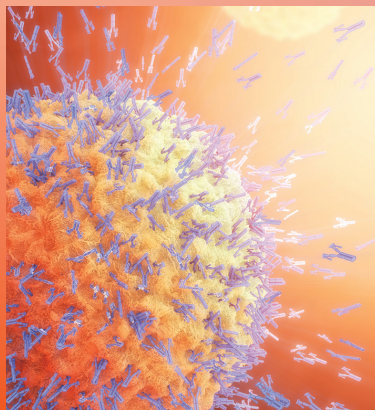
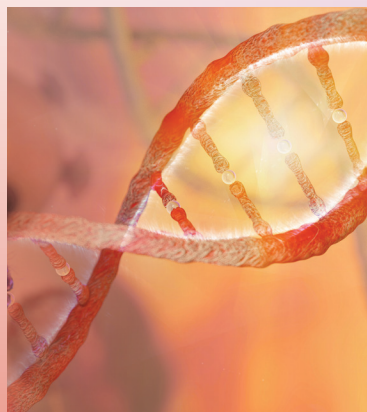
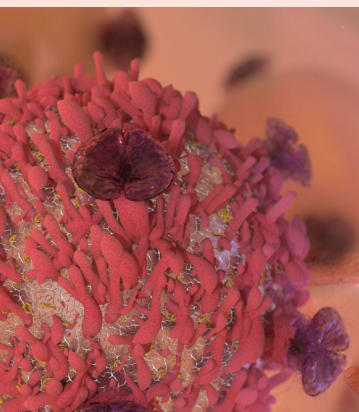


MULTIPLE MYELOMA IMMUNOTHERAPY



MULTIPLE MYELOMA
Research Foundation

themmrf.org

ABOUT THE MULTIPLE MYELOMA RESEARCH FOUNDATION

The Multiple Myeloma Research Foundation (MMRF) was established in 1998 by identical twin sisters Kathy Giusti and Karen Andrews shortly after Kathy's diagnosis with multiple myeloma. Kathy and Karen soon learned that little progress against this disease had been made in decades and that myeloma patients had few treatment options. They decided that it was time to accelerate change. Their mission was to ensure more access to better treatments and bring the promise of a cure for every myeloma patient.

Since its founding, the MMRF has remained steadfast in the pursuit of its mission. It is now the leading cancer research organization focused on the development and delivery of more precise therapies, and it is aggressively pursuing a world without myeloma. Working with its partners in industry, research, government, and academia, the MMRF has helped launch 15 new drugs in the past 18 years, an achievement that has almost tripled the life expectancy for myeloma patients. The MMRF is a patient-focused organization that stands with the entire myeloma community and is speeding the discovery of cures through precision medicine. Driven by data and innovative research, the MMRF is committed to empowering every patient with precisely what he or she needs to prevent or defeat multiple myeloma.

As the multiple myeloma community's most trusted source of information, the MMRF supports patients from the time of diagnosis throughout the course of the disease. All information on the MMRF website (www.themmr.org) is organized by disease stage, so patients can get the information they need, when they need it.

To learn more about the MMRF, visit www.themmr.org.

To speak to a Patient Navigator at the Patient Navigation Center, call **1-888-841-MMRF (6673)** or email patientnavigator@themmr.org.

Updates to and distribution of this booklet were supported by Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, CURE Magazine, Genentech, GlaxoSmithKline, Karyopharm Therapeutics, Oncopeptides, and Takeda Oncology.

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INTRODUCTION

Multiple myeloma is a cancer of the blood cells (specifically, **white blood cells**, which are one of several types of **B cells**). Blood cells are formed in the bone marrow (the soft, spongy tissue located inside the long bones of your body). Myeloma cells grow and crowd out the normal blood cells in the bone marrow, and a consequence of this is a reduction in normal white blood cells. Having a reduced number of white blood cells in your body makes infections harder to fight off.

