brain are more likely to move with the normal motion of the body, such as with breathing or digesting.

Therefore, the radiation beams cannot be targeted as precisely as they are in stereotactic radiosurgery. For this reason, stereotactic body radiation is usually given in more than one dose. You may have up to five doses, given once per day.



▲ FIGURE 9.1

Patient prepared for radiation therapy.

A radiation therapist prepares a patient (lying on back) for radiation treatment using the “Tomotherapy” machine. Tomotherapy is often used for patients with limited metastatic cancer. It delivers high-dose radiation yet reduces radiation exposure to healthy surrounding tissue.

Source: National Cancer Institute

Creator: Rhonda Baer

Public Domain

53. What is internal radiation therapy (brachytherapy)?

Brachytherapy is a type of internal radiation therapy in which seeds, ribbons, or capsules that contain a radiation source are placed in your body, in or near the tumor. Brachytherapy is a local treatment and treats only a specific part of your body. It is often used to treat cancers of the head and neck, breast, cervix, prostate, and eye.

There are three types of brachytherapy:

- **Low-dose rate (LDR) implants:** In this type of brachytherapy, the radiation source stays in place for one to seven days. You are likely to be in the hospital during this time. Once your treatment is finished, your doctor will remove the radiation source and the catheter or applicator.
- **High-dose-rate (HDR) implants:** In this type of brachytherapy, the radiation source is left in place for just ten to twenty minutes at a time and then taken out. You

may have treatment twice a day for two to five days or once a week for two to five weeks. The schedule depends on your type of cancer. During the course of treatment, your catheter or applicator may stay in place, or it may be put in place before each treatment. You may be in the hospital during this time, or you may make daily trips to the hospital to have the radiation source put in place. As with LDR implants, your doctor will remove the catheter or applicator once you have finished treatment.

- **Permanent implants:** After the radiation source is put in place, the catheter is removed. The implants remain in your body for the rest of your life, but the radiation gets weaker each day. As time goes on, almost all the radiation will go away. When the radiation is first put in place, you may need to limit your time around other people and take other safety measures. Be extra careful not to spend time with children or pregnant women.

CHAPTER 10

Hormone Therapy



54. What are hormones?

Hormones are chemical substances produced by specialized cells in glands of the endocrine system. Hormones function as chemical messengers in the body. They affect the actions of cells and tissues at various locations in the body, often reaching their targets through the bloodstream. Each type of hormone affects only certain tissues and organs. When considered in their entirety, hormones affect a vast number of body processes.

Hormones exert their effects after selectively binding to receptors located inside or on the surface of target cells. In this manner, hormones act according to the cell signaling process, as discussed in Question 5. Hormonal therapy is used for several types of cancers derived from hormonally responsive tissues. Hormonal therapy has found its greatest application in the treatment of breast and prostate cancers and has also had limited use in treating uterine and adrenocortical cancer.

55. How does hormone therapy block the action of hormones?

Three primary means are employed to block the action of hormones (OncoLink 2019):

- Prevent the hormone from binding to its receptor. A therapeutic compound is administered that selectively binds to the hormone receptor, thus preventing the hormone from binding to the receptor.
- Prevent hormone production by the body. Medication can be given that blocks production of the hormone, or the organ that produces the hormone can be surgically removed.
- Deactivate the receptor by changing its shape. The hormone thereby can no longer bind to the receptor.



When hormone therapy involves the use of drugs that act on specific molecules associated with cancer it is known as targeted therapy (Part 3)

56. How is hormone therapy used in breast cancer?

Breast cancer tumors will only be sensitive to hormone therapy if they have hormone receptors. In order to check for receptors, physicians test samples of tumor tissue obtained by biopsy or surgery.

Several strategies are used to treat hormone-sensitive breast cancer:

- Blocking ovarian function: Because the ovaries are the main source of estrogen in premenopausal women, estrogen levels in these women can be reduced by eliminating or suppressing ovarian function. Blocking ovarian function is called ovarian ablation. Ovarian ablation can be done surgically in an operation to remove the ovaries (called oophorectomy) or by treatment with radiation. This type of ovarian ablation is usually permanent. Ovarian function can be suppressed temporarily by treatment with drugs called gonadotropin-releasing hormone (GnRH) agonists.
- Blocking estrogen production: Drugs called aromatase inhibitors are used to block the activity of an enzyme called aromatase, which the body uses to make estrogen in the ovaries and other tissues.
- Blocking estrogen's effects: Drugs such as selective estrogen receptor modulators (SERMs)



For details on the use of hormone therapy for breast cancer, please visit:
<https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet>

and fulvestrant bind to estrogen receptors, preventing estrogen from binding.

57. How is hormone therapy used in prostate cancer?

Androgens (male sex hormones) are a class of hormones that control the development and maintenance of male characteristics. Testosterone and dihydrotestosterone (DHT) are the most abundant androgens in men. Almost all testosterone is produced in the testicles; a small amount is produced by the adrenal glands. Prostate cancer cells may also have the ability to produce testosterone.

Androgens are required for normal growth and function of the prostate, a gland in the male reproductive system that helps make semen. Androgens are also necessary for prostate cancers to grow. Androgens promote the growth of both normal and cancerous prostate cells by binding to and activating the androgen receptor, a protein that is expressed in prostate cells. Once activated, the androgen receptor stimulates the expression of specific genes that cause prostate cells to grow.

Early in their development, prostate cancers need relatively high levels of androgens to grow. Such prostate cancers are referred to as androgen-dependent or androgen-sensitive, because treatments that decrease androgen levels or block androgen activity can inhibit their growth.

Most prostate cancers eventually become “castration-resistant,” which means that they can continue to grow even when androgen levels in the body are extremely low or undetectable.

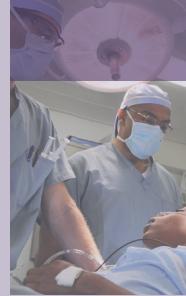
Hormone therapy for prostate cancer—also called androgen suppression therapy or androgen deprivation therapy—can block the production and use of androgens. Currently available treatments can:

For details on the use of hormone therapy for prostate cancer, please visit:

<https://www.cancer.gov/types/prostate/prostate-hormone-therapy-fact-sheet>



- Reduce androgen production by the testicles
- Block the action of androgens in the body
- Block the production of androgens throughout the body



References

CHAPTER 7

1. Canadian Cancer Society. "Surgery in Cancer Treatment." <http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/surgery/?region=on>.
2. National Cancer Institute. "Surgery to Treat Cancer." April 29, 2015, <https://www.cancer.gov/about-cancer/treatment/types/surgery>.
3. Tohme, Samer, Richard Simmons, and Allan Tsung. "Surgery for Cancer: A Trigger for Metastasis." *Cancer Research* 77, no. 7 (2017): 1548–1552. <http://cancerres.aacrjournals.org/content/canres/77/7/1548.full.pdf>.

CHAPTER 8

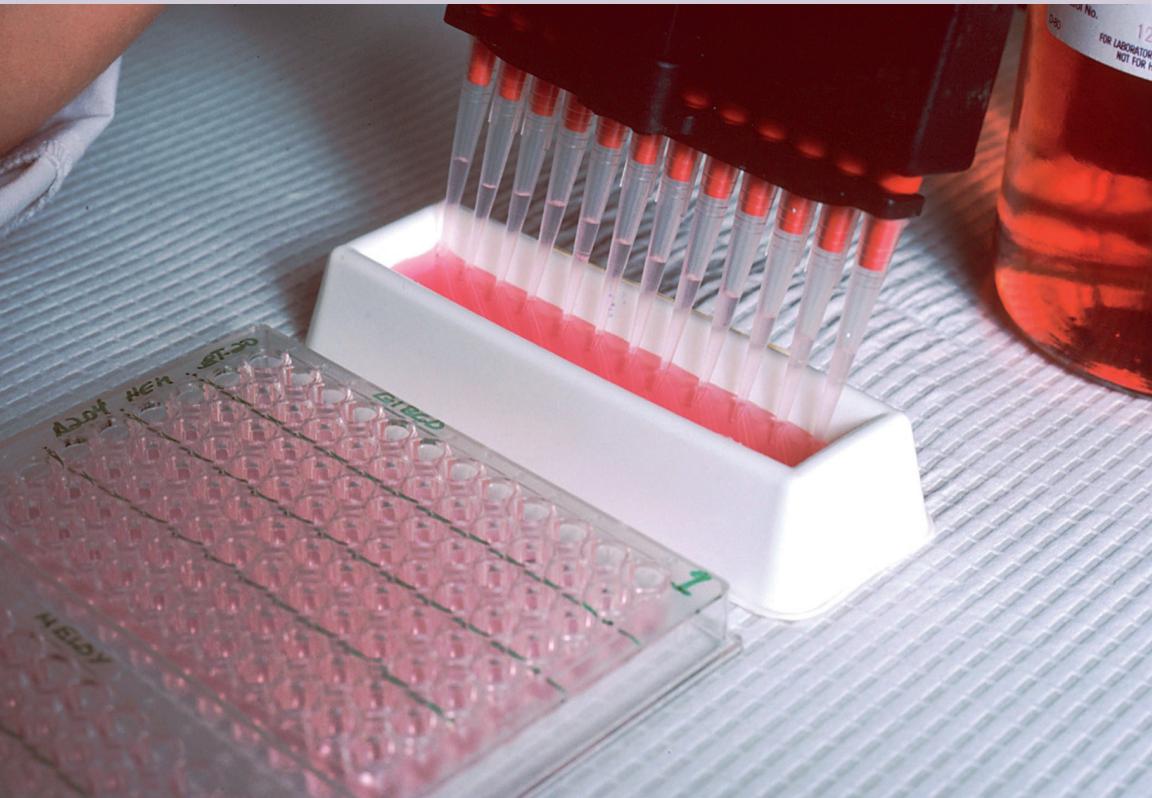
4. CancerQuest. "Chemotherapy." Emory University. 2018, <https://www.cancerquest.org/patients/treatments/chemotherapy>. This article describes the various chemotherapy drugs.
5. Cancer Research UK. "What Is Chemotherapy?" November 17, 2017, <https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy>.
6. DeGregori, James, and Robert Gatenby. "Darwin's Cancer Fix." *Scientific American* (August 2019): 52–57. <https://www.scientificamerican.com/article/darwins-ideas-on-evolution-drive-a-radical-new-approach-to-cancer-drug-use/>.

CHAPTER 9

7. CancerQuest. "Radiation Therapy." Emory University. 2018, <https://www.cancerquest.org/patients/treatments/radiation-therapy>.
8. National Cancer Institute "Radiation Therapy to Treat Cancer" 2019 <https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy>

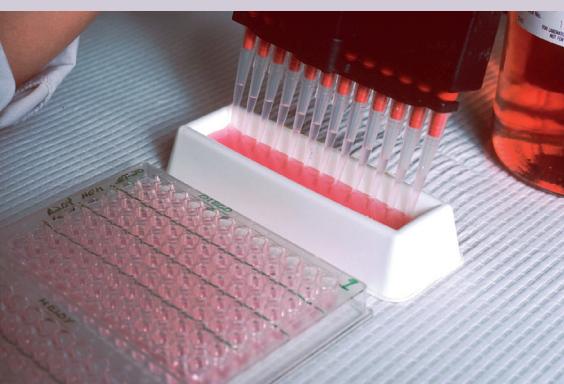
CHAPTER 10

8. OncoLink. "Hormone Therapy: The Basics." Penn Medicine. February 27, 2018, <https://www.oncolink.org/cancer-treatment/hormone-therapy/hormone-therapy-the-basics>.



PART THREE

Targeted Cancer Therapy



Monoclonal antibodies.
National Cancer Institute
Creator: Linda Bartlett
Public Domain

CHAPTER 11

Development of Targeted Therapy

CHAPTER 12

Disadvantages of Targeted Therapies

Development of Targeted Therapy

58. What are targeted cancer therapies?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules (“molecular targets”) that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called “molecularly targeted drugs,” “molecularly targeted therapies,” “precision medicines,” or similar names.

Targeted therapies are notable for their specificity. This specificity invites comparisons between targeted therapies and standard chemotherapy as follows:

- Targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells.
- Targeted therapies are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells.
- Targeted therapies are often cytostatic (that is, they block tumor cell proliferation, whereas standard chemotherapy agents are cytotoxic (that is, they kill tumor cells).

Targeted therapies are currently the focus of much anticancer drug development. They are a cornerstone of precision medicine, a form of medicine that uses information about a person’s genes and proteins to prevent, diagnose, and treat disease.

Many targeted cancer therapies have been approved by the Food and Drug Administration (FDA) to treat specific types of cancer. Others are being studied in clinical trials (research studies with people), and many more are in preclinical testing (research studies with animals).



59. How are targets for targeted cancer therapies identified?

The development of targeted therapies requires the identification of good targets—that is, targets that play a key role in cancer cell growth and survival. (It is for this reason that targeted therapies are sometimes referred to as the product of “rational” drug design.)

One approach to identify potential targets is to compare the amounts of individual proteins in cancer cells with those in normal cells. Proteins that are present in cancer cells but not normal cells or that are more abundant in cancer cells would be potential targets, especially if they are known to be involved in cell growth or survival. An example of such a differentially expressed target is the human epidermal growth factor receptor 2 protein (HER-2). HER-2 is expressed at high levels on the surface of some cancer cells. Several targeted therapies are directed against HER-2, including trastuzumab (Herceptin®), which is approved to treat certain breast and stomach cancers that overexpress HER-2.

Another approach to identify potential targets is to determine whether cancer cells produce mutant (altered) proteins that drive cancer progression. For example, the cell growth signaling

protein BRAF is present in an altered form (known as BRAF V600E) in many melanomas. Vemurafenib (Zelboraf[®]) targets this mutant form of the BRAF protein and is approved to treat patients with inoperable or metastatic melanoma that contains this altered BRAF protein.

Researchers also look for abnormalities in chromosomes that are present in cancer cells but not in normal cells. Sometimes these chromosome abnormalities result in the creation of a fusion gene (a gene that incorporates parts of two different genes) whose product, called a protein, may drive cancer development. Such fusion proteins are potential targets for targeted cancer therapies. For example, imatinib mesylate (Gleevec[®]) targets the BCR-ABL fusion protein, which is made from pieces of two genes that get joined together in some leukemia cells and promotes the growth of leukemic cells.

60. How are targeted therapies developed?

Once a candidate target has been identified, the next step is to develop a therapy that affects the target in a way that interferes with its ability to promote cancer cell growth or survival. For example, a targeted therapy could reduce the activity of the target or prevent it from binding to a receptor that it normally activates, among other possible mechanisms.

There are two main types of targeted therapy:

- Small-molecule compounds are typically developed for targets that are located inside the cell because such agents can enter cells relatively easily.
- Monoclonal antibodies are relatively large and generally cannot enter cells, so they are used only for targets that are outside cells or on the cell surface.

Candidate small molecules are usually identified in what are known as “high-throughput screens,” in which the effects of thousands of test compounds on a specific target protein are examined. Compounds that affect the target (sometimes called “lead compounds”) are then chemically modified to produce numerous closely related versions of the lead compound. These related compounds are then tested to determine which are most effective and have the fewest effects on nontarget molecules.

Monoclonal antibodies are developed by injecting animals (usually mice) with purified target proteins, causing the animals to make many different types of antibodies against the target. These antibodies are then tested to find the ones that bind best to the target without binding to non-target proteins.

