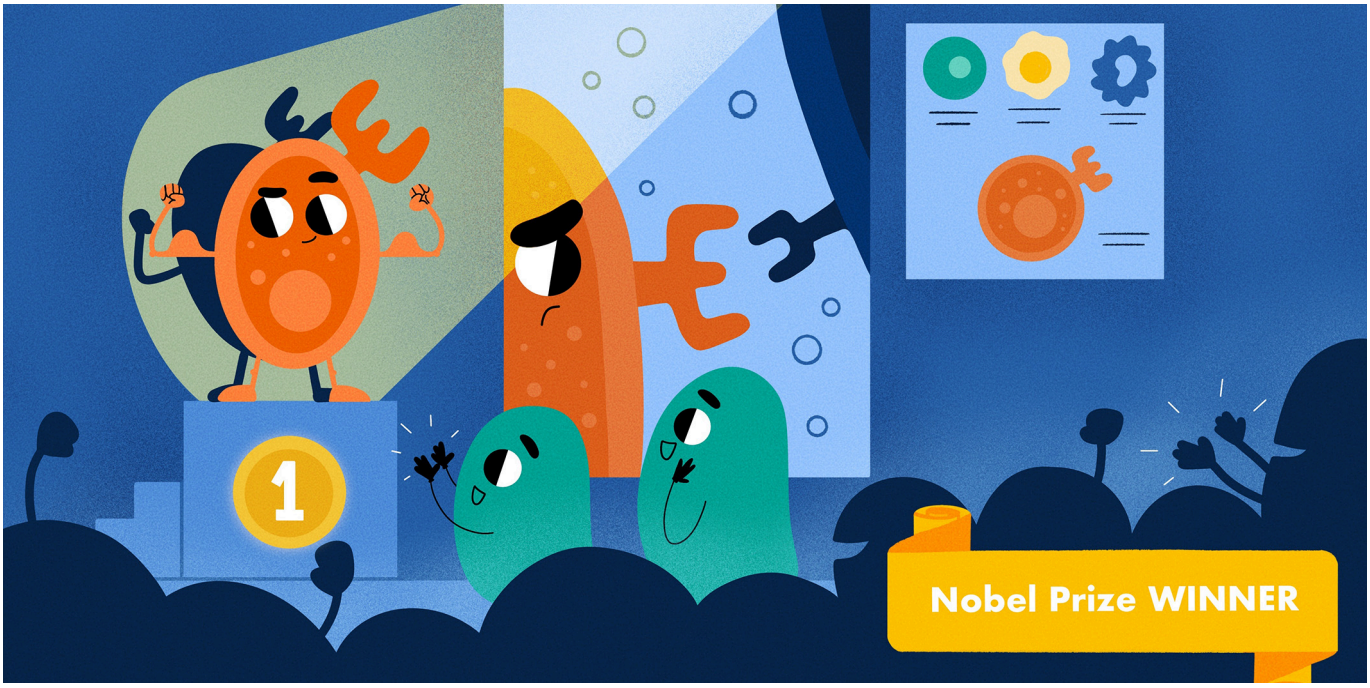
frontiers | Frontiers for Young Minds

HUMAN HEALTH
Published: 29 January 2024
doi: 10.3389/frym.2023.1145559



KILLER T CELLS: IMMUNE SYSTEM HEROES

Peter Doherty [1,2*] ***and Noa Segev*** [3*]

[1] *Department of Microbiology and Immunology, The University of Melbourne, Melbourne, VIC, Australia*
[2] *Emeritus, St. Jude Faculty, St. Jude Children's Research Hospital, Memphis, TN, United States*
[3] *Frontiers for Young Minds, Lausanne, Switzerland*

YOUNG REVIEWERS:

ARMAAN
AGE: 11

LOYOLA ELEMENTARY SCHOOL, MRS. RUBINSTEIN'S CLASS
AGES: 10–11

This article is based on an interview between the two authors.

The human body is like a jungle, with trillions of fascinating things happening inside it every second, most of which occur without our awareness. In this article, we will zoom in on a very interesting part of this jungle of human-body activities—the immune system. The immune system protects the body from intruders with its experts in martial arts, called killer T cells. Killer T cells are responsible for eliminating virus-infected cells so that the virus cannot reproduce itself and spread throughout the body. Join me for an adventurous journey into the immune system, in which we will find out how killer T cells know which cells to attack and which to leave alone.