Some multiple myeloma therapies, such as the immunomodulatory drugs (IMiDs), work against myeloma cells partly by supporting the function of a patient's **immune system**. The use of a patient's immune system to fight cancer—cancer **immunotherapy**—is an exciting area of multiple myeloma research. For myeloma immunotherapy treatments to work, they must be designed to recognize myeloma cells. This has long been a challenge, because myeloma cells—like all cancer cells—have the ability to hide from the body's normal **immune response**. Myeloma cells also have the ability to weaken the body's immune response to such an extent that they can continue to grow and thrive in a patient. Restoring the immune protection lost to myeloma is believed to be an important potential pathway to new levels of treatment success. Fortunately, there are many types of immunotherapies that can rev up or improve a patient's immune response, including:

- **Antibody**-based treatments
- Cell-based treatments, such as immune cells from the patient or a transplant donor
- **Cancer vaccines**

This booklet is designed to help patients with multiple myeloma—as well as their friends, families, and caregivers—better understand the concept and the promise of immunotherapy. Words that may be unfamiliar are **bolded** and defined in the Glossary (page 11).

The information in this booklet is not intended to replace the services or advice of trained health care professionals. Please consult with your health care professional regarding specific questions relating to your health, especially questions about myeloma diagnosis or treatment.

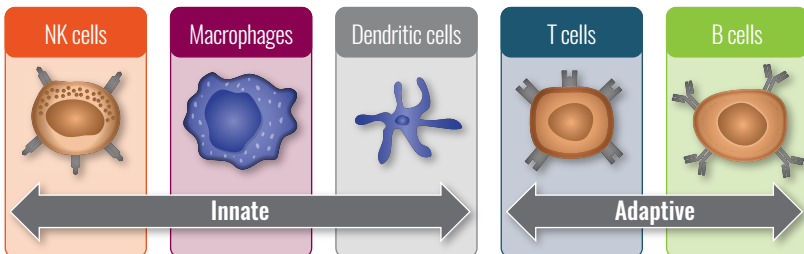
THE IMMUNE SYSTEM

Understanding immunotherapy starts with understanding the immune system. The immune system is made up of certain cells that protect the body from foreign invaders (**Figure 1**). These cells act as the body's army, working to defend against various germs (such as bacteria, viruses, fungi, and parasites) that are present in the environment and can cause infections, illness, or diseases. The cells of the immune system also protect the body against cancer cells.

The immune system is divided into two distinct phases:

1. Phase 1, or **innate immunity**, is made up of cells like **macrophages**, **natural killer (NK) cells**, and **dendritic cells**. Like an army infantry, these cells stand ready to immediately fight off an attack—they are the immune system's first responders. These cells patrol throughout the body, quickly sensing the presence of germs or cancer cells and rallying the rest of the immune system to handle the invader.
2. Phase 2, or **adaptive immunity**, is made up of special cells called **lymphocytes (T cells and B cells)**. These cells are like a special army task force; they take time to train for a specific mission—seeking out and attacking particular targets. Once these cells detect the invader they have been trained to recognize, they rapidly increase in number—expanding to create a large platoon of cells that can attack. These cells provide long-lasting protection even after the invader is eliminated, because the encounter with the invader enables them to recognize and respond to that invader more readily and rapidly when it is encountered again.

Figure 1. The immune system.



For more information about multiple myeloma and its treatment, please refer to the companion booklets *Multiple Myeloma Disease Overview*, *Multiple Myeloma Treatment Overview*, *Autologous Stem Cell Transplantation*, and *The Path to Precision Medicine*— and also the MMRF website, www.themmr.org.

If the immune system is primed and ready to attack and kill foreign invaders, why do cancers—like multiple myeloma—still grow and survive? There are a number of reasons why the immune system is ineffective against myeloma.

- Myeloma cells arise from normal **plasma cells** and therefore they may not look like invaders.
- Myeloma cells can fool the immune system by disguising themselves in a way that lets them go unnoticed by immune cells.
- They can actively resist the immune system—myeloma cells are able to produce substances that inactivate existing immune cells.