Before monoclonal antibodies are used in humans, they are “humanized” by replacing as much of the mouse antibody molecule as possible with corresponding portions of human antibodies. Humanizing is necessary to prevent the human immune system from recognizing the monoclonal antibody as “foreign” and destroying it before it has a chance to bind to its target protein. Humanization is not an issue for small-molecule compounds, because they are not typically recognized by the body as foreign.

61. What types of targeted therapies are available?

Many different targeted therapies have been approved for use in cancer treatment. These therapies include hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules.

- **Hormone therapies** slow or stop the growth of hormone-sensitive tumors, which require certain hormones to grow. Hormone therapies act by preventing the body from producing the hormones or by interfering with the action of the hormones. Hormone therapies have been approved for both breast cancer and prostate cancer.
- **Signal transduction inhibitors** block the activities of molecules that participate in signal transduction, the process by which a cell responds to signals from its environment. Signal transduction was discussed in Question 5. During this process, once a cell has received a specific signal, the signal is relayed within the cell through a series of biochemical reactions that ultimately produce the appropriate response(s). In some cancers, the malignant cells are stimulated to divide continuously without being prompted to do so by external growth factors. Signal transduction inhibitors interfere with this inappropriate signaling. **Tyrosine kinase inhibitors** are important examples of signal transduction inhibitors.

- **Gene expression modulators** modify the function of proteins that play a role in controlling gene expression. Question 3 described how genes in DNA are first transcribed into messenger RNA, followed by translation into proteins which carry out the role of genes. Transcription modulators are proteins that control transcription factor activity. Gene expression modulators block the action of transcription modulators that could activate an aberrant gene. Drugs block gene expression by blocking locations of DNA containing the problem genes.
- **Apoptosis inducers** cause cancer cells to undergo a process of controlled cell death called apoptosis. Apoptosis is one method the body uses to get rid of unneeded or abnormal cells, but cancer cells have strategies to avoid apoptosis. Apoptosis inducers can get around these strategies to cause the death of cancer cells. Tumor suppressor genes (Question 8) induce apoptosis of abnormal cells to prevent their propagation through the cell cycle.
- **Angiogenesis inhibitors** block the growth of new blood vessels to tumors (a process called tumor angiogenesis). A blood supply is necessary for tumors to grow beyond a certain size because blood provides the oxygen and nutrients that tumors need for continued growth. Treatments that interfere with angiogenesis may block tumor growth. Some targeted therapies that inhibit angiogenesis interfere with the action of vascular endothelial growth factor (VEGF), a substance that stimulates new blood vessel formation. Other angiogenesis inhibitors target other molecules that stimulate new blood vessel growth.
- **Immunotherapy** often involves the use of targeted therapy. Immunotherapy will be discussed in depth in Part 4. Immunotherapies trigger the immune system to destroy cancer cells. Some immunotherapies are monoclonal antibodies that recognize specific molecules on the surface of cancer cells. Binding of the monoclonal antibody to the target molecule results in the immune destruction of cells that express that target molecule. Other monoclonal antibodies bind to certain immune cells to help these cells better kill cancer cells.

- **Monoclonal antibodies that deliver toxic molecules** can cause the death of cancer cells specifically. Once the antibody has bound to its target cell, the toxic molecule that is linked to the antibody—such as a radioactive substance or a poisonous chemical—is taken up by the cell, ultimately killing that cell. The toxin will not affect cells that lack the target for the antibody—that is, the vast majority of cells in the body.



DEFINITION

Gene therapy introduces genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein. Gene therapy has found applications in cancer therapies and is also used in treating other genetic diseases.

Cancer vaccines and gene therapy are sometimes considered targeted therapies because they interfere with the growth of specific cancer cells. Cancer vaccines are discussed in Chapter 15.

62. Can therapies target tumors that have inactivated tumor suppressor genes?

Two classes of genes are frequently mutated in cancer: oncogenes and tumor suppressor genes. Although genetic alterations leading to cancer more commonly affect tumor suppressor genes rather than oncogenes, it is easier to develop drugs that target oncogenes. Question 8 discussed the importance of tumor suppressor genes for eliminating abnormal cells. Cancer cells have developed the ability to inactivate tumor suppressor genes, allowing them to grow and spread.

There are two major strategies for targeting tumor suppressor genes:

- Reintroduce a functional copy of the tumor suppressor gene via gene therapy
- Develop small molecule inhibitors that reactivate tumor suppressor function

How is it determined whether a patient is a candidate for targeted therapy?

For some types of cancer, most patients with that cancer will have an appropriate target for a particular targeted therapy, and thus will be candidates to be treated with that therapy. Chronic myeloid leukemia patients, for example, have an abnormal gene, BCR-ABL. These patients may be treated with tyrosine kinase inhibitors. For other cancer types, however, a patient's tumor tissue must be tested to determine whether or not an appropriate target is present. The use of targeted therapy may be restricted to patients whose tumor has a specific gene mutation that codes for the target; patients who do not have the mutation would not be candidates because the therapy would have nothing to target.

Sometimes a patient is a candidate for a targeted therapy only if they meet specific criteria (for example, their cancer did not respond to other therapies, has spread, or is inoperable). These criteria are set by the FDA when it approves a specific targeted therapy.

63. What targeted therapies have been approved for specific types of cancer?

The FDA has approved targeted therapies for the treatment of some patients with the following types of cancer (some targeted therapies have been approved to treat more than one type of cancer):

Adenocarcinoma of the stomach or gastroesophageal junction: Trastuzumab (Herceptin®), ramucirumab (Cyramza®)

Bladder cancer: Atezolizumab (Tecentriq™), nivolumab (Opdivo®), durvalumab (Imfinzi™), avelumab (Bavencio®), pembrolizumab (Keytruda®)

Brain cancer: Bevacizumab (Avastin®), everolimus (Afinitor®)

Breast cancer: Everolimus (Afinitor®), tamoxifen (Nolvadex), toremifene (Fareston®), Trastuzumab (Herceptin®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), lapatinib (Tykerb®), letrozole (Femara®), pertuzumab (Perjeta®), ado-trastuzumab emtansine (Kadcyla®), palbociclib (Ibrance®), ribociclib (Kisqali®), neratinib maleate (Nerlynx™), abemaciclib (Verzenio™), olaparib (Lynparza™)

Cervical cancer: Bevacizumab (Avastin®), pembrolizumab (Keytruda®)

Colorectal cancer: Cetuximab (Erbitux®), panitumumab (Vectibix®), bevacizumab (Avastin®), ziv-aflibercept (Zaltrap®), regorafenib (Stivarga®), ramucirumab (Cyramza®), nivolumab (Opdivo®), ipilimumab (Yervoy®)

Dermatofibrosarcoma protuberans: Imatinib mesylate (Gleevec®)

Endocrine/neuroendocrine tumors: Lanreotide acetate (Somatuline® Depot), avelumab (Bavencio®), lutetium Lu 177-dotataate (Lutathera®)

Head and neck cancer: Cetuximab (Erbitux®), pembrolizumab (Keytruda®), nivolumab (Opdivo®)

Gastrointestinal stromal tumor: Imatinib mesylate (Gleevec®), sunitinib (Sutent®), regorafenib (Stivarga®)

Giant cell tumor of the bone: Denosumab (Xgeva®)

Kidney cancer: Bevacizumab (Avastin®), sorafenib (Nexavar®), sunitinib (Sutent®), pazopanib (Votrient®), temsirolimus (Torisel®), everolimus (Afinitor®), axitinib (Inlyta®), nivolumab (Opdivo®), cabozantinib (Cabometyx™), lenvatinib mesylate (Lenvima®), ipilimumab (Yervoy®)

Leukemia: Tretinoin (Vesanoid®), imatinib mesylate (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), rituximab (Rituxan®), alemtuzumab (Campath®), ofatumumab (Arzerra®), obinutuzumab (Gazyva®), ibrutinib (Imbruvica®), idelalisib (Zydelig®), blinatumomab (Blinacyto®), venetoclax (Venclexta™), ponatinib hydrochloride (Iclusig®), midostaurin (Rydapt®), enasidenib mesylate (Idhifa®), inotuzumab ozogamicin (Besponsa®), tisagenlecleucel (Kymriah®), gemtuzumab ozogamicin (Mylotarg™), rituximab and hyaluronidase human (Rituxan Hycela™), ivosidenib (Tibsovo®)

Liver cancer: Sorafenib (Nexavar®), regorafenib (Stivarga®), nivolumab (Opdivo®)

Lung cancer: Bevacizumab (Avastin®), crizotinib (Xalkori®), erlotinib (Tarceva®), gefitinib (Iressa®), afatinib dimaleate (Gilotrif®), ceritinib (LDK378/Zykadia™), ramucirumab (Cyramza®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), osimertinib (Tagrisso™), necitumumab (Portrazza™), alectinib (Alecensa®), atezolizumab (Tecentriq™), brigatinib (Alunbrig™), trametinib (Mekinist®), dabrafenib (Tafinlar®), durvalumab (Imfinzi™)

Lymphoma: Ibrutumomab tiuxetan (Zevalin®), denileukin diftitox (Ontak®), brentuximab vedotin (Adcetris®), rituximab (Rituxan®), vorinostat (Zolinza®), romidepsin (Istodax®), bexarotene (Targretin®), bortezomib (Velcade®), pralatrexate (Folotyn®), ibrutinib (Imbruvica®), siltuximab (Sylvant®), idelalisib (Zydelig®), belinostat (Beleodaq®), obinutuzumab (Gazyva®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), rituximab and hyaluronidase human (Rituxan Hycela™), copanlisib hydrochloride (Aliqopa™), axicabtagene ciloleucel (Yescarta™), acalabrutinib (Calquence®), tisagenlecleucel (Kymriah®), venetoclax (Venclexta™)

Microsatellite instability-high or mismatch repair-deficient solid tumors: Pembrolizumab (Keytruda®)

Multiple myeloma: Bortezomib (Velcade®), carfilzomib (Kyprolis®), panobinostat (Farydak®), daratumumab (Darzalex™), ixazomib citrate (Ninlaro®), elotuzumab (Empliciti™)

Myelodysplastic/myeloproliferative disorders: Imatinib mesylate (Gleevec®), ruxolitinib phosphate (Jakafi®)

Neuroblastoma: Dinutuximab (Unituxin™)

Ovarian epithelial/fallopian tube/primary peritoneal cancers: Bevacizumab (Avastin®), olaparib (Lynparza™), rucaparib camsylate (Rubraca™), niraparib tosylate monohydrate (Zejula™)

Pancreatic cancer: Erlotinib (Tarceva®), everolimus (Afinitor®), sunitinib (Sutent®)

Prostate cancer: Cabazitaxel (Jevtana®), enzalutamide (Xtandi®), abiraterone acetate (Zytiga®), radium 223 dichloride (Xofigo®), apalutamide (Erleada™)

Skin cancer: Vismodegib (Erivedge®), sonidegib (Odomzo®), ipilimumab (Yervoy®), vemurafenib (Zelboraf®), trametinib (Mekinist®), dabrafenib (Tafinlar®), pembrolizumab (Keytruda®), nivolumab (Opdivo®), cobimetinib (Cotellic™), alitretinoin (Panretin®), avelumab (Bavencio®), encorafenib (Braftovi™), binimetinib (Mektovi®)

Soft tissue sarcoma: Pazopanib (Votrient®), olaratumab (Lartruvo™), alitretinoin (Panretin®)

Stomach cancer: Pembrolizumab (Keytruda®)

Systemic mastocytosis: Imatinib mesylate (Gleevec®), midostaurin (Rydapt®)

Thyroid cancer: Cabozantinib (Cometriq®), vandetanib (Caprelsa®), sorafenib (Nexavar®), lenvatinib mesylate (Lenvima®), trametinib (Mekinist®), dabrafenib (Tafinlar®)

CHAPTER

12



Disadvantages of Targeted Therapies

64. What are the limitations of targeted cancer therapies?

Targeted therapies do have some limitations. One is that cancer cells can become resistant to them. Resistance can occur in two ways: the target itself changes through *mutation* so that the targeted therapy no longer interacts well with it, or the tumor finds a new pathway to achieve tumor growth that does not depend on the target.

For this reason, targeted therapies may work best in combination. For example, a recent study found that using two therapies that target different parts of the cell-signaling pathway that is altered in melanoma by the BRAF V600E mutation slowed the development of resistance and disease progression to a greater extent than using just one targeted therapy.

Another approach is to use targeted therapy in combination with one or more traditional chemotherapy drugs. For example, the targeted therapy trastuzumab (Herceptin®) has been used in combination with docetaxel, a traditional chemotherapy drug, to treat women with metastatic breast cancer that overexpresses the protein HER2/neu.

Another limitation of targeted therapy at present is that drugs for some identified targets are difficult to develop because of the target's structure or the way its function is regulated in the cell. One example is Ras, a signaling protein that is mutated in as many as one-quarter of all cancers (and in the majority of certain cancer types, such as pancreatic cancer). To date, it has not been possible to develop inhibitors of Ras signaling with existing drug development technologies. However, promising new approaches are offering hope that this limitation can soon be overcome.

65. What are the challenges in developing targeted therapies?

- Tumor heterogeneity

Tumor biology is very complex. As tumors develop, they acquire many genetic mutations, making most tumors unique in some respect. Even within a given patient, tumors evolve. This variability in tumors may account for the successes and failures of small molecule and monoclonal antibody treatments. It is necessary, therefore, to evaluate every patient for their unique gene profile. Advances in gene sequencing have permitted analysis of tumors at reasonably low cost to reveal molecular aberrations that are critical for carcinogenesis and tumor growth.

- Cancer stem cells (CSCs) are slow-growing cancer cells that can eventually differentiate into fast-growing cancer cells. CSCs have different gene expression profiles, so they can evade targeted therapy for differentiated cancer cells. Therefore, different approaches must be taken to develop targeted therapies for CSCs.
- Epithelial-mesenchymal transition (EMT) was discussed in Question 9 related to how cancers spread. Solid tumors initially have epithelial characteristics and cannot migrate. When the epithelial cells acquire mesenchymal

cell properties, they can migrate and metastasize. Studies have found that inhibiting the action of transforming growth factor-beta can block the EMT process.

Although targeted therapies have shown great successes as cancer treatments, all too often a patient does not respond well to the selected drug therapy. The Institute for Personalized Cancer Therapy (IPCT) at the MD Anderson Cancer Center has worked to remedy this situation by developing a database that serves as a resource for physicians and patients on possible therapeutic options. <https://pct.mdanderson.org>

With the greatly reduced cost of genome analysis, an extensive database has been developed on a large variety of cancer tumors (a genome is the total of all the genes in a tumor's DNA). The IPCT team mined the literature databases to find associations between detected genomic alterations with (1) tumor growth and development and (2) increased or decreased responses to certain therapies. The website also lists the relevant drugs that are FDA approved or are used in clinical trials.

66. What are the side effects of targeted cancer therapies?

Scientists had expected that targeted cancer therapies would be less toxic than traditional chemotherapy drugs, because cancer cells are more dependent on the targets than are normal cells. However, targeted cancer therapies can have substantial side effects.

