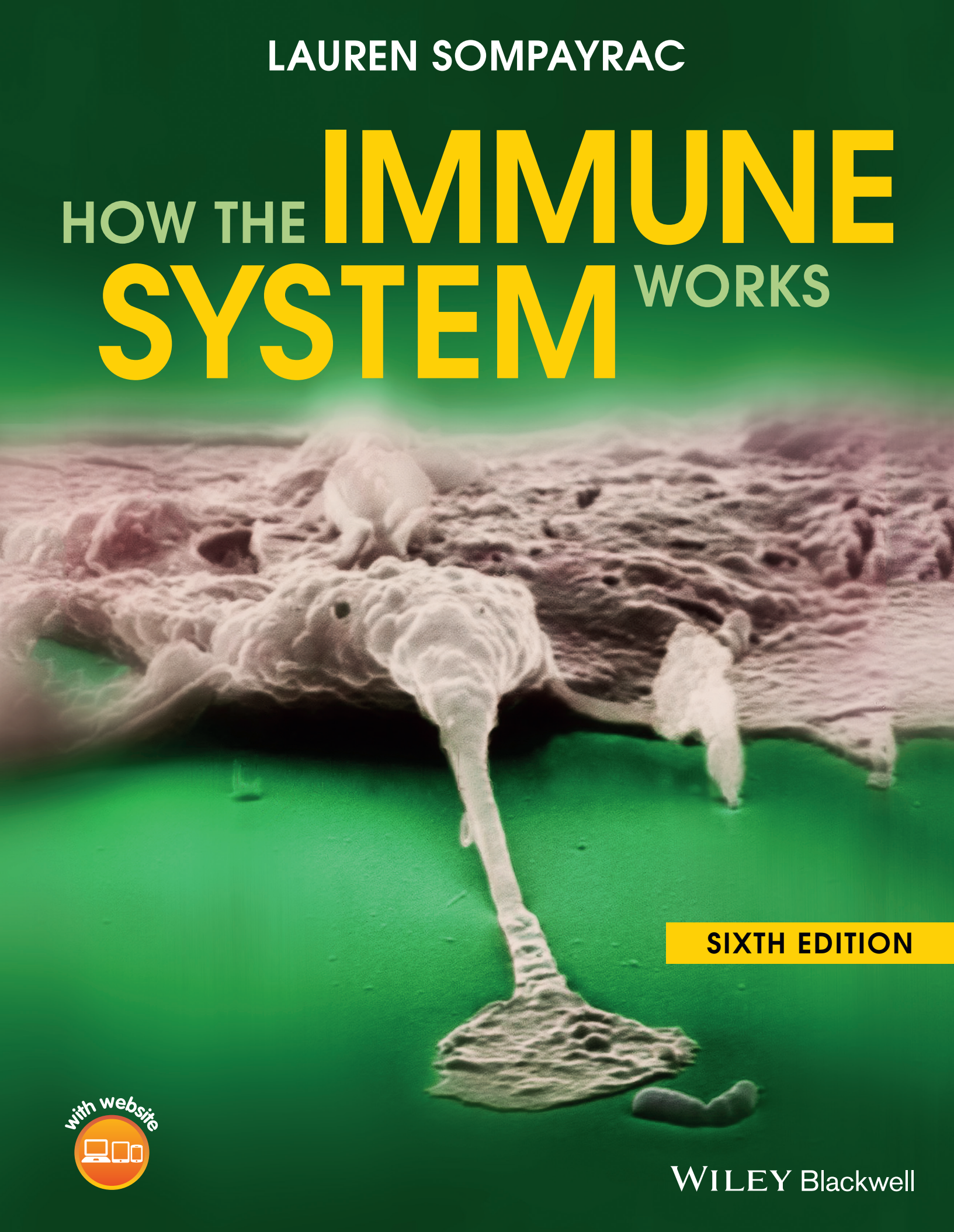
LAUREN SOMPAYRAC

HOW THE IMMUNE SYSTEM WORKS



SIXTH EDITION

with website

WILEY Blackwell

How the Immune System Works

I dedicate this book to my sweetheart, my best friend,
and my wife: Vicki Sompayrac.

