CAR T 101: CAR T Cell Science

Bristol Myers Squibb™

CAR T Academy: CAR T 101 – CAR T Cell Science

01: IMMUNITY AND HEMATOLOGIC MALIGNANCIES

02: INTRODUCTION TO THE CAR T CELL

03: CAR T CELL TARGETS

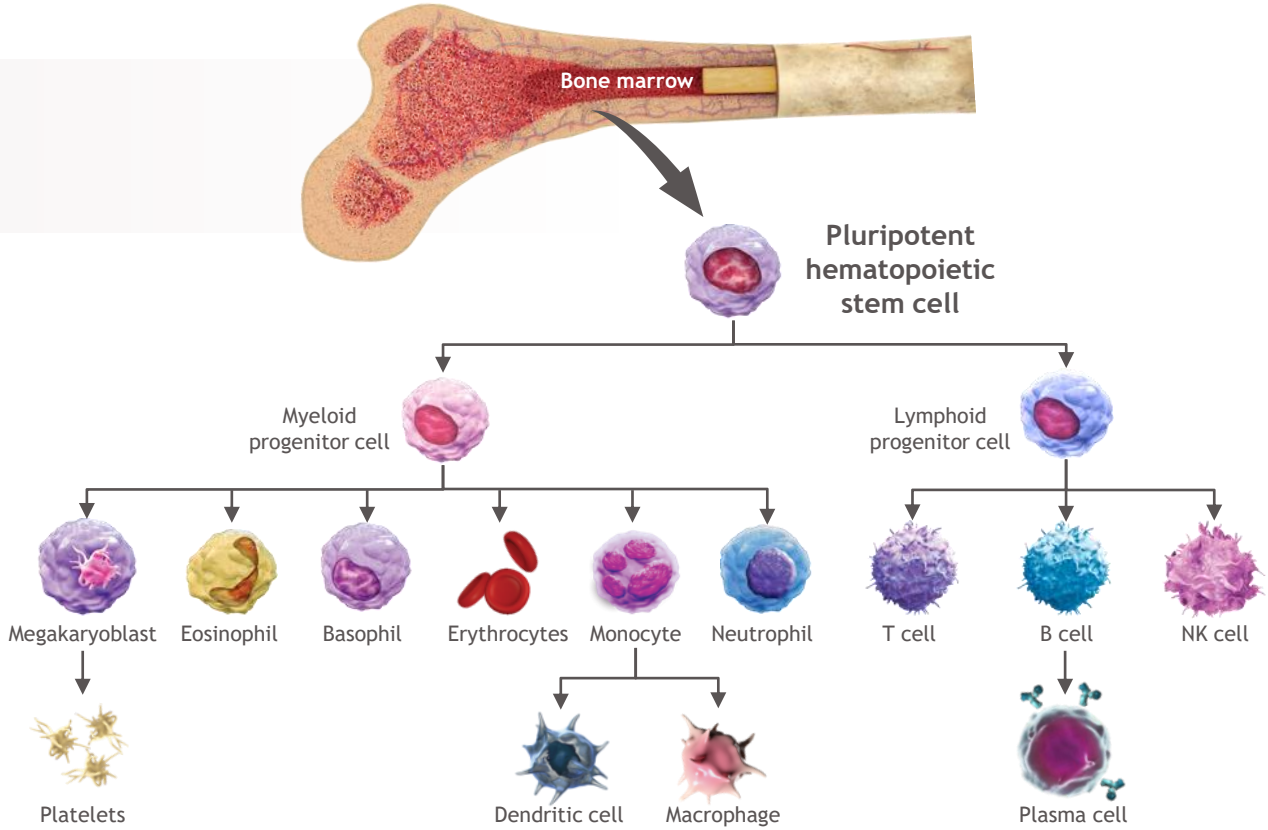
Blood Cells Are Formed Through a Process Known as Hematopoiesis

Hematopoietic stem cells produce all blood cells.
This process is known as hematopoiesis

Hematopoietic stem cells generate **two lineages of blood cells** through distinct progenitors, known as **myeloid** and **lymphoid progenitor cells**

Both myeloid and lymphoid progenitor cells give rise to important components of the immune system

- A lymphoid progenitor can differentiate into 3 types of lymphocytes. These include T cells, B cells, and natural killer (NK) cells
- The myeloid progenitor can differentiate into all other blood cells, including red blood cells