The most common side effects seen with targeted therapies are diarrhea and liver problems such as *hepatitis* and elevated liver enzymes. Other side effects seen with targeted therapies include:

- Skin problems (acneiform rash, dry skin, nail changes, hair depigmentation)
- Problems with blood clotting and wound healing
- High blood pressure
- Gastrointestinal perforation (a rare side effect of some targeted therapies)

Certain side effects of some targeted therapies have been linked to better patient outcomes. For example, patients who develop acneiform rash (skin eruptions that resemble acne)

while being treated with the signal transduction inhibitors erlotinib (Tarceva®) or gefitinib (Iressa®), both of which target the epidermal growth factor receptor, have tended to respond better to these drugs than patients who do not develop the rash. Similarly, patients who develop high blood pressure while being treated with the angiogenesis inhibitor bevacizumab generally have had better outcomes.

The few targeted therapies that are approved for use in children can have different side effects in children than in adults, including immunosuppression and impaired sperm production.



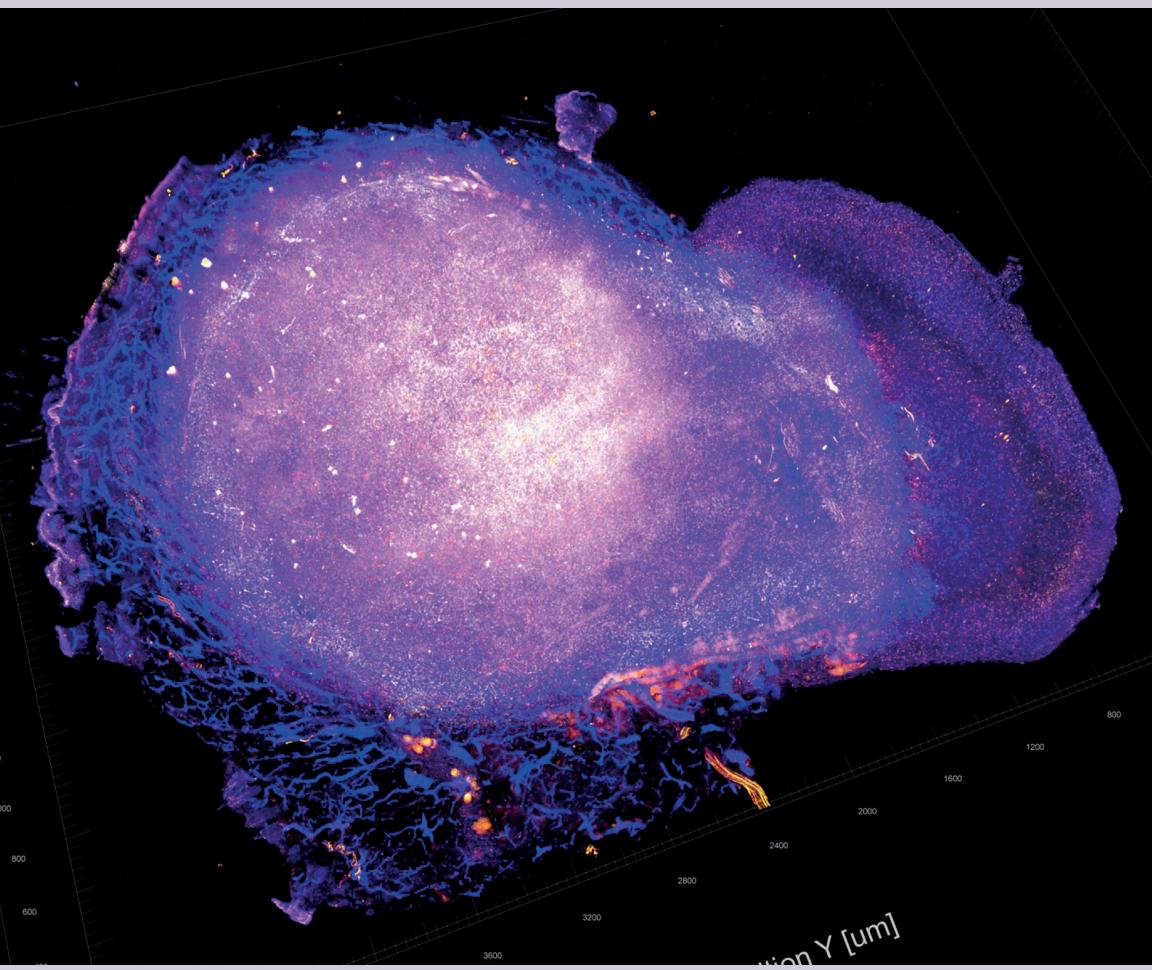
References

CHAPTER 11

1. Cancer.net. "Understanding Targeted Therapy." May 2018, <https://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/understanding-targeted-therapy>
2. CancerQuest. "Targeted Therapy." Emory Winship Cancer Institute. 2018, <https://www.cancerquest.org/patients/treatments/targeted-therapies>.
3. Go, Xuning, Bryan Ngo, Aram Sandaldjian Modrek, and Wen-Hwa Lee. "Targeting Tumor Suppressor Networks for Cancer Therapeutics." *Curr Drug Targets* 15, no. 1 (2014): 2–16. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4032821/>
4. Joo, Won Duk, Irene Visintin, and Gil Mor. "Targeted Cancer Therapy – Are the Days of Systemic Chemotherapy Numbered?" *Maturitas* 76, no. 4 (2013): 308–314. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610026/pdf/nihms534114.pdf>.
5. Ke, Xing, and Lisong Shen. "Molecular Targeted Therapy of Cancer: The Progress and Future Prospect." *Frontiers in Laboratory Medicine* 1, no. 2 (June 2017): 69–75. <https://www.sciencedirect.com/science/article/pii/S2542364917300596>.
6. National Cancer Institute. "Targeted Cancer Therapies." May 20, 2019. <https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet>
7. Padma, Viswanadha. "An Overview of Targeted Cancer Therapy." *Biomedicine* 5, no. 4 (2015): 1–6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4662664/pdf/40681_2015_Article_19.pdf.
8. Rahman, M., et al. "Stem cell and cancer stem cell: a tale of two cells." *Progress in Stem Cell.* 3, no. 2 (2016): 97–108. <http://www.cellstemcell.org/index.php/PSC/article/view/12>

CHAPTER 12

9. American Cancer Society. "Side Effects of Targeted Cancer Therapy Drugs." June 6, 2016, <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/targeted-therapy/side-effects.html#references>.
10. Dumbrava, E. and Funda Meric-Bernstam. "Personalized cancer therapy—leveraging a knowledge base for clinical decision-making." *Cold Spring Harb Mol Case Stud* 4 (2018): a001578 <http://molecularcasestudies.cshlp.org/content/4/2/a001578?cited-by=yes&legid=cshmcs;4/2/a001578&related-urls=yes&legid=cshmcs;4/2/a001578>

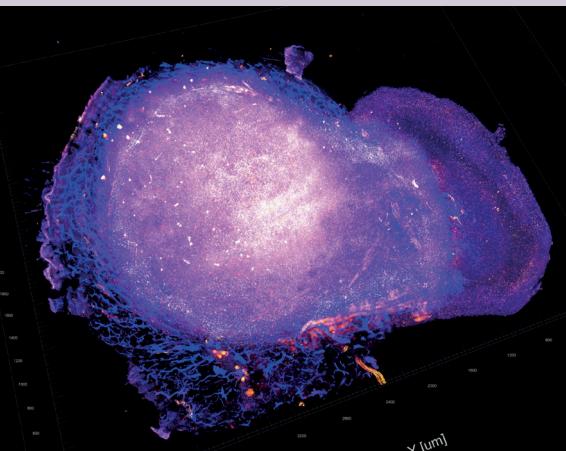


PART FOUR

Immunotherapy

Immunotherapy is a form of cancer treatment that involves stimulating the immune system to attack and destroy cancer cells. The immune system can be a powerful weapon against cancer due to its specificity regarding the cells it targets. Immunotherapy has been particularly promising with patients suffering from advanced-stage cancers who may have few treatment options. Immunotherapy has an additional advantage over other cancer therapies—responses against remaining cancer cells can be sustained after the treatment has finished.

Historically, the challenge in applying immunotherapy has been to get the immune system to recognize the cancer cells as foreign. Part 4 describes how this challenge has been overcome by several approaches. Although the central theme of immunotherapy is to target cancer cells while leaving normal cells unharmed, immunotherapy must be carefully applied, or normal tissues can indeed be attacked.



Antitumor immune response.
National Cancer Institute
Creator: Steve Seung-Young Lee
Public Domain

CHAPTER 13

The Immune System as It Relates to Cancer

CHAPTER 14

Immune Checkpoint Inhibitors

CHAPTER 15

Cancer Vaccines

CHAPTER 16

Adoptive Cell Therapy

CHAPTER 17

New Developments in Cancer Immunotherapy

The Immune System as It Relates to Cancer

67. What is the basic function of the immune system?

The basic function of the immune system is to protect the body against harmful microorganisms, their products, and toxins. The body has to be able to distinguish “self,” which consists of the body’s tissues, from “non-self,” which are materials foreign to the body.

68. What are the main components of the immune system?

The immune system has two divisions: innate and acquired. Innate immunity is the body’s first line of defense and is prepared to attack pathogens as they enter the body. Since innate immunity is carried out by a variety of white blood cells (lymphocytes), it is also called cellular immunity. Acquired immunity develops as a result of an infection and is carried out by antibodies. Since antibodies circulate in the blood, it is also called humoral immunity.

The immune system acts by recognizing antigens on the surfaces of invading bacteria or viruses that are not normally part of the body.

69. What are the types of innate immune cells?

Important types of innate immune cells include the following:

- Antigen-presenting cells (APCs) include dendritic cells and macrophages. APCs are also known as phagocytes. APCs constantly monitor the environment for potential pathogens and other foreign material, collectively known as antigens. When found, the antigens are engulfed, broken down in the cell, and displayed as fragments on the cell surface. For this reason, these cells are known as antigen-presenting cells.
- Natural killer (NK) cells also patrol the environment looking for abnormal cells, such as virus-infected or cancerous cells. The NK cell surface contains both activating receptors and inhibitory receptors (receptors are illustrated in Figure 3.1).

Normal cells contain high levels of a cell-surface molecule known as MHC 1 (major histocompatibility complex 1).

When MHC 1 binds to inhibitory receptors on the NK cell, the NK cell will not attack normal cells.

Cancer cells or infected cells can have low or modified levels of MHC that do not bind to the inhibitory receptor. As a result, NK cells are activated and kill abnormal cells. NK cells kill infected or abnormal cells by releasing toxic chemicals or by prompting the cells to self-destruct (in a process known as apoptosis).



Major histocompatibility complexes (MHC) are molecules found on antigen-presenting cells and play a role in processing antigen proteins, breaking them down into fragments called peptides. MHCs consist of two main classes: MHC Class I (MHCI) activates CD8 T cells, while MHC Class II (MHCII) activates CD4 T cells (Question 71).

70. What are the types of acquired immune cells?

The acquired immune system consists of B cells and T cells:

- T cells develop and differentiate into different types of T cells in the thymus gland. They are considered “naive” or inactivated until activated by an antigen. T cells consist of the following:
 - Killer T cells, also called CD8⁺ cytotoxic T cells, kill damaged cells or those that have been infected by a virus. Killer T cells only recognize antigens coupled to Class 1 MHC molecules. The APCs deliver a second signal (co-stimulation) to the T cells to alert it to the presence of an infection. This second signal involves the binding of MHC 1 to a co-receptor (CD 8) on the killer T cell.
 - Helper T cells, also called CD 4⁺ T cells, support various aspects of an immune response, stimulating B cells to make antibodies and helping killer T cells develop. Helper T cells and regulatory T cells (described as follows) only recognize antigens coupled to Class II MHC molecules. Activation of helper T cells is aided by a second signal involving the binding of MHC II to a CD 4 co-receptor on the helper T cells.
 - Memory T cells recognize antigens they've previously attacked. These are the cells vaccines use to recognize specific viruses.

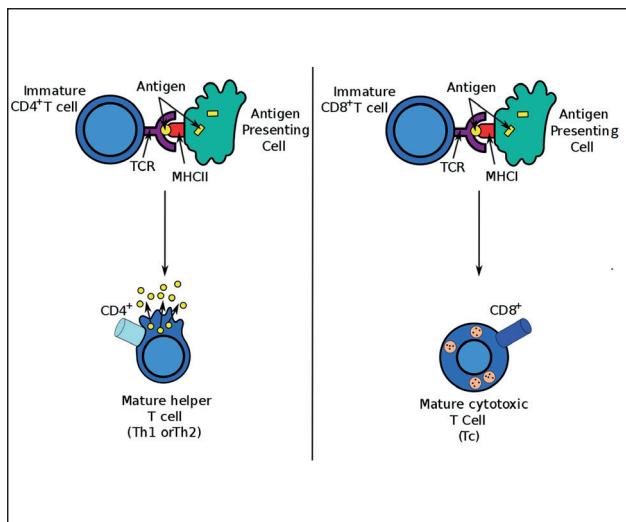
- Natural killer T cells (NK cells). After launching an initial attack like an innate immune cell, NK cells can also remember and recognize certain viruses like an adaptive immune cell.
- Regulatory T cells shut down the immune process when the immune response is complete. The regulatory T cell process is important to prevent the immune cells from beginning to attack the body's own tissues, leading to autoimmunity.
- B cells are produced in the bone marrow. Once B cells are activated by helper T cells, they differentiate into plasma cells, which produce and secrete antibodies that then enter the blood. Antibodies are very specific to each antigen. The B cell antigen-specific receptor is an antibody molecule on the B cell surface and recognizes whole pathogens without any need for antigen processing.

Regulatory B cells (B_{reg}), a subset of B cells, also play an important role in shutting down the immune process, largely through the secretion of the anti-inflammatory mediator interleukin-10 (IL-10). B_{reg} suppress CD4 $^{+}$ T cell proliferation and pro-inflammatory cytokine production and can even induce CD4 $^{+}$ T cell death. Through complex mechanisms, B_{reg} can either inhibit or foster tumor growth.

71. What are signaling molecules?

Signaling molecules are small proteins that play an essential role in communication between cells. The cytokines are the most important signaling molecules for the immune system. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes, and mast cells.

Each cytokine has a matching cell-surface receptor. Cytokines moderate the balance between humoral (blood) and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways.



◀ FIGURE 13.1

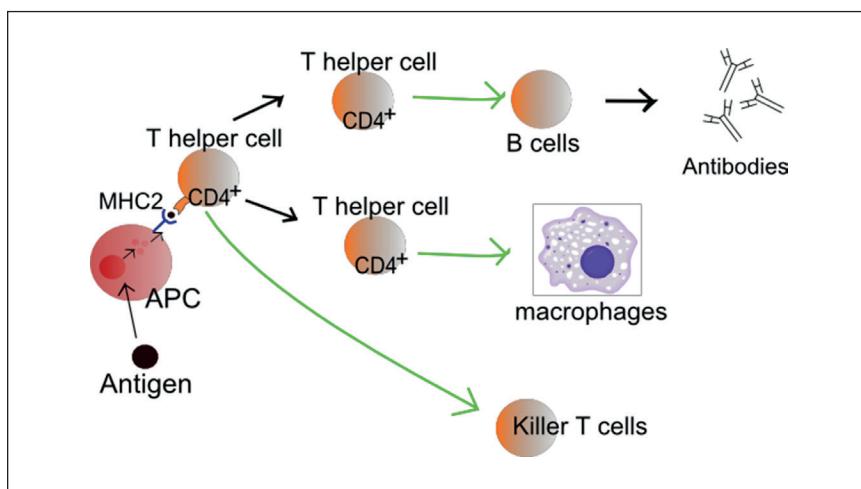
Antigen presentation.