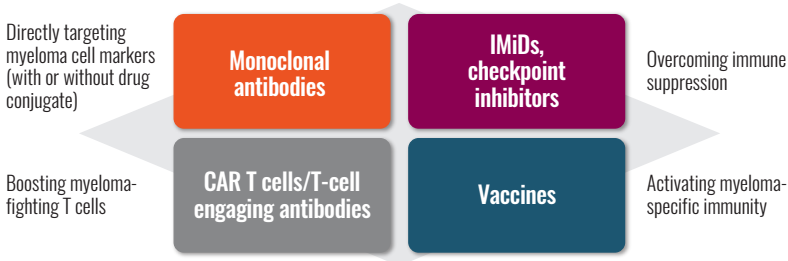
Immunotherapy is a therapeutic strategy that is specifically designed to overcome these defensive tactics used by myeloma cells.

TYPES OF IMMUNOTHERAPY

The excitement that immunotherapy brings to the myeloma community is its unique approach to treatment—immunotherapy works in a manner that is completely different from conventional myeloma therapies, such as **chemotherapy**. In general, immunotherapy selectively targets myeloma cells. Activated immune cells that are programmed to recognize and remember myeloma cells circulate throughout the body, inducing a long-term response to therapy and helping to hold off a myeloma relapse.

There are four main types of immunotherapy currently being used or studied in patients with multiple myeloma (**Figure 2**).

Figure 2. Types of immunotherapy.



Reproduced from Rodriguez-Otero P et al. Is immunotherapy here to stay in multiple myeloma? *Haematologica*. 2017 Mar;102(3):423-432. Used with permission of the Ferrara Storti Foundation.

MONOCLONAL ANTIBODIES

A **monoclonal antibody** is produced in a laboratory and engineered to bind to a specific protein found on the surface of a myeloma cell. In antibody therapy, monoclonal antibodies are injected or infused into the body to attack the myeloma cells. Several different types of monoclonal antibodies are used in antibody therapy. The different types are:

1. **Naked antibodies**
2. **Antibody–drug conjugates (ADCs)**
3. **Bispecific antibodies or bispecific T-cell engagers (BiTEs)**

When used on their own as a therapy, monoclonal antibodies are referred to as naked antibodies. As noted, naked antibodies recognize and target a specific protein on the surface of myeloma cells, which enables them to help the patient's immune system identify and eliminate the targeted myeloma cells. Darzalex (daratumumab), Sarclisa (isatuximab), and Emluciti (elotuzumab) are naked antibodies that are currently approved for use in patients with multiple myeloma. Darzalex and Sarclisa target a protein called CD38 that is found on the surface of myeloma cells (**Table 1**). Emluciti works in two ways. Like Darzalex and Sarclisa, it targets and binds to a protein found on the surface of myeloma cells (in this case, a protein called SLAMF7). However, Emluciti also activates a particular group of cells of the immune system—the NK cells. These activated NK cells seek out and destroy myeloma cells.

A separate class of naked antibodies called **checkpoint inhibitors** works slightly differently. Instead of simply flagging myeloma cells for destruction, checkpoint inhibitors release the hold on T cells that have been “turned off” by myeloma cells. Checkpoint inhibitors interfere with cell surface proteins that enable a myeloma cell to avoid the immune system; by blocking these proteins, the “brakes” on the immune system are released and the T cells are able to kill myeloma cells. Checkpoint inhibitors (such as pembrolizumab and nivolumab) have been used successfully in patients with solid tumors but are not approved for use in patients with multiple myeloma.