Professor Peter Doherty won the Nobel Prize in Physiology or Medicine in 1996, jointly with Prof. Rolf Zinkernagel, for their discoveries concerning the specificity of cell-mediated immune defense.

THE BODY'S GUARDIAN CELLS

The **immune system** is one of the body's vital systems. It is made up of **white blood cells** and the substances they produce. The immune system is responsible for keeping us healthy by successfully fighting off infections (To learn more about the immune system, see the Additional Materials.). Viruses are one type of intruder that can invade the body and make people sick. Viruses are tiny particles that infect the cells of an organism, which is called the host. Viruses "trick" the host cells into making more copies of the virus. The infected cells usually die, releasing many newly made viruses that can spread throughout the body and infect more cells (To learn more about viruses, see this Nobel Collection article.).

The immune system has two main ways of dealing with viral infections. One strategy involves the production of **antibodies** [1]. Certain **lymphocytes**, called B cells, are responsible for antibody production. Antibodies bind to the virus and inactivate it before it can infect additional cells (Figure 1A). You can think of antibodies like a bunch of football players jumping on the opponent runner (the virus) to prevent the opponent from advancing with the ball.

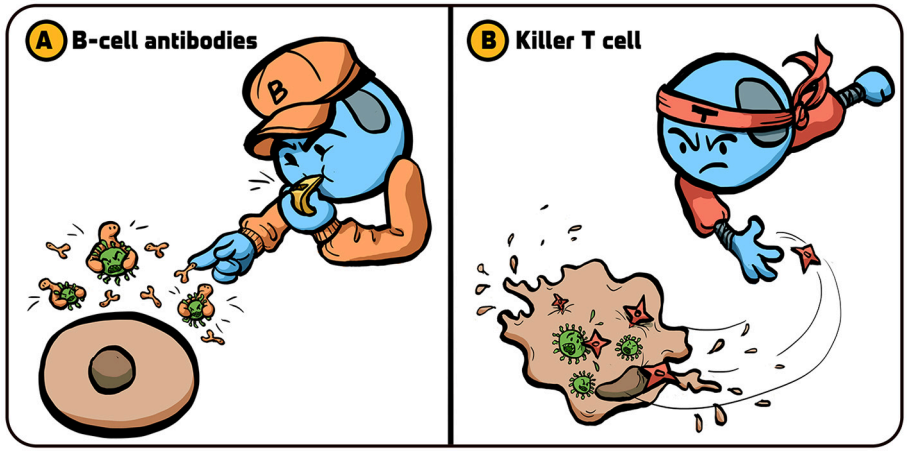


Figure 1

As another strategy, the immune system also kills cells that are infected with viruses (Figure 1B). This prevents infected cells from producing many copies of the virus. The lymphocytes that kill virus-infected cells are called **cytotoxic T lymphocytes**, or killer T cells for short [2]. When killer T cells encounter a virus-infected cell, they kill it by making channels in the cell membrane and triggering the infected cell to self-destruct, through a process called **apoptosis** (To learn more about apoptosis, read this article.).

IMMUNE SYSTEM

The defense system of the body that protects us against infections and certain diseases.

WHITE BLOOD CELLS

the main players in the immune system that help the body fight infections.

ANTIBODIES

Proteins that attach to viruses and inactivate them.

LYMPHOCYTES

White blood cells responsible for producing antibodies and killing infected cells. B cells and T cells are lymphocytes.

Figure 1

Strategies used by the immune system to fight viruses. The immune system has several strategies for dealing with viral infections. **(A)** B cells release proteins called antibodies (small "pliers") that attach to viruses (green) and prevent them from penetrating into the body's cells. **(B)** Killer T cells kill cells that are infected by viruses, preventing the production of new viruses that can infect additional cells. Illustration by: Iris Gat.

CYTOTOXIC T LYMPHOCYTES

Also called killer T cells; white blood cells that kill virus- infected cells.

APOPTOSIS

A "suicide" process of cells that gets rid of damaged or infected cells.

IS IT ME OR IS IT NOT ME?