Antigen-presenting cells contain MHC I and MHC II (shown in red) and can activate either immature CD8⁺ T cells or CD 4⁺ T cells. The antigen fragments are held in grooves in the MHC. The resulting antigen-MHC complex then binds to a specific T cell receptor (TCR in purple) on the CD8⁺ or CD4⁺ T cells. Cytotoxic CD8⁺ cells directly attack other cells carrying certain foreign or abnormal molecules on their surfaces. Helper CD4⁺T cells, or Th cells, coordinate immune responses by communicating with other cells.

Creator: Sjef

[http://commons.wikimedia.org/wiki/
Image:Antigen_presentation.jpg](http://commons.wikimedia.org/wiki/Image:Antigen_presentation.jpg)

Creative Commons Attribution-Share Alike 3.0 Unported license



▲ FIGURE 13.2

Function of T-helper cells.

Antigen-presenting cells (APCs) present antigens on their Class II MHC molecules (MHC2). Helper T cells recognize these, with the help of their expression of CD4 co-receptor CD4+. The activation of a resting helper T cell causes it to release cytokines and other stimulatory signals (green arrows) that stimulate the activity of macrophages, killer T cells, and B cells, the latter producing antibodies. The stimulation of B cells and macrophages results from a proliferation of T helper cells.

Creator: Mikael Haggstrom

[https://en.wikipedia.org/wiki/Immune_system#/media/
File:Lymphocyte_activation_simple.png](https://en.wikipedia.org/wiki/Immune_system#/media/File:Lymphocyte_activation_simple.png)

Public Domain

For a comprehensive discussion of the immune system, visit:

[https://en.wikipedia.org/
wiki/Immune_system](https://en.wikipedia.org/wiki/Immune_system)



ON THE WEB

[https://en.wikipedia.org/
wiki/Immune_system](https://en.wikipedia.org/wiki/Immune_system)



A ligand is a molecule that produces a signal by binding to a receptor protein.

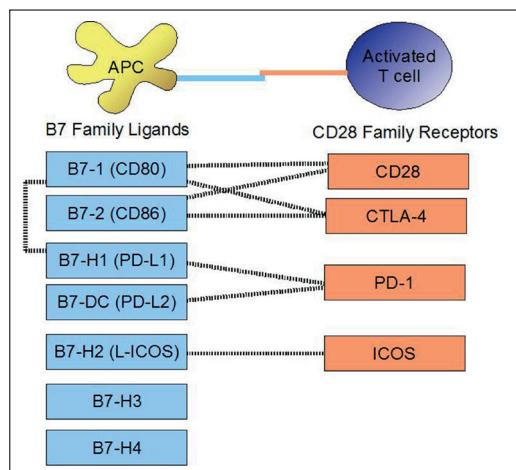
72. What is the role of co-stimulatory molecules for activation of the immune system?

The body has developed complex immune mechanisms in order to distinguish between self and non-self so that the immune response can be effectively directed against foreign antigens, including cancer cells, but does not damage the body's own healthy cells. The full activation of the immune system requires two signals:

- Binding by a T-cell receptor of a specific antigen presented by the MHC complex on APCs (Figure 13.1).
- Binding of a co-stimulatory molecule from the APC to a second T-cell receptor. After the binding of the antigen to the receptor, signals are sent to the T cell to express the CD28 receptor on its surface, and to the APC to express the B7 ligand. The binding of CD28 to B7 provides the co-stimulation necessary for activation. Other activation signals take place.

In the absence of a co-stimulatory receptor, the T cell remains inactive.

73. What is the role of co-inhibitory molecules?



▲ FIGURE 13.3

Interactions of B7 ligands on APCs with CD28 receptors on T cells. Note that both CD28 and CTLA4 receptors can bind to B7 ligands. The ligands PD-L1 & PD-L2 are found on cancer cells as well as T cells.

Author: The Immunologist

https://commons.wikimedia.org/wiki/File:B7_family_ligands_and_CD28_family_receptors.JPG

Public Domain

When the foreign antigens are removed from the body, it is essential to deactivate the immune system before it can attack the body's own tissues. This is the role of co-inhibitory molecules, which bind to other T cell receptors. A common co-inhibitory receptor is CTLA4, which binds to B7 ligands, thereby blocking the binding of the CD-28 receptor to the B7 ligands. The result is to prevent activation of the T cell. The binding of the PD-1 receptor to the PD-L1 or PD-L2 ligands also blocks T cell activation. These interactions are shown in Figure 13.3.

The role of co-stimulatory and co-inhibitory molecules as they relate to cancer will be discussed in detail in Chapter 14 (immune checkpoint inhibitors).

74. How can cancer cells evade detection and destruction by the immune system?

Cancer cells can circumvent the immune system in two primary ways:

- Avoid recognition by T cells
- Activate the co-inhibitory pathway to prevent T-cell activation

Cancer cells (similar to invading microorganisms such as viruses) can manufacture foreign proteins (antigens) on their cell surfaces that can be recognized by APCs of the immune system. However, cancer cells have unique characteristics to avoid recognition. Tumors can escape T-cell recognition by increased frequency of mutations and genetic deletions that result in a decreased presentation of antigens on their cell surface. Eventually, a cell or cells may emerge with the ability to slow down immune reactions or stop them completely. This phenomenon, known as anergy, commonly occurs in chronic infections.

The tumor microenvironment may lack the necessary inflammatory mediators to stimulate the APCs, resulting in impaired antigen presentation. Tumor cells secrete several small molecules and cytokines that suppress dendritic cell and T-cell function and induce regulatory T-cell function. As you will recall, regulatory T cells have an immunosuppressive function. The immune system, therefore, can evolve from recognizing and destroying cancer cells to a tolerance of the cancer cells.

A tumor can even recruit the immune system for its own growth and development. Tumor-infiltrating macrophages are brought into the tumor together with cytokines. The macrophages then produce growth factors and interleukins leading to tumor proliferation and angiogenesis.



Since the activation of co-receptors performs such an essential role in the functioning of the immune system, they are called immune checkpoints. Cancer cells have found the means of taking control of immune checkpoints to protect themselves from immune system attack. Drugs called immune checkpoint inhibitors have been developed to counteract this action of cancer cells by activating dysfunctional or exhausted T cells, thereby revitalizing the immune system (checkpoint inhibitors are discussed in Chapter 14).

As discussed in Question 70, the immune system has developed safeguards to protect the body against autoimmunity when the immune system has completed its work. This process, involving co-inhibitory molecules, shuts down the immune system. When the proteins B-7 or PDL-1 found on APCs bind to CTLA-4 or PD-1 receptors on the T cell, the T cell activity shuts down. Blocking the activity of co-inhibitory molecules is the basis for checkpoint inhibitor drugs (Chapter 14).

In summary, cancer cells can suppress the immune response by the following means:

- Impaired antigen processing and presentation in the tumor microenvironment
- Lack of T-cell activation due to defects in T-cell signaling
- Secretion of biologically active agents (including cytokines and growth factors) by tumor cells that exert suppressive effects on the immune system
- Inappropriate activation of co-inhibitory molecule checkpoints
- Regulatory T-cell expansion, recruitment, and activation by tumor cells
- Apoptosis of previously activated T cells upon subsequent encounter with antigen

CHAPTER 14

Immune Checkpoint Inhibitors

75. What are immune checkpoint inhibitors?

Monoclonal antibodies are antibodies that are made in the laboratory by identical immune cells that are all clones of a unique parent cell. A monoclonal antibody is made so that it binds to only one substance. Monoclonal antibodies are being used to treat some types of cancer. They can be used alone or to carry drugs, toxins, or radioactive substances directly to cancer cells.



Immune checkpoints are signals used by the immune system to regulate the immune response to foreign antigens. As discussed in Questions 72 and 73, these signals affect receptors on T cells and can either stimulate or inhibit an immune response. Cancer cells can find ways to activate checkpoint inhibitors to suppress the immune response. Drugs known as monoclonal antibodies

have been developed to block the inhibitory checkpoint molecules and thereby reactivate the immune system against cancer. The checkpoint inhibitor drugs currently in use block PD-1, PD-L1, and CTLA-4 receptors.

76. What drugs have been developed to block PD-1?

The binding of PD-1 with PD-L1 or PD-L2 leads to inactivation of T-cells (Question 73). As a result T-cells can not kill cancer cells. Checkpoint inhibitors have been developed to block PD-1 action and activate T-cells to kill cancer cells.

Checkpoint inhibitors that block PD-1 action include:

Nivolumab – approved for advanced melanoma as monotherapy (not used with other drugs) or in combination with ipilimumab; approved as monotherapy in lung cancer, renal cancer, Hodgkin's lymphoma, urothelial cancer, head and neck cancer, colorectal cancer, and hepatocellular carcinoma

Pembrolizumab – approved as monotherapy for advanced melanoma, lung cancer (first-line treatment in tumors with a high PD-L1 expression, after chemotherapy in tumors with a low PD-L1 expression), Hodgkin's lymphoma, large B-cell lymphoma, urothelial cancer, head and neck cancer, gastric cancer, cervical cancer, breast cancer

77. What drugs have been developed to block PD-L1?

Since PDL-1 is frequently found on cancer cells (Question 73 and Figure 13.3), it is an attractive target for development of checkpoint inhibitor drugs. Drugs that block the binding of PD-L1 to PD-1 include:

Atezolizumab – approved as monotherapy for advanced urothelial carcinoma, lung cancer, colorectal cancer, breast cancer, renal cancer

Avelumab – approved as monotherapy for metastatic Merkel cell carcinoma

Darvulizumab – approved as monotherapy for urothelial cancer

78. What drugs have been developed to block CTLA-4?

The binding of CD28 to B7-1 or B7-2 leads to activation of T cells (Question 73). When CTLA-4 binds to B7-1/B7-2 in replacement to CD28, T-cells are inactivated and cannot kill cancer cells.

The following drugs have been approved for blocking CTLA-4 action:

Ipilimumab – approved for advanced melanoma as monotherapy or combined with nivolumab

Tremelimumab – investigated in melanoma, mesothelioma, and NSCLC but not approved due to a lack of significant effect

The binding of CD28 to B7-1 or B7-2 leads to activation of T cells (Question 73). When CTLA-4 binds to B7-1/B7-2 in replacement to CD28, T-cells are inactivated and cannot kill cancer cells.

79. What new checkpoint inhibitor drugs are being developed?

LAG-3, a co-inhibitory receptor, inhibits CD4+ cell function and the cytotoxic function of CD8+ cells. Drugs have been investigated to block LAG-3 in renal cancer, breast cancer, and pancreatic cancer as monotherapy or combined with other therapies.

The TIM-3 ligand decreases interferon production and induces T-cell death. Drugs have been investigated to block TIM-3 in many solid tumors and leukemia.

80. Why do regulatory T cells need to be considered in checkpoint inhibitor therapy?

Although regulatory T (Treg) cells have the essential function of protecting the body against an autoimmune response, they can also protect cancer cells from immune system attack.

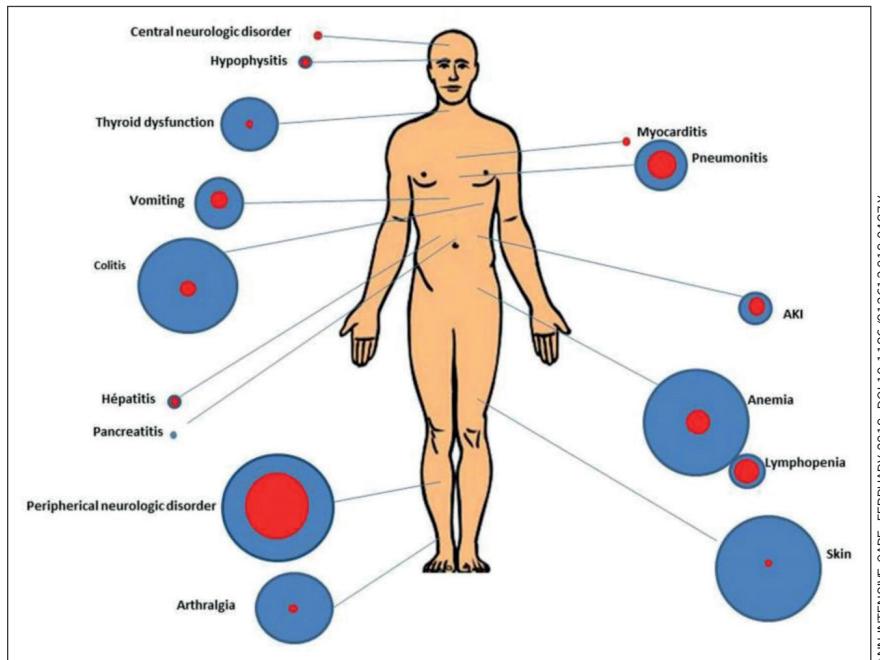
Infiltration of large numbers of Treg cells into tumor tissues is often associated with poor prognosis.

Immunotherapy treatments seek to reduce or eliminate Treg cells in the tumor while minimizing autoimmune responses. Some studies have shown that Treg cells have an increased expression of the CCR4 receptor, which is involved in

chemokine signaling and immune cell migration. Suppressing CCR4 may be a means of suppressing Treg cell activity. Another strategy may be to target the effector Treg cells (found in the tumor).

81. What are the side effects of immunotherapy, and how are these side effects controlled?

The following article, obtained from the National Cancer Institute, provides an excellent summary of the subject.



▲ FIGURE 14.1

Side effects of targeted checkpoint inhibitors.

PD-1/PD-L1 targeted checkpoint inhibitors can affect many parts of the body. Circle size represents side effect incidence; blue color is any side effect; red is severe toxicity.

Creative Commons 4.0.

https://www.cancer.gov/PublishedContent/Images/news-events/cancer-currents-blog/2019/side-effects-of-pd-1-pd-l1-enlarge._v300155187.jpg.

A growing number of people with cancer have benefited in recent years from immunotherapy—treatments that strengthen the ability of the immune system to detect and destroy cancer.

Some patients have had dramatic and lasting responses to these new treatments, which include immune checkpoint inhibitors and CAR T cell therapies. In rare cases, patients with advanced

cancers have had their tumors disappear completely following treatment with immunotherapy.

But immunotherapy drugs, like all medicines, can cause side effects, including rare complications that, for some patients, may be life-threatening.

“Side effects related to immunotherapy drugs occur frequently and can affect almost any organ in the body,” said Sarah Dubbs, MD, an emergency medicine physician at the University of Maryland School of Medicine who has written about the side effects of cancer immunotherapy.

“Most side effects are mild to moderate in severity and respond to treatments such as steroids,” Dr. Dubbs continued. Doctors caring for patients who are receiving immunotherapy must be vigilant, however, because some patients may develop serious health problems, she added.

As immunotherapy has become a more widely used treatment for cancer, researchers have gained insights into the side effects associated with these treatments, including some complications not previously linked to other cancer treatments.

Building on that work, researchers are now trying to understand better how and why these side effects occur in certain patients and develop strategies for managing them.

An Overly Active Immune System

Drugs that stimulate the immune system to attack tumor cells can, in some patients, cause the immune system to recognize some of the body’s healthy tissues as foreign and attack them.

Some patients receiving immunotherapy develop inflammation of the inner lining of the colon, the lungs, or heart muscle, among other side effects associated with an overly active immune system.

Understanding more about the causes of immunotherapy-related side effects and being able to identify patients most at risk for them could help doctors to select immunotherapy drugs for patients in the future, noted Dr. Dubbs.