How the Immune System Works

SIXTH EDITION

Lauren Sompayrac, PhD

WILEY Blackwell

This edition first published 2019 © 2019 by John Wiley & Sons Ltd

Edition History
John Wiley & Sons, Ltd (1e, 1999; 2e, 2003; 3e, 2008; 4e, 2012; 5e 2016)

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

A catalogue record for this book is available from the Library of Congress and the British Library.

ISBN 9781119542124

Cover image and figure on page 2: © Lennart Nilsson Photography/TT NYHETSBYRÅN
Cover design by Wiley

Set in 9.5/13pt Palatino LTStd by Aptara Inc., New Delhi, India

10 9 8 7 6 5 4 3 2 1

Contents

Acknowledgments, viii

How to Use This Book, ix

This book is neither a comprehensive text nor an exam-review tool. It is an overview of the immune system, designed to give anyone who is learning immunology a feel for how the system fits together.

About the Companion Website, x

LECTURE 1 An Overview, 1

The immune system is a "team effort," involving many different players who work together to provide a powerful defense against invaders. Focusing on one player at a time makes it hard to understand the game. Here we view the action from the grandstands to get a wide-angle picture of what the immune system is all about.

LECTURE 2 The Innate Immune System, 13

The innate immune system is a "hard-wired" defense that has evolved over millions of years to recognize pathogens that commonly infect humans. It provides a rapid and powerful response against "everyday" invaders.

LECTURE 3 B Cells and Antibodies, 27

B cells and the antibodies they produce are part of the adaptive immune system – a system that protects us against pathogens both common and rare.

LECTURE 4 The Magic of Antigen Presentation, 42

T cells, another weapon of the adaptive immune system, only recognize invaders which are "properly presented" by specialized antigen presenting cells. This feature keeps T cells focused on the types of attackers they can defend against.

LECTURE 5 T Cell Activation, 55

Before they can spring into action, T cells must be activated. This requirement helps insure that only useful weapons will be mobilized.

LECTURE 6 T Cells at Work, 62

Once they have been activated, helper T cells orchestrate the immune response, and killer T cells destroy infected cells.

LECTURE 7 Secondary Lymphoid Organs and Lymphocyte Trafficking, 71
B and T lymphocytes travel through secondary lymphoid organs looking for the intruders they can defend against. Once activated in the secondary lymphoid organs, B and T cells are dispatched to the particular areas of the body where they can be most useful.

LECTURE 8 Restraining the Immune System, 83
The powerful weapons of the immune system must be restrained lest they become over-exuberant. In addition, once an invader has been defeated, the immune system must be "reset" to prepare for future attacks.

LECTURE 9 Self Tolerance and MHC Restriction, 87
T cells must be "tested" to be sure they focus on appropriately presented antigens, and B and T lymphocytes must be screened to eliminate those which might attack our own bodies.

LECTURE 10 Immunological Memory, 98
The innate immune system remembers pathogens which have been attacking humans for millions of years. In contrast, B and T cells remember pathogens we have encountered during our lifetime. Memory B and T lymphocytes respond more quickly and effectively to a subsequent attack by the same invader.

LECTURE 11 The Intestinal Immune System, 104
The human intestines are home to trillions of bacteria, viruses, fungi, and parasites. How the immune system deals with these potentially dangerous intestinal residents, which frequently invade the tissues surrounding the intestines, is a hot topic in immunology.

LECTURE 12 The Immune System Gone Wrong, 111
The immune system usually does a good job of defending us. Sometimes, however, mistakes are made. Two examples of the "immune system gone wrong" are allergies and autoimmunity.

LECTURE 13 Immunodeficiency, 120
Serious disease may result when our immune system does not operate at full strength. Humans who are infected with the AIDS virus have profoundly impaired immune systems.

LECTURE 14 Vaccines, 125
Vaccines safely mimic a microbial attack so that our immune system will be primed and ready for a future challenge by the same pathogen.