The immune system uses extreme measures, like killing cells, to deal with potential hazards. How does the immune system know which structures to make antibodies against or which cells to kill? In other words, how does it eliminate infections without harming the body itself? Research has shown that this is a fine balance, and at the heart of it lies a fundamental question: what is me, or "self" (my own cells and molecules) vs. not-me, or "non-self" (intruders)? It is critical that the immune system answers this question correctly. If, on the one hand, the immune system does not recognize intruders well-enough, then the host remains unprotected against those threats. On the other hand, if the immune system mistakenly recognizes *the body's own cells* as intruders, it might attack the body and cause serious damage. Diseases resulting from a misguided immune system attacking the body are called **autoimmune diseases**, and many of them do not have effective treatments (Researchers are currently checking the possibility that the SARS-CoV-2 virus causing the COVID disease is triggering some rare form of autoimmunity in infected people. Such autoimmunity could be one possible cause of the long-COVID manifestations we are seeing.).

AUTOIMMUNE DISEASES

Diseases where the body is being attacked by its own immune system.

TWO RECEPTORS VERSUS ONE?

When I started working on killer T cells in the early 1970s, scientists did not yet understand how these lymphocytes could tell "self" from "non-self." After we discovered that killer T cells are in some way targeting "self" molecules (the transplant proteins recognized in organ graft rejections), most scientists thought that killer T cells had two different types of **receptors** (proteins that recognize specific molecules) on their surfaces: one type of receptor that could recognize "self" molecule and another type that could recognize foreign (virus), "non-self" molecules (Figure 2A). The idea was that that "self" molecules and "non-self" molecules are two distinctly different types of elements in the body, that require two different types of receptors to be recognized.

RECEPTOR

A protein on the surface of a cell that binds to a specific molecule that matches its shape, triggering a cellular response.

My colleague Rolf Zinkernagel and I argued that this was not the case—there is actually only *one* type of receptor on the killer T cell changes in "self" molecules (Figure 2B). This idea allowed a different interpretation of **immunology** which, as the technical approaches to answering the question improved, turned out to be right. Before I tell you how the recognition of dangerous invaders happens using only one receptor, let me tell you about some of the milestones that led us to this finding.

IMMUNOLOGY

The study of how the immune system functions.

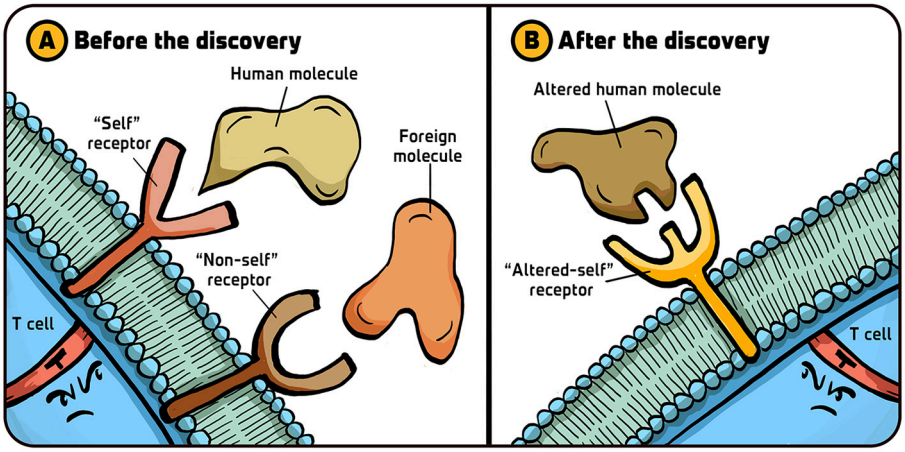


Figure 2

Figure 2

Killer T-cell receptor hypotheses. **(A)** Before our Nobel discovery linking killer T cell recognition to "self," the view that dominated the thinking of those working with "helper" $CD4^+$T cells was that these lymphocytes have two types of receptors on their surfaces—one that recognizes the body's molecules ("self") and another that recognizes foreign molecules ("non-self"). **(B)** After our discovery, it eventually became clear that all T cells have only one immunologically specific receptor, which recognizes changes in the body's molecules ("altered-self"). Illustration by: Iris Gat.

MY PERSONAL JOURNEY: FROM FEEDING THE WORLD TO DECIPHERING IMMUNE SECRETS

When I was 17 years old, I decided to study veterinary medicine. It was a strange decision because I was a city kid in Queensland, Australia. But I thought that learning veterinary medicine would be a great adventure, and that I could contribute to feeding the world by improving animal production. Today, due to climate change, we know that we will be better off, at least in the advanced countries, by focusing on plant products, but back then we had different ideas. During my Ph.D. studies, I became very interested in how infections cause diseases. So, I went on to study infections in sheep and cattle.