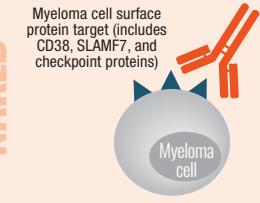
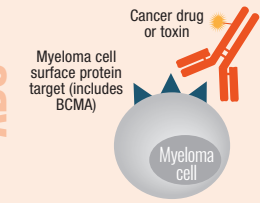
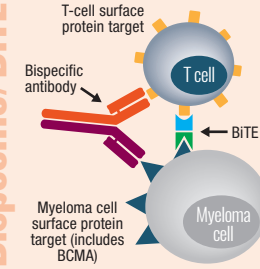
Another type of antibody-based treatment uses a monoclonal antibody that is coupled to a cancer drug or a **toxin**; this type of agent is called an antibody–drug conjugate or ADC. The antibody part of the conjugate binds to a myeloma cell—just as naked antibodies do—and the attached cancer drug kills the myeloma cell. Blenrep (belantamab mafodotin) is an ADC approved for use in patients with multiple myeloma; it targets a protein called **B-cell maturation antigen (BCMA)**. Several other anti-BCMA ADCs are in **clinical trials** for treatment of myeloma.

BCMA is a unique cell surface protein that is found on all myeloma cells, making it an attractive target for drug therapy. Many immunotherapies in development for multiple myeloma target the BCMA protein, including ADCs, BiTEs, and CAR T-cells.

Other antibody-based therapies being studied in myeloma are bispecific antibodies and bispecific T-cell engagers or BiTEs. Bispecific antibodies are made from pieces of two different antibodies that have been fused together. BiTEs, on the other hand, are made from two antibody fragments that have been fused together.

Bispecific antibodies and BiTEs work in the same way: one part targets myeloma cells, making them easier for the immune system to find, and the other part helps immune cells by boosting their ability to find myeloma cells. Several of the bispecific antibodies and BiTEs currently in clinical trials target BCMA (other bispecific antibodies and BiTEs target different surface proteins) and bind to a protein called CD3 that is found on the surface of T cells.

Table 1. Types of monoclonal antibodies and T-cell engagers.

	Type of antibody	Myeloma cell surface protein	Targeted antibody
NAKED	 <p>Myeloma cell surface protein target (includes CD38, SLAMF7, and checkpoint proteins)</p> <p>Myeloma cell</p>	CD38	<ul style="list-style-type: none"> • Darzalex (daratumumab) • Sarclisa (isatuximab)
		SLAMF7	<ul style="list-style-type: none"> • Emlipiciti (elotuzumab)
ADC	 <p>Myeloma cell surface protein target (includes BCMA)</p> <p>Myeloma cell</p> <p>Cancer drug or toxin</p>	BCMA	<ul style="list-style-type: none"> • Blenrep (belantamab mafodotin) • CC-99712 • MEDI2228
Bispecific/BiTE	 <p>T-cell surface protein target</p> <p>T cell</p> <p>Bispecific antibody</p> <p>Myeloma cell surface protein target (includes BCMA)</p> <p>Myeloma cell</p> <p>BiTE</p>	BCMA	<ul style="list-style-type: none"> • AMG701 • CC-93269 • Cevostamab • REGN5458 • Teclistamab • Talquetamab

Adapted from *Cancer Res* 2009 Jun 15;69(12):4941-4944, Baeuerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy, with permission from AACR.

CAR T-CELL THERAPY

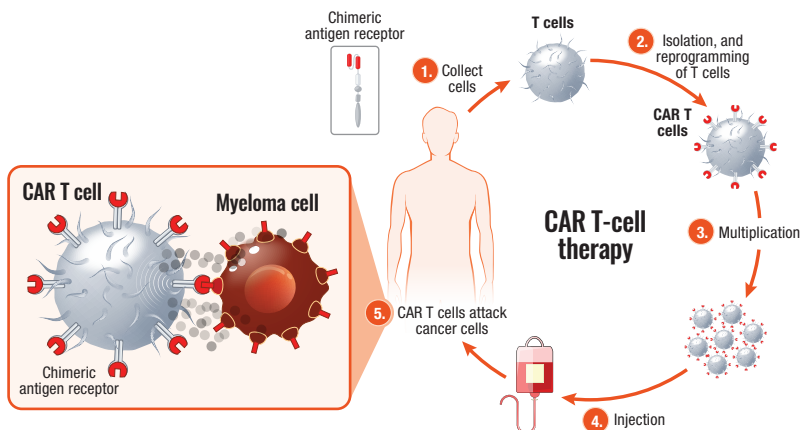
Immune cell therapy—also known as cell-based therapy, cellular therapy, or adoptive cell therapy—is the process of collecting a patient’s own immune cells (mostly T cells), engineering them in a lab so they are better able to identify and attack myeloma cells, and then returning them to the patient.