LECTURE 15 Cancer and the Immune System, 132
The human immune system is not very good at defending us against cancer. Indeed, there is a built-in conflict between the need to minimize the chance that its weapons will attack our own bodies and the need to destroy cancer cells.

LECTURE 16 Immunotherapy, 139
Although the immune system evolved to keep invaders from infecting us, physicians are "borrowing" some of the weapons of the immune system and using them to treat disease.

Glossary, 146

Here are definitions of some of the terms that immunologists use – but which "normal" people wouldn't.

List of Acronyms and Abbreviations, 150

Immunologists are big on acronyms and abbreviations, but they can drive you crazy. So I've made a list to which you can refer.

Index, 151

Acknowledgments

I would like to thank the following people, whose critical comments on earlier editions were most helpful: Drs. Mark Dubin, Linda Clayton, Dan Tenen, Jim Cook, Tom Mitchell, Lanny Rosenwasser, and Eric Martz. Thanks also go to Diane Lorenz, who illustrated the first and second editions, and whose wonderful artwork still can be found in this book. Finally, I wish to thank Vicki Sompayrac, whose wise suggestions helped make this book more readable, and whose editing was invaluable in preparing the final manuscript.

How to Use This Book

I wrote *How the Immune System Works* because I couldn't find a book that would give my students an overall view of the immune system. Sure, there are as many good, thick textbooks as a person might have money to buy, but these are crammed with every possible detail. There are also lots of "review books" that are great if you want a summary of what you've already learned – but they won't teach you immunology. What was missing was a short book that tells, in simple language, how the immune system fits together – a book that presents the big picture of the immune system, without the jargon and the details.

How the Immune System Works is written in the form of "lectures," because I want to talk to you directly, just as if we were together in a classroom. Although Lecture 1 is a light-hearted overview, meant to give you a running start at the subject, you'll soon discover that this is not "baby immunology." *How the Immune System Works* is a concept-driven analysis of how the immune system players work together to protect us from disease – and, most importantly, why they do it this way.

In Lectures 2 through 10, I focus more closely on the individual players and their roles. These lectures are short, so you probably can read them all in a couple of afternoons. In fact, **I strongly suggest that you begin by reading quickly through Lectures 1–10**. The whole idea is to get an overall view of the subject, and if you read one lecture a week, that won't happen. Don't "study" these ten lectures your first time through. Don't even bother with the Thought Questions at the end of each lecture. Just rip through them. Then, once you have a feel for the system, go back and spend a bit more time with these same ten lectures to get a clearer understanding of the "hows and whys."

In Lectures 11–16, I discuss the intestinal immune system, vaccines, allergies, autoimmune disease, the AIDS virus, cancer, and immunotherapy. These lectures will let you "practice" what you have learned in the earlier lectures by examining real-world examples of the immune system at work. So after you have gone through Lectures 1–10 twice, I'd suggest you read these last six lectures. When you do, I think you'll be amazed by how much you now understand about the immune system.

As you read, you will encounter passages highlighted in **green**, and words that are highlighted in **red**. These highlights are to alert you to important concepts and terms. They also will help you review a lecture quickly, once you have read it through.

In some settings, *How the Immune System Works* will serve as the main text for the immunology section of a larger course. For a semester-long undergraduate or graduate immunology course, your professor may use this book as a companion to a comprehensive textbook. As your course proceeds, reviewing the appropriate lectures in *How the Immune System Works* will help you keep the big picture in focus as the details are filled in. It's really easy to get lost in the details.

No matter how your professor may choose to use this book, you should keep one important point in mind: I didn't write *How the Immune System Works* for your professor. This book is for you!

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/sompayrac

The website includes:

- Powerpoint files of all the images in the book

LECTURE 1 An Overview

HEADS UP!

The immune system is a "team effort," involving many different players. These players can be divided roughly into two groups: those that are members of the innate immune system team and those that are part of the adaptive immune system. Importantly, these two groups work together to provide a powerful defense against invaders.