Research in this area continues to advance. Investigators have been documenting complications associated with immunotherapy drugs, studying the biological mechanisms, modifying immunotherapy drugs to reduce their side effects, and increasing awareness of potential side effects among clinicians and patients.

For example, the side effects of immunotherapy drugs and new ways to manage them were discussed at a recent scientific meeting on emergency medicine for treating patients with cancer, hosted by the University of Texas MD Anderson Cancer Center.

“As emergency room doctors, we are the first line of care, and we need to educate ourselves about new technologies in medicine and be ready to care for our patients,” Dr. Dubbs said.

“When we get a patient’s medical history, we ask what immunotherapy treatment they’re on, and it’s important to be specific,” she continued. “With different types of chemotherapy, it was not as important to know exactly which type, because the drugs behave similarly in the body.

“But with immunotherapy drugs it matters, because there are different adverse events associated with different medications, and treatment may vary depending upon which immunotherapy drug a patient had received,” Dr. Dubbs added.

Enhancing the Immune Response

The immune-related side effects of immunotherapy highlight a fundamental difference between these drugs and other cancer treatments: Conventional treatments such as chemotherapy kill tumor cells directly, whereas immunotherapy does not.

Immune checkpoint inhibitors, for example, block proteins that help keep the immune response inactive, such as CTLA-4, PD-1, or PD-L1 (a protein that PD-1 attaches to). Blocking one of these proteins “releases the brakes” on the immune system, boosting the ability of immune cells to attack tumor cells.

CAR T-cell therapy uses a different approach to reach the same goal: A patient’s T cells are modified in the laboratory to enhance their ability to recognize and bind to cancer cells and kill them. These modified cells are then expanded in number and infused back into the patient.

Treatment-Related Side Effects Vary

The types of side effects a person receiving immunotherapy experiences will depend on several factors, including the type of immunotherapy, the dose, how healthy the person was before treatment, the type of cancer, and how advanced the cancer is.

For patients receiving immunotherapy drugs that are given intravenously, the most common side effects include skin reactions at the site of the injection, such as pain, swelling, and soreness. Some immunotherapy drugs may cause severe or even fatal allergic reactions, though this is rare.

Not all patients receiving immunotherapy drugs develop immune-related complications. And among patients who do develop these side effects, there is substantial variation in which organs are affected, noted Sang T. Kim, MD, and Maria E. Suarez-Almazor, MD, PhD, of MD Anderson in a recent commentary on managing side effects associated with checkpoint inhibitors.

Among patients receiving checkpoint inhibitors, the most commonly affected parts of the body are the skin, colon, endocrine system, liver, lungs, heart, musculoskeletal system, and central nervous system, Drs. Kim and Suarez-Almazor added.

Many patients who receive CAR T-cell therapy develop a condition known as cytokine release syndrome, which can cause a fever, fast heart rate, low blood pressure, and rash, among other symptoms. The syndrome is caused by the large and rapid release of proteins called cytokines into the blood from immune cells affected by immunotherapy.

Cytokine release syndrome generally develops within hours to days after an infusion; most patients have a mild reaction to the infusion, but some have more severe responses. Patients also may experience neurologic symptoms such as confusion, tremors, or difficulty communicating.

Unusual and Unexpected Side Effects

The timing of immunotherapy-related side effects is less predictable than with other types of cancer treatments. Patients receiving immunotherapy may develop side effects soon after

receiving the first dose of a drug or long after a course of treatment has ended.

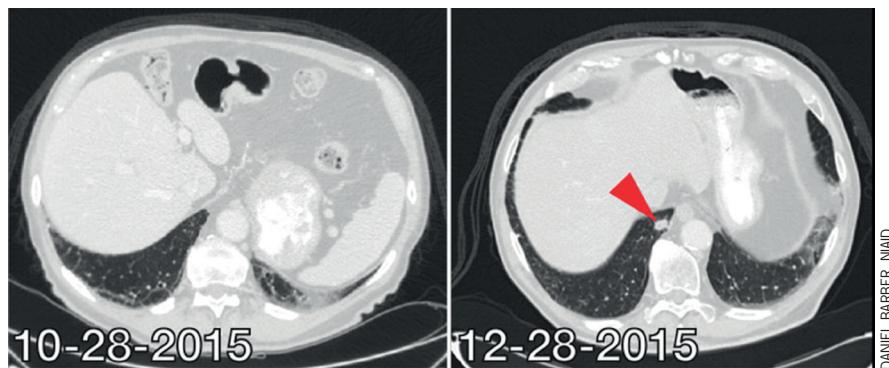
Physicians at MD Anderson reported recently, for example, that a patient being treated for sarcoma developed a serious complication of diabetes about three weeks after receiving a single dose of the immunotherapy drug pembrolizumab (Keytruda).

The 47-year-old woman, who had no known history of diabetes and had not received immunotherapy previously, was diagnosed with diabetic ketoacidosis during a trip to the emergency room.

“This case of abrupt adult-onset type 1 diabetes mellitus is an example of the undesirable side effects that can emerge after only a brief exposure to an immune checkpoint inhibitor,” Patrick Chaftari, MD, and his colleagues wrote in a case report about the patient.

Patients receiving checkpoint inhibitors should “be monitored closely” so that potentially life-threatening complications can be diagnosed early and treated, the authors added.

It was after a routine scan a few years ago that doctors identified a suspicious mass in the lungs of an 83-year-old man participating in a clinical trial. The man had been receiving pembrolizumab for about five months to treat a type of skin cancer called Merkel cell carcinoma.



DANIEL BARBER, NIAID

▲ FIGURE 14.2

Chest CT scan images from a patient with skin cancer who had been treated with checkpoint inhibitors. The arrow shows a nodule in the lungs that turned out to be treatment-related tuberculosis.

Further testing revealed something completely unexpected: While receiving a drug that strengthens the immune response against cancer, the patient developed tuberculosis.

“I was, of course, floored,” said Elad Sharon, MD, MPH, of NCI’s Cancer Therapy Evaluation Program, who monitored side effects on the clinical trial for NCI. Nothing in the patient’s health history indicated that he’d been infected with the bacterium that causes tuberculosis, *Mycobacterium tuberculosis* (Mtb).

The patient was treated for both tuberculosis and cancer by infectious disease specialists and oncologists who worked in close consultation, and he is still alive, Dr. Sharon noted.

To understand what had happened, Dr. Sharon and his colleagues conducted an analysis of the patient’s disease with Daniel Barber, PhD, of the National Institute of Allergy and Infectious Diseases (NIAID), who has studied Mtb and immune responses in mice.

Their results were consistent with findings in mice showing that the use of an immunotherapy drug to boost the immune response can increase the risk or severity of tuberculosis, Dr. Barber and his colleagues reported last year. Dr. Barber’s team observed a second case of tuberculosis in a patient following immunotherapy.

“We’ve known for a long time that when we boost the responses of immune cells, it can be a good thing or a bad thing,” said Dr. Barber. Among individuals infected with Mtb, boosting the immune response “may be detrimental,” he added.

Managing Treatment-Related Side Effects in Patients

Because cancer immunotherapy drugs are relatively new, there is limited evidence from clinical trials about how to manage treatment-related side effects. “These drugs are so new that many emergency physicians and even some oncologists might not be aware of the potential side effects,” said Dr. Dubbs.

Recognizing this gap in knowledge, the American Society of Clinical Oncology and the National Comprehensive Cancer Network in 2018 issued guidelines for clinicians on managing complications of checkpoint inhibitors. The guidelines include

recommendations on when to use steroids and when to discontinue immunotherapy, for example.

A panel of experts developed the guidelines based on a review of the scientific literature. These guidelines provide “best practices” for the management of immune-related side effects within the constraints of limited scientific evidence, noted Drs. Kim and Suarez-Almazor in their editorial. Other organizations also have developed guidance on how to best manage immunotherapy side effects.

Even though many questions about managing immune-related side effects remain unanswered, experts agree on the importance of diagnosing immune-related side effects before they progress to more serious complications.

“Our responsibility is to treat any side effect related to immunotherapy early and effectively,” said Monjur Ahmed, MD, a gastroenterologist at Thomas Jefferson University, who has written about the side effects of checkpoint inhibitors.

Dr. Ahmed noted that for some patients, this would involve stopping an immunotherapy drug, at least temporarily, and employing drugs such as steroids to treat the immune-related side effects.

“Some patients go back on the same treatment, and some do not,” he said. Identifying the optimal approaches for managing certain side effects will require more research, he added.

“Am I Eligible for Immunotherapy?”

In 2018, the most common question that Emil Lou, MD, PhD, heard from patients with cancer in his clinic at the University of Minnesota was: “Am I eligible for immunotherapy?”

“Most of these patients had seen advertisements for immunotherapy on television or heard a story about a patient’s tumor melting away, and they wanted to know if they could get immunotherapy,” said Dr. Lou, who treats patients with gastrointestinal cancers.

His patients had heard of dramatic and lasting responses to immunotherapy drugs among some patients with advanced cancers.

Although few of his patients have been candidates for immunotherapy based on the genetic features in their tumors, Dr. Lou has discussed the treatment—and possible side effects—when it has been an option.

In these conversations, he would introduce the idea that immunotherapy drugs have side effects. “In that respect, immunotherapy drugs are like all treatments for cancer,” he tells his patients. “They can cause rashes and joint pain and diarrhea. And in a small percentage of patients, immunotherapy can cause shortness of breath and other more serious complications.”

Dr. Lou added, “Immunotherapy drugs are not perfect.”

More Research Needed on Immunotherapy-Related Side Effects

Knowledge gained from decades of treating autoimmune disorders has informed the ways that doctors identify and manage immune-related side effects, noted Dr. Sharon.

But he pointed out that immunotherapy-related side effects may develop through different biological mechanisms than autoimmune disorders, which suggests that the treatment of these side effects may also differ.



CLIN KIDNEY J. JUNE 2016

◀ FIGURE 14.3

A wide-spread rash on a man with advanced melanoma following combination immune checkpoint inhibitor treatment.

doi:10.1093/ckj/sfw024.
Creative Commons 4.0.

To more effectively explore such questions, doctors and researchers need to establish definitions of immunotherapy-related side effects and develop standards for reporting these side effects as they are observed in patients, Dr. Sharon noted.

Doctors could use definitions of immune-related side effects to identify patients who may need to be referred to specialists for treatment, he added.

“In addition to definitions, new biomarkers and tests for diagnosing immune-related side effects are needed, and that will require collaboration from experts across disciplines,” he said.

Dr. Sharon was one of the organizers of a scientific workshop on cancer, autoimmunity, and immunology held last year that brought together experts from different fields to discuss a range of topics, including immune-related side effects.

During a keynote presentation at the meeting, Jeffrey Bluestone, PhD, of the University of California, San Francisco, said: “We still have a lot to learn.”

Among other questions, it’s not clear why immune-related side effects occur in some patients but not in others or why different drugs induce different diseases in different patients, he added.

Whether treatment-related side effects could be an indication that a patient might be responding to immunotherapy is an area of ongoing research that was discussed at the workshop.

“We’d like to know whether having immune-related side effects could be a good sign for a patient’s treatment,” Dr. Sharon said, noting that there “isn’t any definitive evidence yet on this question one way or the other.”

Answering such questions could take years, but efforts are underway to advance the research.

For example, NCI has established a network of laboratories and a data center that could help identify biomarkers associated with the response to immunotherapy or treatment-related side effects. And researchers are working on developing mouse models for immunotherapy research as well as a biorepository for patients in immunotherapy clinical trials.

Some of these efforts and related ongoing work were discussed at the second workshop on cancer, autoimmunity, and immunology, which was sponsored by the National Institutes of Health and the American Association for Cancer Research on April 15–16, 2019.

“As we did last year, we brought together experts from different fields to help us to understand better these important new immunotherapy drugs, which are a real advance for patients,” said Dr. Sharon.

82. What is the response rate to checkpoint inhibitor drugs?

On December 28, 2015, Dr. James Gulley of the National Cancer Institute discussed the impact of checkpoint inhibitor therapy on patient care, including response rates and future directions.

Checkpoint inhibitors are usually described as therapies that release the brakes on the immune system. Is that the best description?

Yes, that’s a great way to explain it. But it’s also really important to understand that immune checkpoint inhibitors are not directed against the tumor. They have no direct antitumor activity, so if there is no underlying immune response against a tumor before using these drugs, they won’t have any effect. They only take the brakes off of the immune response if you already begin with some immune response.

But it’s hard to tell if there is an existing immune response, and if an individual patient will respond, right?

Yes, we’re still only getting responses in a minority of patients who receive these therapies. But one of the factors driving the excitement around these agents has been the deep, durable—that is, long-lasting—and rapid responses to anti-PD-1 agents like **pembrolizumab** and **nivolumab** (Opdivo®). And we see responses to these therapies across a broad range of tumor types, but, again, patients need to have an underlying immune response.

One possible way to get that underlying response is if there are many mutations in the tumor. Certain tumors—lung, melanoma, bladder—are more likely to have many mutations and so seem to be more likely to generate an immune response.

In most patients with colorectal cancer, for example, we don't see strong immune activity. However, we now know that if colorectal tumors have something called microsatellite instability, which produces many mutations, there is increased immune recognition of the tumor. That's where we have seen checkpoint inhibition work in patients with colorectal cancer.

These treatments are all intravenous medications. What does the administration schedule look like?

Checkpoint inhibitors, all of which are monoclonal antibodies, are typically given over one hour, every two to three weeks. Patients remain on the treatment as long as their disease has not progressed, and as long as they do not have side effects that would require them to stop.

What are the tumor response rates to these therapies, and what are the side effects?

Tumor response rates typically range anywhere from 15 to 25 %. You may see higher numbers quoted, but that's in selected patient populations. In bladder cancer, for example, it can be up to 40 %, but that's in patients who have high PD-L1 expression within the tumor.

When it comes to side effects, particularly with anti-PD-1 and anti-PD-L1 drugs, the side effect profile is less harsh than what's been seen with anti-CTLA-4 checkpoint inhibitors. In general, fewer patients have severe adverse events, and many patients have no side effects.

The first approved checkpoint inhibitor, ipilimumab (Yervoy®), targeted CTLA-4. But it seems like the momentum has shifted toward anti-PD-1 and anti-PD-L1 inhibitors. Why is that?

First, the side effect profile of anti-PD-1 and anti-PD-L1 drugs is much better. Patients tolerate them better, so they can remain on therapy longer.

Also, with ipilimumab, we rarely see rapid regressions. We often see a progression, sometimes followed by regression. That's because the drug mostly works on T cells in the circulation, and

this nonspecific activation may take time to activate enough of the antitumor T cells to produce a response.

With the anti-PD-1 and anti-PD-L1 therapies, however, we see very rapid responses. That's because these drugs primarily act on primed T cells that are already at the tumor; their sleeves are rolled up, and they're ready to go, but they're being blocked. Then we take the blinders off with these drugs, and the T cells can now attack the tumor.

Those two factors are making a world of difference.

What about instances, like that of former President Carter, where patients have complete responses to treatment. In most cases, do those responses last?

The majority of responses we see with these drugs are still partial responses, at rates similar to what we see with chemotherapy and other targeted agents. But often the responses we see are very deep, 80 to 90 % tumor shrinkage.

The more important thing—and the thing that's blown everybody away—is how durable the responses are. Even the partial responses are very durable, compared with what we're used to seeing with chemotherapy or targeted therapies like tyrosine kinase inhibitors.