One form of cellular therapy called **chimeric antigen receptor (CAR) T-cell therapy** is capturing headlines because of its ability to induce responses in most patients—even those who have relapsed from many prior therapies (**Figure 3**). CAR T-cell therapy has already been approved for patients with certain types of leukemia and lymphoma, and in 2021 the first CAR T-cell therapy, Abecma (idecabtagene vicleuce), was approved for patients with myeloma.

In CAR T-cell therapy, the immune cells that are removed from the patient, engineered, and returned to the patient are white blood cells (which includes T cells). The process is similar to the procedure (**stem cell harvest**) performed before an **autologous stem cell transplant (ASCT)**. T cells, which circulate through the body, are important in fighting infections and searching the body for cancer. When cancer cells are detected, T cells kill them by grabbing onto and pumping toxins into them.

Cancer cells have found ways to “hide” from T cells. In CAR T-cell therapy, however, regular/normal T cells are “supercharged,” which helps them see myeloma cells—even when they’re hiding. The process of supercharging the T cells involves collecting them from a myeloma patient, making genetic changes to them in a lab (turning them into more effective myeloma detectors and killers!), and then re-infusing them into the patient. Once back inside the patient, the improved T cells (that is, the CAR T cells) resume their search-and-destroy mission against myeloma cells.

Figure 3. Chimeric antigen receptor (CAR) T-cell therapy.



Most of the cells used in the CAR T-cell therapies being studied have been genetically changed to latch onto a specific protein—BCMA—found on the surface of most myeloma cells.

In clinical trials, all the BCMA-modified CAR T-cell therapies being studied in myeloma patients have produced high response rates; that is, most patients respond to the treatment. However, many patients have been found to experience a common side effect called **cytokine release syndrome (CRS)**,

which is an infection-like syndrome in which a patient experiences fevers, chills, and low blood pressure after the infusion of CAR T cells. The cause of CRS is thought to be from the growth of the CAR T cells and the resulting surge in the immune response, which is mainly driven by a **cytokine** (a protein produced by immune cells) called interleukin-6 (IL-6). Fortunately, there is a drug called tocilizumab that interferes with IL-6 and can stop CRS.

Some patients treated with CAR T cells have had nervous system side effects, which are referred to as **immune effector cell-associated neurotoxicity syndrome (ICANS)**. Most patients experience mild symptoms like confusion, but in some cases patients experience severe symptoms like delirium or seizures. These side effects were less common—and less understood—than CRS, and most resolved over time. However, these nervous system side effects remain an issue and are under study.

In early clinical trials, CAR T-cell therapy has shown encouraging responses. Abecma (idecabtagene vicleucel) was approved for patients with relapsed/refractory myeloma. Many studies are ongoing, as researchers compare different agents in an attempt to determine how long responses last, the maximum number of cells that need to be infused into patients, and whether certain agents are associated with less CRS and fewer nervous system side effects.

BCMA-modified CAR T-cell therapy agents in development:

- Abecma (idecabtagene vicleucel [ide-cel]), approved for use
- ciltacabtagene autoleucel (cilta-cel), phase 3
- P-BCMA-101, phase 2
- bb21217, phase 1
- ALLO-715, phase 1



Though immunotherapy as a treatment option is an exciting and fast-developing area of myeloma management, most immunotherapies are not approved for use in myeloma patients and not all experimental immunotherapies are appropriate for all myeloma patients—talk with your health care team about your disease and what options are best for your care.