INTRODUCTION

Immunology is a difficult subject for several reasons. First, there are lots of details, and sometimes these details get in the way of understanding the concepts. To get around this problem, we're going to concentrate on the big picture. It will be easy for you to find the details somewhere else. Another difficulty in learning immunology is that there is an exception to every rule. Immunologists love these exceptions, because they give clues as to how the immune system functions. But for now, we're just going to learn the rules. Oh sure, we'll come upon exceptions from time to time, but we won't dwell on them. Our goal is to examine the immune system, stripped to its essence.

A third difficulty in studying immunology is that our knowledge of the immune system is still evolving. As you'll see, there are many unanswered questions, and some of the things that seem true today will be proven false tomorrow. I'll try to give you a feeling for the way things stand now, and from time to time I'll discuss what immunologists speculate may be true. But keep in mind that although I'll try to be straight with you, some of the things I'll tell you will change in the future – maybe even by the time you read this!

Although these three features make studying immunology difficult, I think the main reason immunology is such a tough subject is that the immune system is a "team effort" that involves many different players interacting with each other. Imagine you're watching a football game on TV, and the camera is isolated on one player, say, the tight end. You see him run at full speed down the field, and then stop. It doesn't seem to make any sense. Later, however, you see the same play on the big screen, and now you understand. That tight end took two defenders with him down the field, leaving the running back uncovered to catch the pass and run for a touchdown. The immune system is a lot like a football team. It's a network of players who cooperate to get things done, and focusing on a single player doesn't make much sense. You need an overall view. That's the purpose of this first lecture, which you might call "turbo immunology." Here, I'm going to take you on a quick tour of the immune system, so you can get a feeling for how it all fits together. Then in the next lectures, we'll go back and take a closer look at the individual players and their interactions.

PHYSICAL BARRIERS

Our first line of defense against invaders consists of physical barriers, and to cause real trouble viruses, bacteria, parasites, and fungi must penetrate these shields. Although we tend to think of our skin as the main barrier, the area covered by our skin is only about 2 square meters. In contrast, the area covered by the mucous membranes that line our digestive, respiratory, and reproductive tracts measures about 400 square meters – an area about as big as two tennis courts. The main point here is that there is a large perimeter which must be defended.

THE INNATE IMMUNE SYSTEM

Any invader that breaches the physical barrier of skin or mucosa is greeted by the **innate immune system** – our

How the Immune System Works, Sixth Edition. Lauren Sompayrac. © 2019 John Wiley & Sons, Ltd. Published 2019 by John Wiley & Sons, Ltd.
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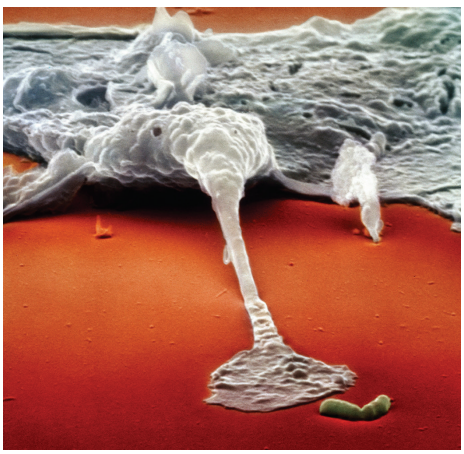
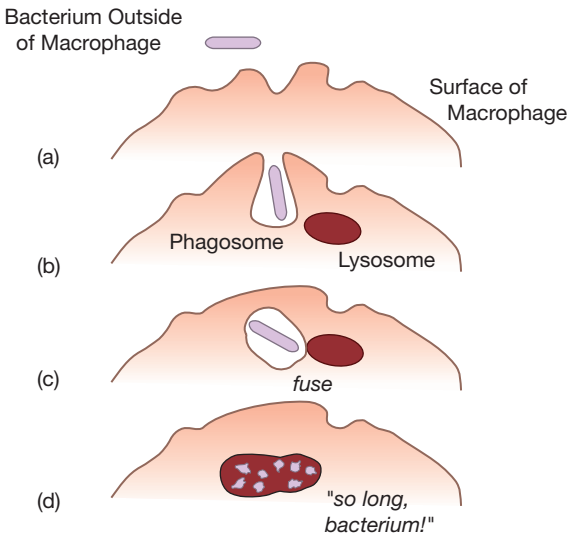
second line of defense. Immunologists call this system "innate" because it is a defense that all animals just naturally seem to have. Indeed, some of the weapons of the innate immune system have been around for more than 500 million years. Let me give you an example of how this amazing innate system works.