What we see in some cases are functional cures. Not in everybody, of course. But, for example, approximately 20 % of the patients with melanoma who were first treated with ipilimumab are still alive up to ten years after the start of treatment.

For patients who have survived for at least three years after starting ipilimumab, the vast majority will still be alive at ten years. Now, melanoma patients are often younger, so there are not as many competing causes of death. But those are still intriguing numbers, and they suggest that if you get a benefit, it will often be prolonged.

What does the future hold for checkpoint inhibitors?

There need to be several areas of focus, all of which can be done in parallel.

Identifying biomarkers that predict response is one important area. For example, one thing we have found is that patients have a higher chance of responding if they have high levels of PD-L1 expression in the tumor microenvironment. That represents a “footprint” of an activated immune response. But we need to be able to look at what’s happening in patients’ tumors at the time we are going to begin therapy, not biopsy samples that might be a year old.

Biopsies are good, but they can be quite invasive and, depending on where the tumor is, may be dangerous. So we’re starting to see if we can measure PD-L1 expression on tumor cells circulating in the blood.

We’re also testing imaging modalities to identify tumors that are inflammatory [a marker of an immune response]. So if you can find a way to safely and specifically image for inflammation within tumors, it would be a big advance. If we see inflammation, then maybe we can treat with the checkpoint inhibitor. If we don’t see it, perhaps we can add a therapy that can cause an immune response at the tumor site and then follow up with a checkpoint inhibitor.

Developing combinations, including those with other checkpoint inhibitors, will also be important and we’re already starting to see those trials. I think that we’re going to find that as we examine the tumor microenvironment, we can start to develop more personalized approaches to treatment. We can determine when one patient requires a cocktail of therapies while another just needs a checkpoint inhibitor.

Can these drugs be used in earlier-stage disease? Are there enough mutations in tumors at that point to establish an underlying immune response?

Absolutely. The mutational burden is already high by the time you have a clinically detectable tumor, and that mutational burden helps with developing the underlying immune response, but the immune system still can’t do its job.

Because the side effect profile is so minimal compared with chemotherapy and other radiation, and because of their rapid response, these drugs should be tested in the first-line setting for many cancers, and I think they will be effective.

The real advances will be building on those strong, durable responses that we're currently seeing in 20 % of patients and making it 40 %, 60 %, and so on. That's where combinations of therapies will come in. Eventually, I think we'll get there.

83. Can a combination of checkpoint inhibitor drugs enhance treatment?

The combination of nivolumab with ipilimumab, which targets PD-1 and CTLA-4, was approved by the FDA in 2015 to treat metastatic melanoma. Since then, this combination has demonstrated efficacy in other cancer types, including melanoma, bladder, kidney, and lung cancer. The idea behind combining checkpoint inhibitor drugs is to improve the response rate to different cancers.

A large number of clinical trials are underway studying this combination, as well as including chemotherapy and radiation treatments.

84. Can other types of cancer treatments enhance the effectiveness of immune checkpoint therapy?

Before checkpoint inhibitors can work, the immune system must be activated. Chemotherapy, radiation (Question 49), and cancer vaccines (Chapter 15) damage and kill malignant cells resulting in inflammation that activates T cells. The therapies work together. After initial treatment with the other therapies, checkpoint inhibitor drugs can continue destroying cancer cells that have disabled the immune system.

CASE STUDIES – Combining radiation therapy with immune checkpoint therapy

The National Cancer Institute reported on work by researchers from the University of Pennsylvania on combining radiation therapy and immunotherapy.

A cross-disciplinary team of scientists and physicians at the University of Pennsylvania is redefining the role of one of cancer medicine's oldest tools and blazing a new trail in the treatment of patients. Their efforts, led by cancer immunologist and oncologist Bob Vonderheide and radiation oncologist Andy Minn, are demonstrating the promise of combining immune checkpoint inhibitors and radiation therapy.

Radiation therapy has been used to treat patients with cancer since the beginning of the 20th century. About half of all cancer patients receive some type of radiation therapy. It is typically used as a local therapy—that is, to treat the specific area of the body where a tumor is located. However, mounting evidence supports the idea that local radiation can also have effects throughout the body and that these effects are mediated by the immune system.

Researchers are finding that as irradiated cancer cells die, they trigger an immune response much as vaccines do. Bob, Andy, and their colleagues—calling themselves the RadVax team (Rad for radiation and Vax for vaccine)—are testing the idea that the immune response triggered by radiation can be improved further by the addition of immune checkpoint inhibitors, a type of treatment that enhances the ability of the immune system to kill a tumor. If successful, the combination therapy will provide additional options for patients with metastatic cancer, including patients who do not respond to checkpoint inhibitors alone.

In 2015, the team reported results from the first clinical trial of radiation therapy combined with the immune checkpoint inhibitor ipilimumab (Yervoy®), which targets a protein called CTLA-4. In addition to testing the combination in patients with metastatic melanoma, they also studied it in mouse models of melanoma to gain further biological insights.

Although responses were observed in some of the patients, most did not benefit. However, studying both the mice and patient samples uncovered a resistance mechanism—a way in which the melanoma cells avoided being killed by the immune system—that likely explained the clinical findings. These findings led the team to their current strategy of deploying multiple checkpoint antibodies along with radiation. The triple combination, effective in mice, is currently being tested in patients in clinical trials.

Additional clinical trials testing combinations of radiation therapy and immune checkpoint inhibitors are currently being conducted. Still, “there are many scientific questions that still need to be answered,” said Andy. With NCI’s support, the RadVax team aims to answer them. For example, the RadVax team plans to study how these treatments interact at the cellular and molecular level. The results may indicate the best way to combine the treatments.

Cancer Vaccines

85. What are vaccines?

A vaccine is a biological preparation that protects against a particular disease through a process known as immunity. A vaccine typically contains a component of a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. As described in Question 68, the immune system reacts to the presence of antigens, foreign proteins found on the surface of the microorganisms. A vaccine stimulates your immune system to produce antibodies, exactly like it would if you were exposed to the disease. After getting vaccinated, you develop immunity to that disease, without having to get the disease first.

86. What are cancer vaccines?

Cancer vaccines stimulate tumor-specific immune responses, particularly cytotoxic CD8⁺ T cells that are specific to tumor antigens. Cancer vaccines can be either conventional, designed to prevent cancer, or prophylactic, designed to treat cancer. Two prevention vaccines have been approved by the FDA to protect against human papilloma virus (HPV) and Hepatitis B virus (HBV) (See Question 63). Only one prophylactic vaccine has been approved by the FDA, Sipuleucel-T, used to treat advanced prostate cancer.

Cancer treatment vaccines are difficult to develop due to the following:

- Cancer cells develop from a person's own healthy cells so that the immune system may recognize the cancer cells as "self."
- Cancer cells can find many ways to circumvent and suppress the immune system. Immunosuppression by cancer cells is considered a major obstacle in the development of effective cancer vaccines.
- People who have weakened immune systems may not be able to produce a strong immune response after vaccination. A weakened immune response may occur in people who are sick, old, or debilitated due to other cancer treatments.
- Cancer vaccines are only useful as a sole treatment when the cancer is in its early stages.

Cancers are notable for being unique for each individual and evolve over time. The earliest approach to cancer vaccination involved immunization with shared tumor antigens expressed by many different patients' tumors. More recently, cancer vaccines are prepared that target mutated antigens present in individual patients. These types of vaccines are produced from the person's tumor samples.

87. What are the types of cancer vaccines?

Cancer vaccines act against antigens on the cancer cell, like conventional vaccines against harmful microorganisms. The following are types of cancer vaccines under development:

- Autologous tumor cell vaccines. These vaccines are prepared from the patient's own tumor cells and have the advantage of presenting a large range of tumor-associated antigens to the patient's immune system. A major disadvantage of these vaccines is the requirement of sufficient tumor specimen to prepare the vaccines. This requirement limits the use of these vaccines to certain tumor types or stages.
- Allogenic tumor cell vaccines. These vaccines are prepared from two or three established tumor cell lines obtained from other patients. These vaccines provide many advantages over autologous tumor cell vaccines for vaccine production and evaluation of clinical outcomes.
- Dendritic cell vaccines. Dendritic cells are the most potent antigen-presenting cells.
- Protein-peptide-based cancer vaccines. Antigens are present in proteins or fragments of proteins known as peptides. Preparing vaccines from peptides greatly simplifies the preparation of vaccines, but it has the limitation of presenting only one or a few antigens.
- Genetic vaccines use carriers to deliver multiple antigens in one immunization. Genetic vaccines consist of the following:
 - DNA vaccines use bacterial plasmids (a small DNA molecule within the bacterium)
 - RNA vaccines use messenger RNA from autologous tumors
 - Viral-based vaccines

Overexpressed antigens are proteins that are amplified at the DNA, mRNA, or protein level and are therefore expressed at a much higher level in tumor cells than in adjacent normal tissue.

88. Can virus infections cause cancer?

A virus is a very small particle consisting of DNA or RNA covered by a protein coat. A virus can only reproduce by infecting a cell and taking over the metabolic machinery of the cell to make new copies of the virus.

The following viral infections have the potential to cause cancer:

- Human papilloma virus (HPV) infections are very widespread, but HPV does not usually cause cancer. HPV is a major cause of cervical cancer, but with the advent of the Pap test, this cancer is now much less common. Vaccines are now available to help protect against infection from the main cancer-causing HPV types.
- Hepatitis B virus (HBV) infections may increase the risk of liver cancer. Vaccination against HBV may lower this risk.
- Epstein-Barr virus (EBV) is a type of herpes virus. EBV infection may rarely increase a person's risk of getting nasopharyngeal cancer, Burkitt's lymphoma, Hodgkin's lymphoma, and stomach cancer. There are no vaccines against EBV.
- Hepatitis B virus (HBV) and hepatitis C virus (HCV) both cause viral hepatitis. When these infections become chronic (long-term), they can increase a person's chance of developing liver cancer. There is a vaccine to prevent HBV infection, but none for HCV.
- Human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS) but only indirectly causes cancer. HIV infects and destroys helper T cells, thereby weakening the body's immune system. This infection might let some other viruses thrive, possibly leading to cancer. HIV infection may increase the risk of developing Kaposi sarcoma and cervical cancer, and it's also linked to certain kinds of non-Hodgkin lymphoma. There is no vaccine to prevent HIV.
- Human herpes virus 8 (HHV-8), also known as Kaposi sarcoma-associated herpes virus (KSHV), has been found in nearly all tumors in patients with Kaposi

sarcoma, a rare, slow-growing cancer (American Cancer Society 2016).

- Human T-lymphotrophic virus-1 (HTLV-1) has been linked with a type of lymphocytic leukemia and non-Hodgkin lymphoma called adult T-cell leukemia/lymphoma. Infection with HTLV-1 is rare in the United States.
- Merkel cell polyomavirus (MCV) causes a rare and aggressive type of skin cancer called Merkel cell carcinoma.

Only a minority of persons infected with a virus listed previously eventually develop cancer as a result. The process is slow and inefficient and depends on additional factors unique to the person infected.

89. Can bacterial infections cause cancer?

Bacterial infections traditionally have not been considered major causes of cancer. Recently, however, two methods have been proposed to link bacterial infections to cancer: the development of chronic inflammation and production of carcinogenic bacterial metabolites. *Helicobacter pylori* infection of the stomach can lead to lifelong chronic inflammation. This inflammation is, in turn, thought to cause cancer by inducing cell proliferation and production of mutagenic free radicals. *Salmonella enteritidis* has been implicated in the development of colon carcinoma. Bacteria can cause cancer through the effect of toxins secreted by the bacteria on host cell transformation. Since bacterial infections can be effectively controlled by antibiotics, it is important to use this treatment method before the infection progresses to cancer.

90. How successful are therapeutic cancer vaccines?

The development of therapeutic cancer vaccines continues to be challenging, with only modest responses found in most clinical trials. Cancer vaccines have been approved by the FDA for the treatment of early-stage bladder cancer (TICE), metastatic castration-resistant prostate cancer (Provenge), and metastatic melanoma (IMLYGIC).

The most promising approach with cancer vaccines may be in combination with other treatments. Several studies have shown promising results when cancer vaccines are combined with

Adoptive Cell Therapy

91. What are the beneficial properties of adoptive T cell therapy?

Adoptive T cell therapy has several beneficial properties that are similar to other types of immunotherapy:

- T cell responses are specific, which can distinguish between healthy and cancerous tissue.
- T cell responses expand rapidly after activation.
- T cells are attracted to antigen sites, thereby efficiently eradicating cancer cells, including cells of distant metastases.
- T cell responses have memory, potentially maintaining therapeutic effects for years after initial treatment.

92. What are the general approaches to adoptive cell therapy?

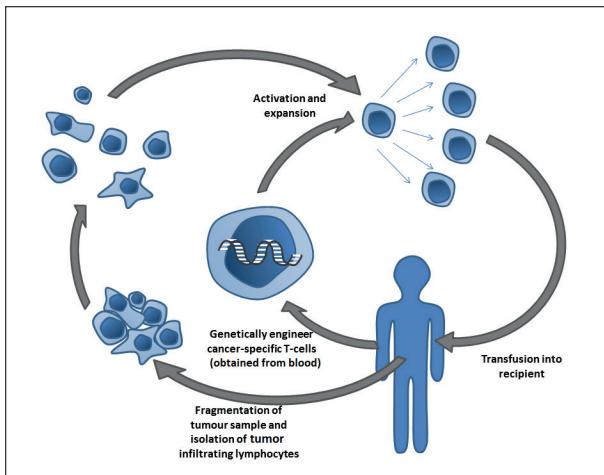
There are three approaches used in adoptive cell therapy (National Cancer Institute 2018):

- Tumor-infiltrating lymphocytes (or TILs). This approach uses T cells that are naturally found in a patient's tumor, called tumor-infiltrating lymphocytes (TILs). TILs that best recognize the patient's tumor cells in laboratory tests are selected, and these cells are grown to large numbers in the laboratory. The cells are then activated by treatment with immune system signaling proteins called cytokines and infused into the patient's bloodstream. The idea behind this approach is that the TILs have already shown the ability to target tumor cells, but there may not be enough of them in the tumor microenvironment to kill the tumor. The TILs present may not be able to overcome the immune suppressive signals that the tumor is releasing. Introducing massive amounts of activated TILs can help to overcome these barriers.

- T-cell receptor (TCR). TCRs use naturally occurring receptors that can also recognize antigens that are inside tumor cells. In this approach, T-cell receptors are isolated from peripheral blood of the patient and transformed by genetic engineering to have a higher affinity for specific tumor antigens compared with TILs. To date, TCR T cells have been tested in patients with a variety of solid tumors, showing promise in melanoma and sarcoma.
- CAR T-cell therapy. With this method, the patient's T cells obtained from peripheral blood are genetically modified in the laboratory to express a specialized receptor known as a chimeric antigen receptor, or CAR. CARs are synthetic molecules but act similarly to natural receptors. Figure 3.1 illustrated how receptors are assembled, including an extracellular antigen binding domain, a transmembrane domain, and an intracellular domain. These engineered T cells home in on tumor targets with enhanced specificity, proliferate rapidly in circulation, terminate tumor cells, and persist to patrol the body for emerging tumors. This method commonly uses viruses that are modified so they can no longer cause disease, but still retain the ability to invade cells and multiply inside the cells. The CAR-T cells are then multiplied and infused into the patient. CARs are designed to allow the T cells to directly attach to specific proteins on the surface of the patient's cancer cells without the necessity for MHC presentation. CAR-T cells can be engineered to deliver antitumor agents to kill cancer cells or to modify the tumor microenvironment. CAR-T therapy has shown to be most effective against cancers of the blood but has not been shown to be effective against solid tumors (in contrast to TCR therapy).