VACCINES

In contrast to vaccines for infectious diseases (like the flu or pneumonia), which are preventive, cancer vaccines are typically therapeutic (that is, used as a treatment). Therefore, the basic principle in myeloma vaccination is to enhance the natural anti-myeloma activity of the immune system to rev up or improve a patient's immune response.

Myeloma vaccines are typically considered therapeutic, NOT preventive like infectious disease vaccines.

In multiple myeloma, vaccines are generally believed to be most effective when used in combination with other effective immunotherapies. The premise is that myeloma vaccines may increase the chance that the patient will respond to the immunotherapy and may help the response to last longer. Vaccine therapy is a newer myeloma management strategy, and it has received particular attention for patients undergoing ASCT. However, vaccines are not yet approved for use in myeloma patients and clinical trials are ongoing using vaccines during the recovery period after the transplant to determine whether vaccines that prime a patient's immune system are effective to quickly and powerfully attack myeloma cells if the disease recurs. One early cell-based myeloma vaccine approach was shown to improve complete response rates after ASCT. Additional studies of vaccines combined with other immunotherapies such as checkpoint inhibitors are also continuing.

The MMRF would like to thank Jesus G. Berdeja, MD, Director of Multiple Myeloma Research and Senior Investigator, Hematologic Malignancies at the Sarah Cannon Research Institute in Nashville, Tennessee, and our patient advocate Mary Elizabeth Graft of Scottsdale, Arizona, for their contributions to this booklet.

MMRF PATIENT SUPPORT AND RESOURCES

The MMRF is dedicated to supporting the myeloma community by providing a broad range of resources for myeloma patients and their family members and caregivers. The MMRF is available to help guide you through your multiple myeloma journey every step of the way.



YOUR QUESTIONS ANSWERED

Speak to an MMRF Patient Navigator at the Patient Navigation Center for answers to your questions about disease management, treatments, clinical trials, and assistance with finding financial and other available resources.

Telephone: 1.888.841.6673

Monday–Friday, 9:00 AM to 7:00 PM ET

Email: patientnavigator@themmrf.org

Connect with an MMRF Myeloma Mentor™:

themmrf.org/resources/myeloma-mentors

This is a phone-based program offering the opportunity for patients and/or caregivers to connect one-on-one with a trained patient and/or caregiver mentor to share their patient journeys and experiences.

FIND AND PARTICIPATE IN A CLINICAL TRIAL

Search for a clinical trial in your area or let MMRF Patient Navigator help guide you through the process.

Clinical Trial Search: themmrf.org/resources/clinical-trial-finder

SUPPORT THE MMRF

Help support the MMRF's efforts to accelerate research and find a cure! Participate in an event or donate today.

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GLOSSARY

adaptive immunity The part of the immune system that is composed of highly specialized cells designed to recognize foreign invaders and attack them any time they enter the body

antibody Protein produced by plasma cells that helps protect the body from infection and disease (also called *immunoglobulin*; see also *monoclonal antibody*)

antibody-drug conjugate (ADC) A monoclonal antibody that is coupled to an anti-tumor drug (such as a toxin, a radioactive isotope, or a drug)

autologous stem cell transplant (ASCT) Procedure in which stem cells collected from a patient are transplanted back into that patient; the most common type of transplant performed in myeloma

B cell (or B lymphocyte) White blood cell that gives rise to a plasma cell (plasma cells produce antibodies, which fight infections)