Imagine you are getting out of your hot tub, and as you step onto the deck, you get a large splinter in your big toe. On that splinter are many bacteria, and within a few hours you'll notice (unless you had a lot to drink in that hot tub!) that the area around where the splinter entered is red and swollen. These are indications that your innate immune system has kicked in. Your tissues are home to roving bands of white blood cells that defend you against attack. To us, tissue looks pretty solid, but that's because we're so big. To a cell, tissue looks somewhat like a sponge with holes through which individual cells can move rather freely. One of the defender cells that is stationed in your tissues is the most famous innate immune system player of them all: the **macrophage**. If you are a bacterium, a macrophage is the last cell you want to meet after your ride on that splinter! Here is an electron micrograph showing a macrophage about to devour a bacterium.



You will notice that this macrophage isn't just waiting until it bumps into the bacterium purely by chance. No, this macrophage actually has sensed the presence of the bacterium and is reaching out a "foot" to grab it. But how does a macrophage know that a bacterium is out there? The answer is that macrophages have antennae (receptors) on their surface which are tuned to recognize "danger molecules" characteristic of common microbial invaders. For example, the membranes that surround bacteria are made up of certain fats and carbohydrates that normally are not found in the human body. Some of these foreign molecules represent "find me and eat me" signals for macrophages. And when macrophages detect danger molecules, they begin to crawl toward the microbe that is emitting these molecules.

When it encounters a bacterium, a macrophage first engulfs it in a pouch (vesicle) called a **phagosome**. The vesicle containing the bacterium is then taken inside the macrophage, where it fuses with another vesicle termed a **lysosome**. Lysosomes contain powerful chemicals and enzymes which can destroy bacteria. In fact, these agents are so destructive that they would kill the macrophage itself if they were released inside it. That's why they are confined within vesicles. Using this clever strategy, the macrophage can destroy an invader without "shooting itself in the foot." This whole process is called **phagocytosis**, and this series of snapshots shows how it happens.

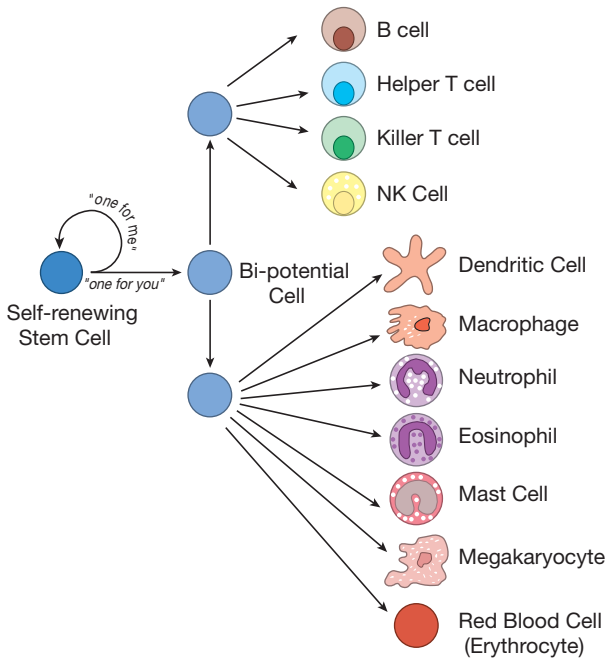


Macrophages have been around for a very long time. In fact, the ingestion technique macrophages employ is simply a refinement of the strategy that amoebas use to feed themselves – and amoebas have roamed Earth for about 2.5 billion years. So why is this creature called a macrophage? "Macro," of course, means large – and a macrophage is a large cell. Phage comes from a Greek word meaning "to eat." So a macrophage is a big eater. In fact, in addition to defending against invaders, the macrophage also functions as a garbage collector. It will eat almost anything. Immunologists can take advantage of this appetite by feeding macrophages iron filings. Then, using a small magnet, they can separate macrophages from other cells in a cell mixture. Really!