One of my early discoveries was made when I was studying a virus infection of the brains of sheep. At that time, scientists were just starting to understand the role of lymphocytes, but they did not yet understand the specific mechanisms by which those cells operate. In Edinburgh, Hugh Reid and I showed that antibody-producing B cells were present in the brains of the virus-infected sheep, and that those B cells were producing antibodies to fight the virus [3]. This was the first direct evidence that antibody-producing cells could be found in an infected tissue. This discovery inspired me very much, and I wanted to know more about what immune cells were doing in tissues.

While working on sheep in Edinburgh, I realized I need to know more about T cells, and arranged to spend a couple of years at the Australian National University in Canberra where there was a very active group of researchers in this area. The experimental system I chose was lymphocytic choriomeningitis (LCMV) infection of mice. From earlier studies, I adapted a technique to tap the cerebrospinal fluid compartment that bathes the brain to obtain the inflammatory WBCs, which were largely T cells that invade the brain and its surrounding membranes (the meninges) following LCMV infection. Then, a medical graduate from Basel University named Rolf Zinkernagel arrived in the

lab. Together, we conducted the experiments that, some 20 year later, won us the Nobel Prize in Physiology or Medicine.

ONE RECEPTOR RECOGNIZING ALTERED-SELF

Rolf and I did the following experiment: we infected laboratory mice with LCMV and, after a week (at the peak of their immune response), we collected the killer T cells the mice produced against LCMV (Figure 3). We placed these killer T cells in little tubes containing LCMV-infected mouse cells. The killer T cells came from LCMV-infected mouse strains that did, or did not, share the same transplantation molecules (called H2 in mice, HLA in humans) as the LCMV-infected 'target' cells. We found that the H2 identical, LCMV-immune T cells did a fantastic job of killing the H2 identical targets, while the H2 different killers totally ignored them. Based on these results, we hypothesized that a killer T cell has a *single receptor that recognizes altered-self (infected cells)* and developed a new theory of T cell immunology around that.

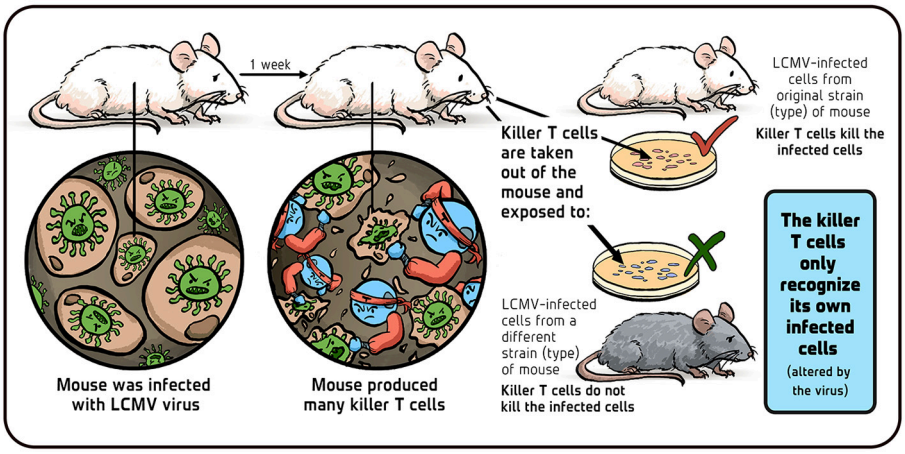


Figure 3

Do Killer T cells attack cells from different mouse strains? Illustration by: Iris Gat.

In other words, we assumed that the virus changes one of the normal self-molecules—molecules of non-infected cells, which are similar in genetically identical mice and different in genetically different mice. These self-molecules are always present on the surface of host cells and we figured that killer T cells spot this virus-induced change as a signal of infection and respond by killing the infected cell [4].

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

Self-molecules found on the surface of cells.

At that time, we did not have the experimental techniques to prove that our hypothesis was correct. But technological advances that happened in the next two decades allowed others to prove that we were right [5–8]. Using these new techniques, self- molecules called **major histocompatibility complex (MHC)** molecules were found on the surface of cells. When a virus invades a cell, the viral proteins get chopped up, and small virus fragments are displayed on the surface of

the cell, "held" by MHC molecules (Figure 4). Holding the piece of virus changes the shape of the MHC molecules, and this change in shape is what the killer T cells "see" and react to [9]. In other words, T cells recognize an infected, "altered-self" cell by the modified structure of its MHC molecules.