Recent advances in CAR T-cell therapy have involved the addition of co-stimulatory signaling molecules to CAR T cells to improve their ability to produce more T cells after infusion and survive longer in the circulation.

Before receiving the expanded T cells, patients also undergo a procedure called lymphodepletion, which consists of a round of chemotherapy and, in some cases, whole-body radiation. The lymphodepletion gets rid of other immune cells that can impede the effectiveness of the incoming T cells.



▲ FIGURE 16.1

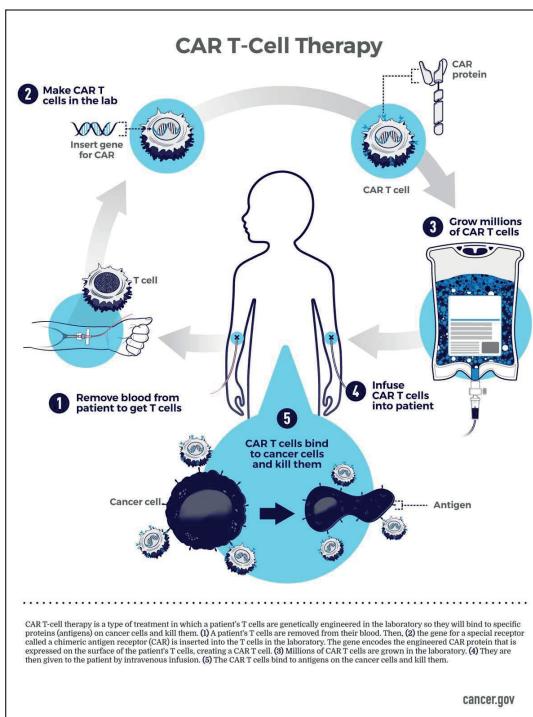
Adoptive T-cell therapy.

Cancer-specific T cells can be obtained by fragmentation and isolation of tumor-infiltrating lymphocytes (TILs) found in the patient's tumor, or by genetically engineering T cells obtained from peripheral blood. The cells are activated and grown in the lab to produce specialized T-cell receptors. The cells are then transfused into the recipient (tumor bearer).

Creator: Simon Caulton

https://en.wikipedia.org/wiki/Cancer_immunotherapy#/media/File:Adoptive_T-cell_therapy.png

CC BY-SA 3.0



◀ FIGURE 16.2

This schematic shows the steps for creating CAR T-cell therapy, a type of treatment in which a patient's T cells are changed in the laboratory so they will attack cancer cells. The steps for creating TCR cells are similar, except for Step 2. In this step, modified natural T cells are used instead of inserting a CAR gene into the cell.

National Cancer Institute

Public Domain

<https://www.cancer.gov/about-cancer/treatment/research/car-t-cell-therapy-infographic>

93. How is adoptive T-cell therapy used in cancer treatment?

Adoptive T-cell transfer was first studied for the treatment of metastatic melanoma, because melanomas often cause a substantial immune response, with many TILs. The use of activated TILs has been effective for some patients with melanoma and has produced encouraging positive findings in other cancers (e.g., cervical squamous cell carcinoma and cholangiocarcinoma). CAR T-cell therapy has been most effective against blood-based cancers, but researchers question whether the therapy will be effective against solid tumors.

Two CAR T-cell therapies have been approved:

- Tisagenlecleucel (Kymriah™) is approved for the treatment of some adults and children with acute lymphoblastic leukemia that is not responding to other treatments and for treatment of adults with certain types of B-cell non-Hodgkin lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. In clinical trials, many patients' cancers have disappeared entirely, and several of these patients have remained cancer-free for extended periods.
- Axicabtagene ciloleucel (Yescarta™) is approved for patients with certain types of B-cell non-Hodgkin lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.

Both therapies involve the modification of a patient's own immune cells.



For an excellent summary of cancer immunotherapy, as well as a listing and description of immunotherapeutic drugs currently on the market, Visit:
https://en.wikipedia.org/wiki/Cancer_immunotherapy#cite_note-Waldmann-23

94. Why is it difficult to treat solid tumors with CAR-T cell therapy?

The microenvironment of solid tumors is different from blood-based cancers in many ways:

- Blood-based cancers such as leukemias and lymphomas have been successfully treated with CAR-T therapies. All cells of these blood-based cancers typically have the same antigen that can be used as a target for the development of CAR-T therapies. However, the rapid expansion of

CAR-T cells could lead to a phenomenon called cytokine release syndrome or cases of autoimmunity.

- Cancer cells of a solid tumor do not preset the same mix of antigens on their surface, so a given CAR-T drug that targets one antigen will likely miss some cells. A tumor consists of thousands of layers of cells, making it difficult for T cells to penetrate. Instead of administering a drug via a blood infusion, the drug must be administered directly into the tumor or tumor microenvironment. Studies have shown success with the use of combination therapies, either combining multiple CAR-T drugs that target different antigens or combining CAR-T drugs with checkpoint inhibitor drugs.

95. What is the future of adoptive T cell therapy?

Adoptive T cell therapy has proven to be effective in inducing regression in many established tumors, including melanoma, leukemias, and prostate cancer. However, the costs for treatment can be considerable. Currently, the costs for transplantation using the patient's own T cells can range from \$36,000 to \$88,000, while the costs using a donor's T cells is much higher. To be a truly viable alternative therapy for many patients, the therapy must become more affordable and available.

CHAPTER
17

New Developments in Cancer Immunotherapy

96. What approaches are being taken to overcome cancer cell resistance to immunotherapy?

Cancer immunotherapy has generated tremendous excitement within the scientific and medical communities due to its ability to demonstrate dramatic and lasting improvements in patients suffering from certain cancers. For example, cancer immunotherapy has been effective for melanoma, non-small cell lung cancer, head and neck cancer, renal cell carcinoma, and Hodgkin's lymphoma. However, even for these cancers, the response rates have ranged between 10% and 61%. The majority of patients do not benefit from the treatment, and some who do respond relapse after a period of response.

Developing resistance to immunotherapy can be attributed to changing factors with the patient or with the cancer cells or their microenvironment. The immune response to cancer cells in a given patient is constantly evolving, either as a result of the patient's own environmental or genetic factors or as a result of treatment interventions. Patients who have primary resistance to immunotherapy drugs do not respond to the initial therapy, while patients with acquired resistance relapse after a period of response. Intrinsic factors are within the cancer cell, while extrinsic factors are within the tumor microenvironment. Primary resistance may be due to lack of recognition by T cells because of the absence of tumor antigens or due to lack of antigen presentation on APCs. Tumor cells may express or repress certain genes and pathways that prevent immune cell function.

Current approaches to overcoming cancer cell resistance to immunotherapy involve combination therapy. The following are examples of combination therapies that are being studied:

- Combining the MAPK pathway targeted therapy with immune checkpoint inhibitors.
- Combining immunotherapy with chemotherapy, radiotherapy, or targeted therapy to make the tumor more immunogenic.
- Combining an antiangiogenic agent with a checkpoint inhibitor.
- Combining checkpoint inhibitors that target both PD-1 and CTLA-4.
- Combining checkpoint inhibitor PD-1 with a neoantigen-based vaccine. Neoantigens are newly formed antigens that have not been previously recognized by the immune system. Neoantigens can arise from altered tumor proteins formed as a result of tumor mutations.

97. What are some specific immunotherapeutic drugs under development?

The following mechanisms of immunotherapy are being studied in clinical trials (Kavecansky 2017):

- Activating checkpoints – CD137 is a tumor necrotic factor receptor found on activated T cells, natural killer cells, and some tumor cells. Binding of CD137 to its ligand, CD137L, found on APCs, results in a signal activating CD4+ and CD8+ cells. Cancer cells can secrete high levels of CD137,

which blocks the interaction of CD137 with CD137L, resulting in an antitumor response. A monoclonal antibody, urelumab, is similar in structure and action to CD137, thereby overcoming the inhibitory action of tumor cells. A clinical trial with urelumab has shown antitumor responses in patients with head and neck cancer.

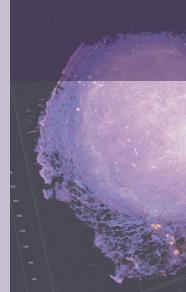
- Dendritic cell vaccines – dendritic cells within tumors have been thought to be deficient in presenting antigens to T cells because of incomplete maturity. Dendritic cells can be activated by combining with other biologically active compounds. Clinical trials are in progress using dendritic cell vaccines against many cancers.
- Oncolytic viruses target cancer cells for replication and toxicity. Oncolytic viruses were initially derived from herpes simplex virus and are engineered to specifically target cancer cells. Oncolytic viruses induce a strong immune response, including both innate and acquired immunity.
- Inhibiting immunosuppressive cells. Checkpoint antibodies LAG-3 and TIM-3 target T_{reg} -activating molecules. T_{reg} cells were discussed in Question 80. Clinical trials with experimental drugs have shown varying effectiveness from T_{reg} inhibition, indicating that improvements are needed in their proper use.

The following journal article provides a comprehensive listing of experimental drugs being studied in clinical trials:

<https://www.gotoper.com/publications/ajho/2017/2017feb/beyond-checkpoint-inhibitors-the-next-generation-of-immunotherapy-in-oncology>



- Integrins are transmembrane proteins expressed on most cells that facilitate communication between cells and their extracellular environment and control proliferation, survival, migration, and adhesion of cells. Tumors can express certain integrins to improve their survival and proliferation. These integrins can suppress immune cells and are the targets of several monoclonal antibodies in clinical trials.



References

CHAPTER 13

1. Ferris, Robert. "Hiding in Plain Sight: Mechanisms of Tumor Immune Evasion." Medscape. June 10, 2015, https://www.medscape.org/viewarticle/841945_2.
2. Rabinovich, Gabriel, Dmitry Gabrilovich, and Eduardo Sotomayer. "Immunosuppressive strategies that are mediated by tumor cells." *Annu Rev Immunol* 25 (2007): 267–296. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895922/pdf/nihms113360.pdf>
3. Wikipedia. "Immune system." April 24, 2019, https://en.wikipedia.org/wiki/Immune_system

CHAPTER 14

4. Bio-Rad. "The Role of Immune Checkpoints in Immunity and Cancer." <https://www.bio-rad-antibodies.com/immune-checkpoint-minireview.html>
5. Grywalska, Ewelina, Marcin Pasiarski, Stanislaw Gozdz, and Jacek Rolinski. "Immune-Checkpoint Inhibitors for Combating T-Cell Dysfunction in Cancer." *Oncotargets and Therapy* 11 (2018): 6505–6524. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6177399/>
6. National Cancer Institute. "Combining Immunotherapy and Radiation against Cancer." Sept. 21, 2017, <https://www.cancer.gov/research/areas/treatment/vonderheide-minttwyman-saint-victor-radiation-checkpoint-inhibitors>.
7. National Cancer Institute. "New Drugs, New Side Effects: Complications of Cancer Immunotherapy." May 10, 2019, <https://www.cancer.gov/news-events/cancer-currents-blog/2019/cancer-immunotherapy-investigating-side-effects>
8. Pardoll, Drew. "The Blockade of Immune Checkpoints in Cancer Immunotherapy." *Nat Rev Cancer* 12, no. 4 (2016): 252–264. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856023/>
9. Tanaka, A. and S. Sakaguchi. "Regulatory T cells in Cancer Immunotherapy." *Cell Research.* 27 (2017): 109–118. <https://www.nature.com/articles/cr2016151.pdf>
10. Wikipedia. "Checkpoint Inhibitor." March 15, 2019, https://en.wikipedia.org/wiki/Checkpoint_inhibitor
11. Zhzo, Y. "Evolving Roles for Targeting CTLA-4 in Cancer Immunotherapy." *Cellular Physiology and Biochemistry.* 47 (2018): 721–734. <https://www.karger.com/Article/Pdf/490025>

CHAPTER 15

12. American Cancer Society. "Viruses that can lead to cancer." July 11, 2016 <https://www.cancer.org/cancer/cancer-causes/infectious-agents/infections-that-can-lead-to-cancer/viruses.html>

13. American Cancer Society. "Newer cancer vaccines." Oct. 31, 2017. <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/whats-new-in-immunotherapy-research.html>
14. Butterfield, Lisa. "Cancer Vaccines." *British Med J* (April 22, 2015). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707521/?report=classic>
15. Cancer.net. "What Are Cancer Vaccines?" June 2018. <https://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/what-are-cancer-vaccines>
16. Espinosa-Delgado, Igor. "Cancer Vaccines." *The Oncologist* 7, suppl 3. (2002): 20–33. https://theoncologist.alphamedpress.org/content/7/suppl_3/20.full.pdf+html
17. Guo, Chunqing, Masoud H. Manjili, John R. Subjeck, Devanand Sarkar, Paul B. Fisher, and Xiang-Yang Wang. "Therapeutic Cancer Vaccines: Past, Present, and Future." *Adv Cancer Res* 119 (2013): 421–475. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3721379/pdf/nihms-475095.pdf>
18. Mougel,A., Magali Terme, and Corinne Tanchot. "Therapeutic Cancer Vaccine and Combinations With Antiangiogenic Therapies and Immune Checkpoint Blockade." *Frontiers in Immunology*.10, Article 467 (March 14, 2019):1–10 <https://www.frontiersin.org/articles/10.3389/fimmu.2019.00467/full>
19. Parsonnet, J. "Bacterial Infection as a cause of Cancer." *Environmental Health Perspectives*. 103, Suppl 8 (1995):263–268. <https://ncbi.nlm.nih.gov/pmc/articles/PMC1518971/>

CHAPTER 16

20. Cancer Research Institute. "Adoptive Cell Therapy: How Cellular Immunotherapies Are Changing the Outlook for Cancer Patients." <https://www.cancerresearch.org/immunotherapy/treatment-types/adoptive-cell-therapy>
21. Grens, Kerry. "The Next Frontier of CAR-T Cell Therapy: Solid Tumors." *The Scientist* (April 1, 2019): 28–35. <https://www.the-scientist.com/features/the-next-frontier-of-car-t-cell-therapy--solid-tumors-65612>
22. National Cancer institute. "Biological Therapies for Cancer." April 26, 2018. <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet>
23. Perica, Karlo, Juan Carlos Varela, Mathias Oelke, and Jonathan Schneck. "Adoptive T Cell Immunotherapy for Cancer." *Rambam Maimonides Medical Journal* 6, no. 1 (2015): e1–9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4327320/pdf/rmmj-6-1-e0004.pdf>
24. Wikipedia. "Cancer Immunotherapy." https://en.wikipedia.org/wiki/Cancer_immunotherapy
25. Zhang, J. and L. Wang. "The Emerging World of TCR-T Cell Trials Against Cancer: A Systematic Review." *Technol Cancer Res Treat.* 18 (Jan 2019): 1–13. <https://www.ncbi.nlm.nih.gov/pubmed/30798772>