Where do macrophages come from? Macrophages and all the other blood cells in your body are the descendants of self-renewing **blood stem cells** – the cells from which all the blood cells "stem." By self-renewing, I mean that

when a stem cell grows and divides into two daughter cells, it does a "one for me, one for you" thing in which some of the daughter cells go back to being stem cells, and some of the daughters go on to become mature blood cells. This strategy of continual self-renewal insures that there will always be blood stem cells in reserve to carry on the process of making mature blood cells.

Macrophages are so important to our defense that they actually take up their sentinel positions in the tissues well before we are born. After birth, blood stem cells, which reside in the bone marrow, can replenish the supply of macrophages and all the other blood cells as they are needed. As the daughters of blood stem cells mature, they must make choices that determine which type of blood cell they will become when they grow up. As you can imagine, these choices are not random, but are carefully controlled to make sure you have enough of each kind of blood cell. For example, some daughter cells become red blood cells, which capture oxygen in the lungs and transport it to all parts of the body. Our stem cell "factories" must turn out more than two million new red blood cells each second to replace those lost due to normal wear and tear. Other descendants of a blood stem cell may become macrophages, neutrophils, or other types of "white" blood cells. And just as white wine really isn't white, these cells aren't white either. They are colorless, but biologists use the term "white" to indicate that they lack hemoglobin, and therefore are not red. Here is a figure showing some of the many different kinds of blood cells a stem cell can become.



When the cells that can mature into macrophages first exit the bone marrow and enter the blood stream, they are called **monocytes**. All in all, you have about two billion of these cells circulating in your blood at any one time. This may seem a little creepy, but you can be very glad they are there. Without them, you'd be in deep trouble. Monocytes remain in the blood for an average of about three days. During this time they travel to the capillaries – which represent the "end of the line" for blood vessels – looking for a crack between the endothelial cells that line the inside of the capillaries. These endothelial cells are shaped like shingles, and by sticking a foot between them a monocyte can leave the blood, enter the tissues, and mature into a macrophage. In the tissues, most macrophages just hang out, do their garbage collecting thing, and wait for you to get that splinter so they can do some real work.

When macrophages eat the bacteria on that splinter in your foot, they give off chemicals which increase the flow of blood to the vicinity of the wound. The buildup of blood in this area is what makes your toe red. Some of these chemicals also cause the cells that line the blood vessels to contract, leaving spaces between them so that fluid from the capillaries can leak out into the tissues. It is this fluid that causes the swelling. In addition, chemicals released by macrophages can stimulate nerves in the tissues that surround the splinter, sending pain signals to your brain to alert you that something isn't quite right in the area of your big toe.

During their battle with bacteria, macrophages produce and give off (secrete) proteins called **cytokines**. These are hormone-like messengers which facilitate communication between cells of the immune system. Some of these cytokines alert monocytes and other immune system cells traveling in nearby capillaries that the battle is on, and encourage these cells to exit the blood to help fight the rapidly multiplying bacteria. Pretty soon, you have a vigorous "inflammatory" response going on in your toe, as the innate immune system battles to eliminate the invaders.

So here's the strategy: You have a large perimeter to defend, so you station sentinels (macrophages) to check for invaders. When these sentinels encounter the enemy, they send out signals (cytokines) that recruit more defenders to the site of the battle. The macrophages then do their best to hold off the invaders until reinforcements arrive. Because the innate response involves warriors such as macrophages, which are programmed to recognize many common invaders, your innate immune system usually responds so quickly that the battle is over in just a few days.

There are other players on the innate team. For example, in addition to the **professional phagocytes** such as

macrophages, which make it their business to eat invaders, the innate system also includes the complement proteins that can punch holes in bacteria, and natural killer cells which are able to destroy bacteria, parasites, virus-infected cells, and some cancer cells. We will talk more about the macrophage's innate system teammates in the next lecture.