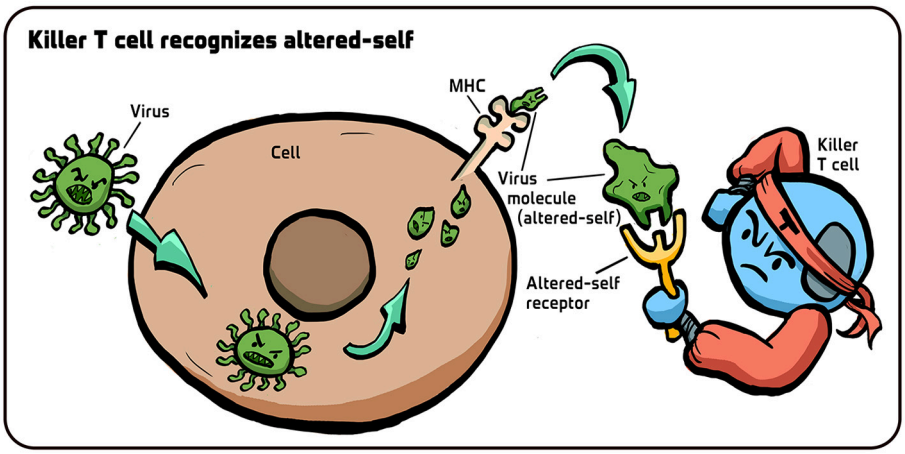


Figure 4

Figure 4

How do killer t cells recognize "altered-self"? When a virus infects a cell, its proteins are chopped up. Small pieces of the virus (small green structures) are then brought to the surface of the cell, held by MHC molecules. The presence of these virus chunks on MHC molecules changes the structure of the MHC molecule, and the receptors on killer T cells recognize this shape change ("altered-self"), thereby realizing that the cell is infected. Illustration by: Iris Gat.

When our theory proved to be correct, it caused a fundamental shift in our understanding of how T cells—one of the most important parts of the immune system—operate.

CAN OUR FINDINGS IMPROVE HUMAN HEALTH?

Our understanding of killer T cells could be helpful in several areas of medicine. First, this knowledge could help us to improve vaccines. Now that we know that the immune system recognizes pieces of viruses "held" by MHC molecules, we can hopefully make better vaccines by including a wide variety of pieces from the virus. The more different pieces a vaccine contains, the easier it is to trigger a strong killer T-cell response. COVID-19 vaccines, for example, only contain pieces of one protein (called the spike protein), while the virus has more than 20 different proteins that could potentially trigger killer T-cell responses.

I also focused a lot of my effort on understanding the nature of the protective, 'resting' memory T cells that are 'recalled' to being killer T cells on reinfection. Others worked out how to 'wake up' killer T cells that had localized to cancers but had apparently 'gone to sleep' (This is how certain anti-cancer treatments work, which you can learn more about here [10]). Other possible uses for this knowledge could involve new treatments for autoimmune diseases, in which we might find ways to restore balance to T cells and B cells that have gone astray and are attacking the body's own cells.

RECOMMENDATIONS FOR YOUNG MINDS

I think that scientific training is quite useful to have, even if you do not eventually become an active scientist. The reason is that, as a trained scientist, you learn how to think through a problem (Figure 5), how to deal with data, how to formulate an argument, and how to clearly write and convey your thoughts and ideas. These are important skills that can be helpful in many situations in life.