CHAPTER 17

26. Kavecansky, Juraj, and Anna Pavlick. "Beyond Checkpoint Inhibitors: The Next Generation of Immunotherapy in Oncology." *American Journal of Hematology/Oncology* 13, no. 2 (2017): 9–20.
<https://www.gotoper.com/publications/ajho/2017/2017feb/beyond-checkpoint-inhibitors-the-next-generation-of-immunotherapy-in-oncology>.
27. Liu, Ying, and Dmitriy Zamarin. "Combination Immune Checkpoint Blockade Strategies to Maximize Immune Response in Gynecological Cancers." *Current Oncology Reports* 20 (2018): 1–11.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6244932/>.
28. Schmidt, Charles. "Combinations on Trial." *Nature* 552 (2017): S67–S69.
<https://www.nature.com/magazine-assets/d41586-017-08702-7/d41586-017-08702-7.pdf>.
29. Sharma, Padmanee, Siwen Hu-Lieskován, Jennifer Wargo, and Antoni Ribas. "Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy." *Cell* 168, no. 4 (2017): 707–723.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5391692/>.
30. Yu, Chune, Xiaowei Liu, Jiqiao Yang, Min Zhang, Hongyu Jin, Xuelei Ma, and Hubing Shi. "Combination of Immunotherapy with Targeted Therapy: Theory and Practice in Metastatic Melanoma." *Frontiers in Immunology* 10, no. 990 (2019): 1–19.
<https://pdfs.semanticscholar.org/2b72/8ffce7ba35203512e17d68d201f80d993b85.pdf>

Index

A

acquired immunity, 76
adenine, 5–6
adenocarcinoma, 29
adoptive T cell therapy, 104–108
 in cancer treatment, 107–108
 future of, 108
 general approaches to
 CAR T-cell therapy, 105, 106,
 107–108
 T-cell receptors, 104–105
 tumor-infiltrating
 lymphocytes, 104
 properties of, 104
 solid tumors, difficulties
 treating, 107–108
alleles, 7
allogenic tumor cell vaccines, 101
androgens, 56
androgen suppression therapy, 56
angiogenesis, 4
angiogenesis inhibitors, 64
antigen-presenting cells (APC), 76
anti-PD-1 agents, 94
APC, *see* antigen-presenting cells
apoptosis inducers, 64
aromatase, 55
aromatase inhibitors, 55
Atezolizumab, 83
autologous tumor cell vaccines, 101
Avelumab, 83

B

bacterial infections, cancer and, 103
basal cell carcinomas, 29
basal lamina, 18
B cells, 78
benign tumors, 2–3
biopsy of tumors, 23, 41
brachytherapy, 53
 high-dose rate implants, 53–54

low-dose rate implants, 53
permanent implants, 54
BRAF protein, 62
brain and spinal cord tumors, 35
breast cancer, 18, 55

C

cancer, 2–3
 adoptive T cell therapy for,
 107–108
 bacterial infections and, 103
 breast, 18, 55
 causes, 8–9
 cells in development of, 3–4,
 16–20, 26, 47–48, 61–62,
 64–65
 appearance, 18
 cycle, 11–13, 14
 mutations, 21
 signaling and, 9–11
 characteristics of, 2–4
 classification of, 27–35
 brain and spinal cord
 tumors, 35
 carcinoid tumors, 35
 carcinomas, 28–29
 germ cell tumors, 35
 leukemias, 31–32
 lymphoblastic leukemia,
 32–33
 lymphoma, 33
 melanomas, 34
 method, 27–28
 multiple myeloma, 34
 neuroendocrine tumors, 35
 sarcomas, 29–30
 diagnosis, 22–27
 biopsy of tumor, 23
 CT scans, 23–25
 imaging tests, 23
 laboratory tests, 22
 MRI scans, 25

- PET scans, 25–26
SPECT scans, 26
tumor grade, 26
genes in, 5–9, 14–15
immune system and, 4, 81–82
immunotherapy for, 75, 85–95
metastatic, 16–20
primary cellular properties, 2
prostate, 56
recurrences, 21–22
 distant, 21
 local, 21
 regional, 21
spread, 16–20, 44–45
stage, 26–27
targeted therapies for, 60–72
tissue changes and, 20–21
treatments
 chemotherapy, 45–48
 hormone therapy, 54–56
 hyperthermia, 42–43
 photodynamic therapy, 43–44
 radiotherapy, 48–54
 surgery, 40–45
tumors, 2–3, 26
vaccines, 100–104
 viral infections and, 102–103
cancer stem cells (CSCs), 70
carcinoid tumors, 35
carcinoma *in situ*, 20
carcinomas, 28–29
 adenocarcinoma, 29
 basal cell, 29
 squamous cell, 29
 transitional cell, 29
CAR T-cell therapy, 105, 106, 107–108
CD137, 109–110
CD137L, 109–110
CD28 receptor, 80, 84
cell cycle, 11–13
 checkpoints, 11
 importance to cancer, 14
 phases, 11–12
relation to cancer, 11
states, 11–13
cells, 2
 cancer *vs.* normal, 3–4, 17
 cycle, 11–13
 epithelial, 17–18
 lung cancer, 3
 mesenchymal, 17
 mitochondria and, 5
 nuclei of, 5
 signaling, 9–11
cell signaling
 insulin-like growth factor-1, 11
 process, 9
 receptors, 10–11
 relation to cancer, 9
 stages, 9
 vascular -endothelial growth factor, 11
cellular immunity, 76
chemotherapy, for cancer
 treatment, 45–48
 maximum effective dose, 48
 resistance to, 47–48
 side effects, 46–47
 vs. targeted cancer therapies, 60
 usage, 45–46
 who receives, 46
 work, 45–46
chondrosarcoma, 30
chromatin, 5
chromosomes, 5, 7
chronicly mphoblastic leukemia (CLL), 32
chronic myeloid leukemia, 66
CLL, *see* chronicly mphoblastic leukemia
clones, 21
co-inhibitory molecules, role of, 80–81
computed tomography (CT), 23–25
coreceptors, 81
co-stimulatory molecules, 80
cryosurgery, 41
CSCs, *see* cancer stem cells

CT, *see* computed tomography (CT)
CTLA-4 receptor, 80, 82, 84, 87, 95, 98
cytosine, 5–6

D

Darvulumab, 83–84
dendritic cell vaccines, 101, 110
deoxyribonucleic acid (DNA), 5–9
 bases pair, 5
 double helix, 5, 6
 human, 5–7
 information in, 5–6
 promoters, 7
 property of, 5–6
 telomeres, 17
DHT, *see* dihydrotestosterone
dihydrotestosterone (DHT), 56
DNA, *see* deoxyribonucleic acid
double helix, 5, 6
dysplasia, 20
dysplastic nevus, 20

E

E-cadherin, 17–18
electron beams, 49
EMT, *see* epithelial-mesenchymal transition
epidermoid carcinomas, *see* squamous cell carcinomas
epithelial cells, 17–18
epithelial-mesenchymal transition (EMT), 70–71
Epstein-Barr virus (EBV), 102
erlotinib (Tarceva®), 72
estrogen receptors, 55–56

F

fusion gene, 62

G

gefitinib (Iressa®), 72
gene expression modulators, 64
genes, 5–8

affected during cancer development, 14–16
amplification, 47
fusion, 62
p53 gene, 15
proto-oncogenes, 14
tumor suppressor, 14–15
genetic vaccines, 101–102
germ cell tumors, 35
gonadotropin releasing hormone (GnRH) agonists, 55
guanine, 5–6

H

Helicobacter pylori infection, 103
helper T cells (CD 4+ T cells), 77, 79
hematopoietic stem cells, 31–32
hepatitis B virus (HBV), 102
hepatitis C virus (HCV), 102
HER-2, *see* human epidermal growth factor receptor 2 protein
high-dose rate (HDR) implants, 53–54
high-throughput screens, 62
Hodgkin lymphoma, 33
hormones, 54
hormone therapy, 54–56, 63
 in breast cancer, 55
 mode of action, 54–55
 in prostate cancer, 56
human epidermal growth factor receptor 2 protein (HER-2), 61
human herpes virus 8 (HHV-8), 102–103
human immunodeficiency virus (HIV), 102
human papilloma virus (HPV) infections, 102
human T-lymphotrophic virus-1 (HTLV-1), 103
humoral immunity, 76

hyperplasia, 20
hyperthermia, 42–43
hypoxia, 17

I

IGF-1, *see* insulin-like growth factor-1 (IGF-1)
imatinib mesylate (Gleevec®), 62
immune checkpoint inhibitors therapy, 82–83
case studies, 98–99
combination drugs, 98
CTLA-4, to block, 84
drugs, 84
effectiveness, 98
PD-1, to block, 83
PDL-1, to block, 83
regulatory T (Treg) cells in, 84–85
response rate to drugs, 94–98
side effects/control of, 85–86, 85–94
immune system
acquired, 76
B cells, 78
helper T cells (CD 4+ T cells), 77, 79
killer T cells (CD8+ cytotoxic T cells), 77
memory T cells, 77
natural killer cells, 78
regulatory B cells, 78
regulatory T cells, 78
basic function of, 76
cancer cells and, 4, 81–82
co-inhibitory molecules, role of, 80–81
components of, 76
co-stimulatory molecules for activation of, 80
innate, 76
antigen-presenting cells, 76
natural killer cells, 76–77
immunotherapy, 64, 85–99; *see also*

adoptive T cell therapy;
immune checkpoint inhibitors therapy;
vaccines, cancer
cancer cell resistance,
approaches to overcome, 108–109
combination therapies, 109
drugs under development, 109–110
IMRT, *see* intensity-modulated radiation therapy
inhibiting immunosuppressive cells, 110
innate immunity, 76
Institute for Personalized Cancer Therapy (IPCT), 71
insulin-like growth factor-1 (IGF-1), 11
intensity-modulated radiation therapy (IMRT), 50
ion channel receptors, 11
ipilimumab (Yervoy®), 84, 95–96

K

killer T cells (CD8+ cytotoxic T cells), 77

L

LAG-3 receptor, 84
laser surgery for cancer treatment, 41–42
leukemias, 2, 31–32
ligands
B7-1, 84
B7-2, 84
CD137L, 109–110
TIM-3, 84
low-dose rate (LDR) implants, 53
lung cancer cell, 3
lymphoblastic leukemia, 32–33
lymphoid stem cell, 31–32
lymphomas, 33

M

magnetic resonance imaging (MRI), 25
major histocompatibility complexes (MHC), 77
malignant tumors, 2
matrix metalloproteases, 18
melanomas, 34
memory T cells, 77
Merkel cell polyomavirus (MCV), 103
mesenchymal cells, 17
messenger RNA (mRNA), 7
metastasis, 16–20
metastatic tumors, 16–20
MHC, *see* major histocompatibility complexes
microenvironment, 3
mitochondria, 5
molecularly targeted therapies, *see* targeted cancer therapies
moles, 34
monoclonal antibodies, 62–63, 65, 82–83
MRI, *see* magnetic resonance imaging
multiple myeloma, 34
myeloid stem cell, 31–32

N

natural killer (NK) cells, 76–77, 78
neuroendocrine tumors, 35
nivolumab (Opdivo®), 83, 94
nodular melanoma, 34
Non-Hodgkin lymphoma, 33
normal cells, 3–4
nucleolus, 7
nucleotides, 5

O

oncolytic viruses, 110
osteosarcoma, 30

P

PDT, *see* photodynamic therapy
pembrolizumab, 83, 94
permanent implants, 54
p53 gene, 15
p-glycoprotein, 47
photodynamic therapy (PDT), 43–44
positron emission tomography (PET) scans, 25, 26
promoters, 7
prostate cancer, 56
protein-peptide-based cancer vaccines, 101
proteins, 6, 8, 62
proton beams, 49
proto-oncogenes genes, 14

R

radiotherapy, for cancer treatments, 48–54
brachytherapy, 53
high-dose rate implants, 53–54
low-dose rate implants, 53
permanent implants, 54
external beam, 49
IMRT, 50
stereotactic body radiation therapy, 52–53
stereotactic radiosurgery, 52
3-D conformal radiation therapy, 50
Tomotherapy®, 51
sources of
electron beams, 49
proton beams, 49
x-rays (photons), 48, 49
types of, 49
Ras, 70
receptors
androgens, 56
CD28, 80, 84

coreceptors, 81
CTLA-4, 80, 82, 84, 87, 95, 98
estrogen, 55–56
LAG-3, 84
TCRs, 104–105
tyrosine kinases, 11
recurrences, cancer, 21–22
distant, 21
local, 21
regional, 21
Reed-Sternberg cells, 33
regimen, 45
regulatory T (Treg) cells, 84–85
ribonucleic acid (RNA), 7
ribosomes, 7
RNA, *see* ribonucleic acid

S

Salmonella enteritidis, 103
sarcomas, 29–30
selective estrogen receptor
modulators (SERMs), 55
SERMs, *see* selective estrogen
receptor modulators
signaling molecules, 78
signal transduction inhibitors, 63
single-photon emission computed
tomography (SPECT)
scans, 26
small-molecule compounds, 62
soft tissue sarcoma, 30
solid tumors, 2, 107–108
squamous cell, 29
squamous cell carcinomas, 29
stereotactic body radiation therapy,
52–53
stereotactic radiosurgery, 52
surgery for cancer treatment,
40–45
cryosurgery, 41
diagnosis, use for, 41
goal of, 41
hyperthermia, 42–43

laser, 41–42
photodynamic therapy, 43–44
preventive/prophylactic, 40
spread of cancer and, 44–45

T

targeted cancer therapies, 60
challenges in development of,
70–71
components, 62–63
development of, 62–63
FDA approved drugs, 66–69
identification of targets, 61–62
limitations of, 69–70
side effects of, 71–72
vs. standard chemotherapy, 60
targeting cancer gene mutations,
65–66
types of, 63–65
angiogenesis inhibitors, 64
apoptosis inducers, 64
gene expression modulators,
64
hormone therapies, 63
immunotherapy, 64
monoclonal antibodies, 65
signal transduction
inhibitors, 63
T-cell receptors (TCRs), 104–105
TCRs, *see* T-cell receptors
telomeres, 17
testosterone, 56
therapeutic cancer vaccines,
103–104
3-D conformal radiation therapy, 50
thymine, 5–6
TILs, *see* tumor-infiltrating
lymphocytes
TIM-3 ligand, 84
tissues, 17, 20–21
Tomotherapy®, 51
trastuzumab (Herceptin®), 61, 70
Tremelimumab, 84

tumor-infiltrating lymphocytes (TILs), 104

tumors, 2

- benign, 2–3
- biopsy of, 23, 41
- brain, 35
- carcinoid, 35
- cells, 18
- germ cell, 35
- grade, 26
- heterogeneity, 70
- malignant, 2
- metastatic, 16–20
- neuroendocrine, 35
- spinal cord, 35

tumor suppressor genes, 14–15

tyrosine kinase inhibitors, 63

V

vaccines, cancer, 100–104

- definition, 100–101
- therapeutic, 103–104
- types of
 - allogenic tumor cell vaccines, 101

autologous tumor cell vaccines, 101

dendritic cell vaccines, 101

genetic vaccines, 101–102

protein-peptide-based cancer vaccines, 101

vascular-endothelial growth factor (VEGF), 11

VEGF, *see* vascular-endothelial growth factor

Vemurafenib (Zelboraf®), 62

viral infections, cancer and, 102–103

Epstein-Barr virus (EBV), 102

hepatitis B virus (HBV), 102

hepatitis C virus (HCV), 102

human immunodeficiency virus (HIV), 102

human papilloma virus (HPV), 102

X

x-rays (photons) beams, 48, 49