THE ADAPTIVE IMMUNE SYSTEM

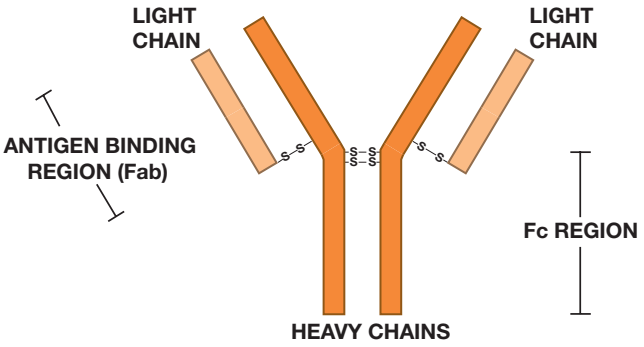
About 99% of all animals get along just fine with only natural barriers and the innate immune system to protect them. However, vertebrates like us have a third level of defense: the **adaptive immune system**. This is a defense system which actually can adapt to protect us against almost any invader. One of the first clues that the adaptive immune system existed came back in the 1790s when Edward Jenner began vaccinating the English against smallpox virus. In those days, smallpox was a major health problem. Hundreds of thousands of people died from this disease, and many more were horribly disfigured. What Jenner observed was that milkmaids frequently contracted a disease called cowpox, which caused lesions on their hands that looked similar to the sores caused by the smallpox virus. Jenner also noted that milkmaids who had contracted cowpox almost never got smallpox (which, it turns out, is caused by a close relative of the cowpox virus).

So Jenner decided to conduct a daring experiment. He collected pus from the sores of a milkmaid who had cowpox, and used it to inoculate a little boy named James Phipps. Later, when Phipps was re-inoculated with pus from the sores of a person infected with smallpox, he did not contract that disease. In Latin, the word for cow is *vacca* – which explains where we get the word vaccine. History makes out the hero in this affair to be Edward Jenner, but I think the real hero that day was the young boy. Imagine having this big man approach you with a large needle and a tube full of pus! Although this isn't the sort of thing that could be done today, we can be thankful that Jenner's experiment was a success, because it paved the way for vaccinations that have saved countless lives.

Smallpox virus was not something humans encountered regularly. So Jenner's experiment showed that if the human immune system was given time to prepare, it could produce weapons that could provide protection against an intruder it had never seen before. Importantly, the smallpox vaccination only protected against smallpox or closely related viruses such as cowpox. James Phipps was still able to get mumps, measles, and the rest. This is one of the hallmarks of the adaptive immune system: **It adapts to defend against specific invaders**.

Antibodies and B cells

Eventually, immunologists determined that immunity to smallpox was conferred by special proteins that circulated in the blood of immunized individuals. These proteins were named **antibodies**, and the agent that caused the antibodies to be made was called an **antigen** – in this case, the cowpox virus. Here's a sketch that shows the prototype antibody, **immunoglobulin G (IgG)**.



As you can see, an IgG antibody molecule is made up of two pairs of two different proteins, the **heavy chain (Hc)** and the **light chain (Lc)**. Because of this structure, each molecule has two identical "hands" (**Fab regions**) that can bind to antigens. Proteins are the ideal molecules to use for constructing antibodies that can grasp attackers because different proteins can fold up into a myriad of complex shapes.

IgG makes up about 75% of the antibodies in the blood, but there are four other **classes** of antibodies: **IgA**, **IgD**, **IgE**, and **IgM**. Each kind of antibody is produced by **B cells** – white blood cells that are born in the bone marrow, and which can mature to become antibody factories called **plasma B cells**.

In addition to having hands that can bind to an antigen, an antibody molecule also has a **constant region (Fc)** "tail" which can bind to receptors (**Fc receptors**) on the surface of cells such as macrophages. In fact, it is the special structure of the antibody Fc region that determines its class (e.g., IgG vs. IgA), which immune system cells it will bind to, and how it will function.