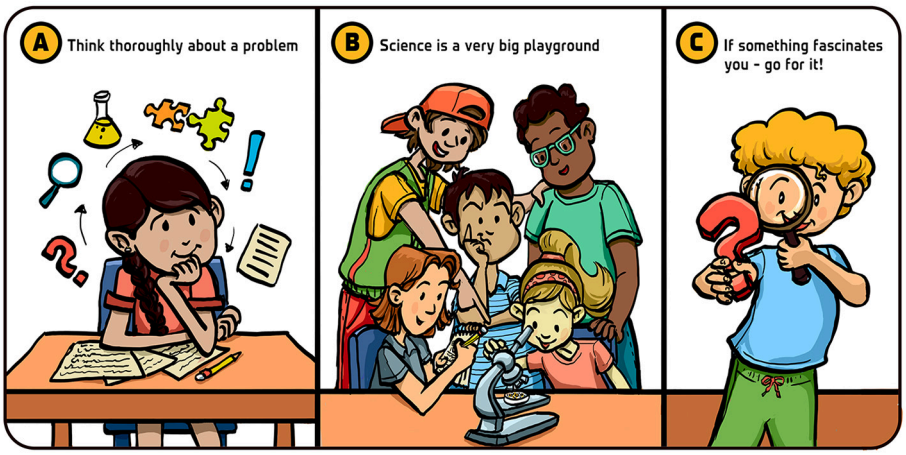


Figure 5

Figure 5

Three recommendations for Young Minds. **(A)** Think thoroughly about a problem. **(B)** Science is a very big playground. **(C)** If something fascinates you - go for it! Illustration by: Iris Gat.

If you *do* wish to become a scientist, and specifically a biologist, then I have some good news for you. First, there is still much more to discover in this field. Second, biology— especially biomedical research—offers great opportunities for many types of people with various skill sets and approaches. Some might have computer skills and want to set up systems that analyze and link data. Others might like to perform thought experiments and formulate new ideas and theories. People with good management or product-development skills can also flourish in biomedical research. It is a very big "playground" that holds space for many types of people. Those of you who enjoy connecting the dots in some way might especially enjoy a career in science.

The last thing I will tell you is: if something fascinates you—go for it! Dive into it as deeply as you can and do everything possible to pursue it. You will never know where your interests might lead you. During this voyage, you will gain unique ways of thinking that will serve you wherever you end up. So, instead of being discouraged by the uncertainty that life brings, be confident in your skills and trust that you will get a chance to use them in exciting ways.

ADDITIONAL MATERIALS

1. How the Innate Immune System Fights for Your Health

2. The Immune System, in Sickness & in Health—Part 1: Microbes and Vaccines
3. Types of immune responses: Innate and adaptive, humoral vs. cell-mediated | NCLEX-RN | Khan Academy
4. Doherty, P. (2006). The Beginner's Guide to Winning the Nobel Prize: Advice for Young Scientists. Columbia University Press.

ACKNOWLEDGMENTS

We wish to thank Prof. Steffen Jung for his valuable comments on the manuscript, Iris Gat for providing the figures, and Susan Debad for copyediting the manuscript.

REFERENCES

1. Johnson, A., Lewis, J., Raff, M., Roberts, K., and Walter, P. 2002. *Molecular Biology of the Cell*. New York, NY: Garland Science p. 4.
2. Andersen, M. H., Schrama, D., thor Straten, P., and Becker, J. C. 2006. Cytotoxic T cells. *J. Investig. Dermatol.* 126:32–41. doi: 10.1038/sj.jid.5700001
3. Doherty, P. C. 1970. *Studies in the experimental pathology of louping-ill encephalitis* (Doctoral dissertation). Edinburgh: University of Edinburgh.
4. Zinkernagel, R. M., and Doherty, P. C. 1979. MHC-restricted cytotoxic T cells: studies on the biological role of polymorphic major transplantation antigens determining T-cell restriction-specificity, function, and responsiveness. *Adv. Immunol.* 27:51–177. doi: 10.1016/S0065-2776(08)60262-X
5. Townsend, A. R. M., Rothbard, J., Gotch, F. M., Bahadur, G., Wraith, D., and McMichael, A. J. 1986. The epitopes of influenza nucleoprotein recognized by cytotoxic T lymphocytes can be defined with short synthetic peptides. *Cell* 44:959–68. doi: 10.1016/0092-8674(86)90019-X
6. Brown, J. H., Jardetzky, T., Saper, M. A., Samraoui, B., Bjorkman, P. J., and Wiley, D. C. 1988. A hypothetical model of the foreign antigen binding site of class II histocompatibility molecules. *Nature* 332:845–50. doi: 10.1038/332845a0
7. Garcia, K. C., Degano, M., Stanfield, R. L., Brunmark, A., Jackson, M. R., Peterson, P. A., et al. 1996. An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR-MHC complex. *Science* 274:209–19. doi: 10.1126/science.274.5285.209
8. Garboczi, D. N., Ghosh, P., Utz, U., Fan, Q. R., Biddison, W. E., and Wiley, D. C. 1996. Structure of the complex between human T-cell receptor, viral peptide and HLA-A2. *Nature* 384:134–41. doi: 10.1038/384134a0
9. Wieczorek, M., Abualrous, E. T., Sticht, J., Álvaro-Benito, M., Stolzenberg, S., Noé, F., et al. 2017. Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation. *Front. Immunol.* 8:292. doi: 10.3389/fimmu.2017.00292
10. Leach, D. R., Krummel, M. F., and Allison, J. P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 271:1734–6. doi: 10.1126/science.271.5256.1734