B-cell maturation antigen (BCMA) A protein found on the surface of myeloma cells

bispecific antibody A monoclonal antibody that can simultaneously bind to two different cell surface proteins

bispecific T-cell engager (BiTE) An engineered anti-myeloma agent created by fusing two antibody fragments together; one antibody fragment binds to surface proteins on myeloma cells and the other binds to a protein found on the surface of immune cells

cancer vaccine A cell-based or protein-based immunotherapy in which cancer cells (such as myeloma cells) are mixed with immune-stimulating agents or engineered and injected into a patient to boost the immune response

checkpoint inhibitor A naked antibody that interferes with proteins that enable a cancer cell to hide from, overpower, or resist the immune system; by blocking these proteins, the “brakes” on the immune system are released and immune cells are able to kill cancer cells

chemotherapy The use of drugs to kill rapidly dividing cancer cells

chimeric antigen receptor T (CAR-T) cell therapy A form of immunotherapy in which a patient’s immune cells (mostly T cells) are collected, engineered in a lab to be better able to identify and attack myeloma cells, and then returned to the patient

clinical trial A study of the safety and effectiveness of a therapeutic agent using consenting human subjects

cytokine A protein produced and secreted by cells of the immune system (for example, interleukins)

cytokine release syndrome (CRS) A common, infection-like side effect following infusion of CAR T cells in which a patient experiences fevers, chills, and low blood pressure

dendritic cell A special type of immune cell that is found in tissues (such as the skin) and that boosts immune responses by showing parts of proteins on its surface to other cells of the immune system

immune effector cell-associated neurotoxicity syndrome (ICANS) Common side effect of the nervous system observed after CAR T-cell treatment that can include confusion or delirium, expressive aphasia, motor weakness, tremor, headache, seizures, and reduced level of consciousness

immune response Reaction of the cells and fluids of the body against a substance or agent (for example, bacteria, a virus, or a foreign cell) that is not recognized as part of the body

immune system Network of cells that protect the body from foreign substances and destroys infected and cancerous cells

immunoglobulin (Ig) Protein that helps protect the body from infection (also called *antibody*)

immunotherapy Prevention or treatment of disease with drugs that stimulate the immune system

innate immunity The nonspecific, rapid immune response that acts as the first line of defense against disease and aids in activating adaptive immunity

lymphocyte A type of immune cell made up of two main types, B cells and T cells

macrophage A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells

monoclonal antibody Antibody produced in a laboratory that is used to diagnose and treat some diseases

naked antibody A monoclonal antibody that can bind to a cell surface protein and that has no drug or toxin attached

natural killer (NK) cell A type of white blood cell that has granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus

plasma cell Antibody-secreting immune cell that develops from a B cell; in myeloma, it is this cell that has become cancerous or abnormal

stem cell Cell that grows and divides to produce red blood cells, white blood cells, and platelets; found in bone marrow and blood

T cell (or T lymphocyte) A type of white blood cell that can be subdivided into two groups, helper and cytotoxic T cells; helper T cells are responsible for *adaptive immunity*; cytotoxic T cells are killers of cells that have been targeted for death

toxin A poisonous substance

white blood cell One of the major cell types in the blood; attacks infection and cancer cells as part of the immune system



MMRF RESOURCES IN PERSON OR ONLINE



Attend a Multiple Myeloma Patient Summit

Learn about standard and emerging therapies including stem cell transplants, promising clinical trials, and more for optimal disease management. Attend a complimentary symposium for all the information you need to make well-informed decisions about your treatment and care.

To register or to view the complete calendar, visit:
themmrf.org/resources/education-programs



View Past Programs on Demand

Access our archive of recorded Patient Summit symposia and webcasts. Hear expert perspectives on key clinical research and the rapidly evolving myeloma treatment landscape.

All available online, and free, at:
themmrf.org/resources/education-programs



Find a Clinical Trial Near You

Clinical trials are critically important to developing new myeloma treatments and better understanding the biology of the disease. The more people who enroll, the faster we can find answers. Patients who enroll in clinical trials have the opportunity to be among the first to receive the newest drugs or drug combinations in development and receive close monitoring.

To find a clinical trial near you, visit:
themmrf.org/resources/clinical-trial-finder

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