The hands of each antibody bind to a specific antigen (e.g., a protein on the surface of the smallpox virus), so in order to have antibodies available that can bind to many

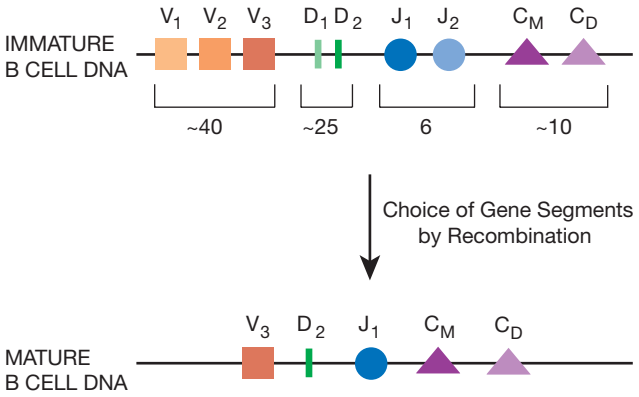
different antigens, many different antibody molecules are required. Now, if we want antibodies to protect us from every possible invader (and we do!), how many different antibodies would we need? Well, immunologists estimate that about 100 million should do the trick. Since each antigen-binding region of an antibody is composed of a heavy chain and a light chain, we could mix and match about 10,000 different heavy chains with 10,000 different light chains to get the 100 million different antibodies we need. However, human cells only have about 25,000 genes in all, so if each heavy or light chain protein were encoded by a different gene, most of a human's genetic information would be used up just to make antibodies. You see the problem.

Generating antibody diversity by modular design

The riddle of how B cells could produce the 100 million different antibodies required to protect us was solved in 1977 by Susumu Tonegawa, who received the Nobel Prize for his discovery. When Tonegawa started working on this problem, the dogma was that the DNA in every cell in the body was the same. This made perfect sense, because after an egg is fertilized, the DNA in the egg is copied. These copies are then passed down to the daughter cells, where they are copied again, and passed down to their daughters – and so on. Therefore, barring errors in copying, each of our cells should end up with the same DNA as the original, fertilized egg. Tonegawa, however, hypothesized that although this is probably true in general, there might be exceptions. His idea was that all of our B cells might start out with the same DNA, but that as these cells mature, the DNA that makes up the antibody genes might change – and these changes might be enough to generate the 100 million different antibodies we need.

Tonegawa decided to test this hypothesis by comparing the DNA sequence of the light chain from a mature B cell with the DNA sequence of the light chain from an immature B cell. Sure enough, he found that they were different, and that they were different in a very interesting way. What Tonegawa and others discovered was that the mature antibody genes are made by modular design.

In every B cell, on the chromosomes that encode the antibody heavy chain there are multiple copies of four types of DNA modules (**gene segments**) called V, D, J, and C. Each copy of a given module is slightly different from the other copies of that module. For example, in humans there are about 40 different V segments, about 25 different D segments, 6 different J segments, and so on. To assemble a mature heavy chain gene, each B cell chooses (more or less at random) one of each kind of gene segment, and pastes them together like this.



You have seen this kind of mix-and-match strategy used before to create diversity. For example, 20 different amino acids are mixed and matched to create the huge number of different proteins that our cells produce. And to create genetic diversity, the chromosomes you inherited from your mother and father are mixed and matched to make the set of chromosomes that goes into your egg or sperm cells. Once Mother Nature gets a good idea, she uses it over and over – and modular design is one of her very best ideas.

The DNA that encodes the light chain of the antibody molecule is also assembled by picking gene segments and pasting them together. Because there are so many different gene segments that can be mixed and matched, this scheme can be used to create about 10 million different antibodies – not quite enough. So, to make things even more diverse, when the gene segments are joined together, additional DNA bases are added or deleted. When this **junctional diversity** is included, there is no problem creating 100 million B cells, each with the ability to make a different antibody. The magic of this scheme is that by using modular design and junctional diversity, only a small amount of genetic information is required to create incredible antibody diversity.

Clonal selection

In the human blood stream there is a total of about three billion B cells. This seems like a lot, but if there are 100 million different kinds of B cells (to produce the 100 million different kinds of antibodies we need for protection), this means that, on average, there will only be about 30 B cells in the blood that can produce an antibody which will bind to a given antigen (e.g., a protein on the surface of a virus).