SUBMITTED: 16 January 2023; **ACCEPTED:** 13 April 2023;
PUBLISHED ONLINE: 29 January 2024.

EDITOR: Bob Knight, University of Southern California, Los Angeles, United States

SCIENCE MENTORS: Dr. Kawaljit Kaur and Linda Yip

CITATION: Doherty P and Segev N (2024) Killer T Cells: Immune System Heroes. Front. Young Minds 11:1145559. doi: 10.3389/frym.2023.1145559

CONFLICT OF INTEREST: The author NS declared that they were an employee of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.
The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ARMAAN, AGE: 11
Armaan is a 6th grader who is a wrestler. His hobbies are video gaming, baking, and wrestling. He also plays basketball. He loves reading and exploring concepts behind science, especially health and disease-related which incites his love for reading more about immune cells.

LOYOLA ELEMENTARY SCHOOL, MRS. RUBINSTEIN'S CLASS, AGES: 10–11
5th graders at Loyola Elementary School never let an opportunity pass them by when it comes to gaining knowledge. Our class took the challenge to read and review an article for Frontiers for Young Minds, which was exciting for all of us to participate in. The article was unique in its timeliness as it was about Killer T-cells and we are just moving past the COVID pandemic. Our school is situated in a little pocket of Silicon Valley with beautiful vistas of the nearby foothills.

AUTHORS

PETER DOHERTY
Prof. Doherty is an Australian immunologist. He studied veterinary medicine and earned his bachelor's and master's degrees at the University of Queensland (Queensland, Australia). During his doctoral studies at the University of Edinburgh (Edinburgh, Scotland), Prof. Doherty studied pathology. He then conducted research at the John Curtin School of Medical Research in Canberra (Australia), where he met

Rolf Zinkernagel. Together, they studied the role of T cells in mice infected with a certain type of virus. This collaborative study led Profs. Doherty and Zinkernagel to discover how T cells distinguish between normal, healthy cells and virus-infected cells. This was a great breakthrough in understanding how the immune system functions, and for this they were awarded the Nobel Prize in Physiology or Medicine (1996). Prof. Doherty is the head of the Peter Doherty Institute for Infection and Immunity, a joint venture between the University of Melbourne and the Royal Melbourne Hospital. Prof. Doherty has won numerous prestigious awards, including the Paul Ehrlich Prize (1983), the Gairdner Foundation International Award (1986), and the Albert Lasker Basic Medical Research Award (1995). He has been awarded more than 20 honorary doctorates and has published some 500 research papers and reviews. He received a Companion of the Order of Australia in 1997, is listed as a living National Treasure and his face appears on a postage stamp. Alongside his scientific career, Prof. Doherty has been deeply involved in science communication and has written several popular science books, including *The Beginners Guide to Winning the Nobel Prize* (2005); *Pandemics: What Everyone Needs to Know* (2013); *The Knowledge Wars* (2015); and *An Insider's Plague Year* (2021). In recent years, Prof. Doherty has also been interested in the science of climate change. He currently lives with his wife Penny in Melbourne, Australia. They have two sons, Michael and James, and six grandchildren. *pcd@unimelb.edu.au

NOA SEGEV

Noa Segev is a scientific writer and project coordinator at Frontiers for Young Minds. She earned her B.Sc. in physics at The Hebrew University of Jerusalem and her M.E. in renewable energy engineering at the Technion-Israel Institute of Technology. Since 2019, she has been interviewing Nobel Prize winners and co-authoring articles for the Nobel Collection at Frontiers for Young Minds. Noa aims to make the science behind Nobel Prize-winning discoveries accessible to all, and to share valuable insights from the vast professional and personal experience of Nobel Laureates. *noasegev@gmail.com