Reference: Betts JG, et al. *Anatomy & Physiology*. 2nd ed. OpenStax, Rice University; 2017. Accessed June 23, 2023. https://openstax.org/details/books/anatomy-and-physiology

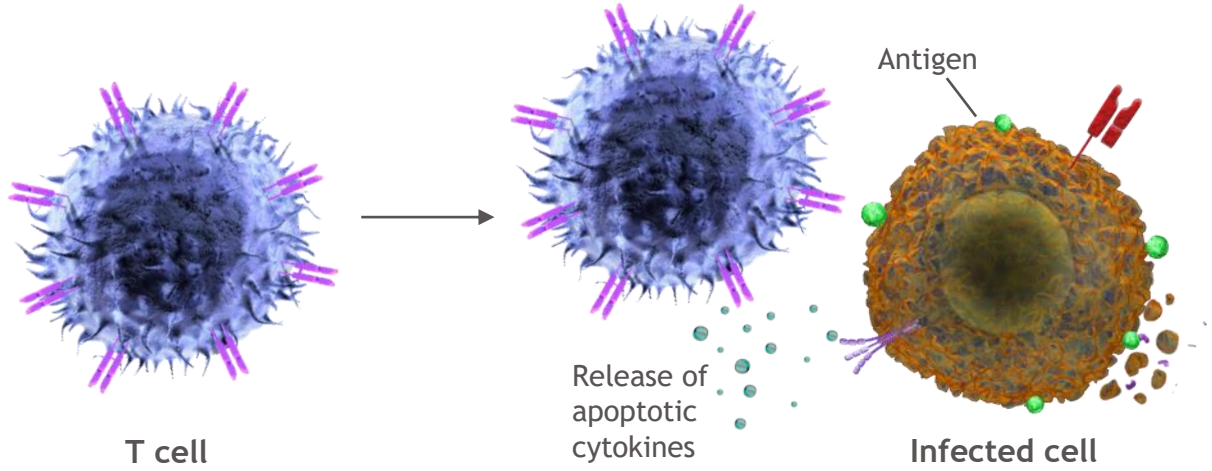
Lymphocytes Are Key Components of the Adaptive Immune System[1,2]

The adaptive immune system uses specific receptors that bind antigens to strategically mount a targeted immune response

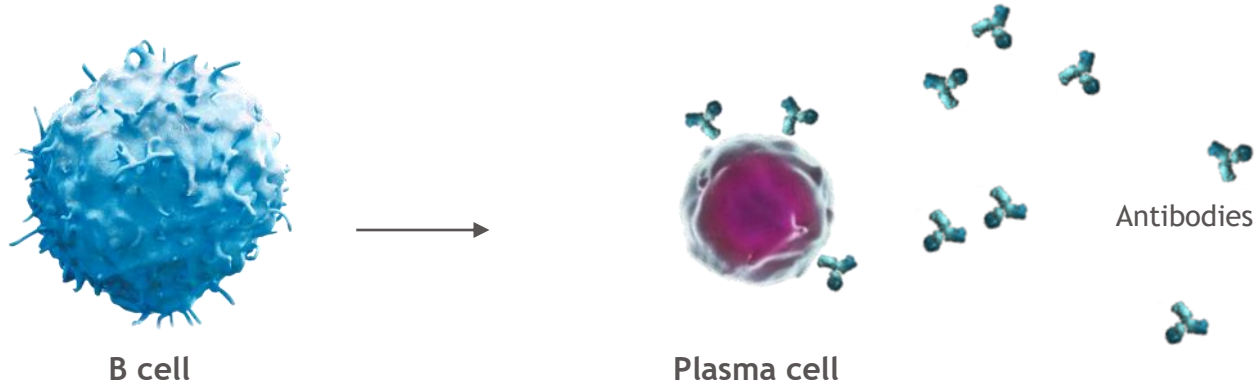
Unlike the innate immune system, which rapidly responds to all threats, adaptive immunity is slower and uses immunological memory to enhance immune responses[1,2]

> Certain cell types can express distinct surface proteins or antigens. For example, B cells highly express “self” surface antigens CD19 and CD20[1,3,4]

T cells mediate apoptosis of damaged or infected cells by releasing apoptotic cytokines and can direct B cell immune responses[2]



B cells are involved in antibody production. Plasma cells are terminally differentiated B cells that continuously secrete specific antibodies[2]



CD, cluster of differentiation.

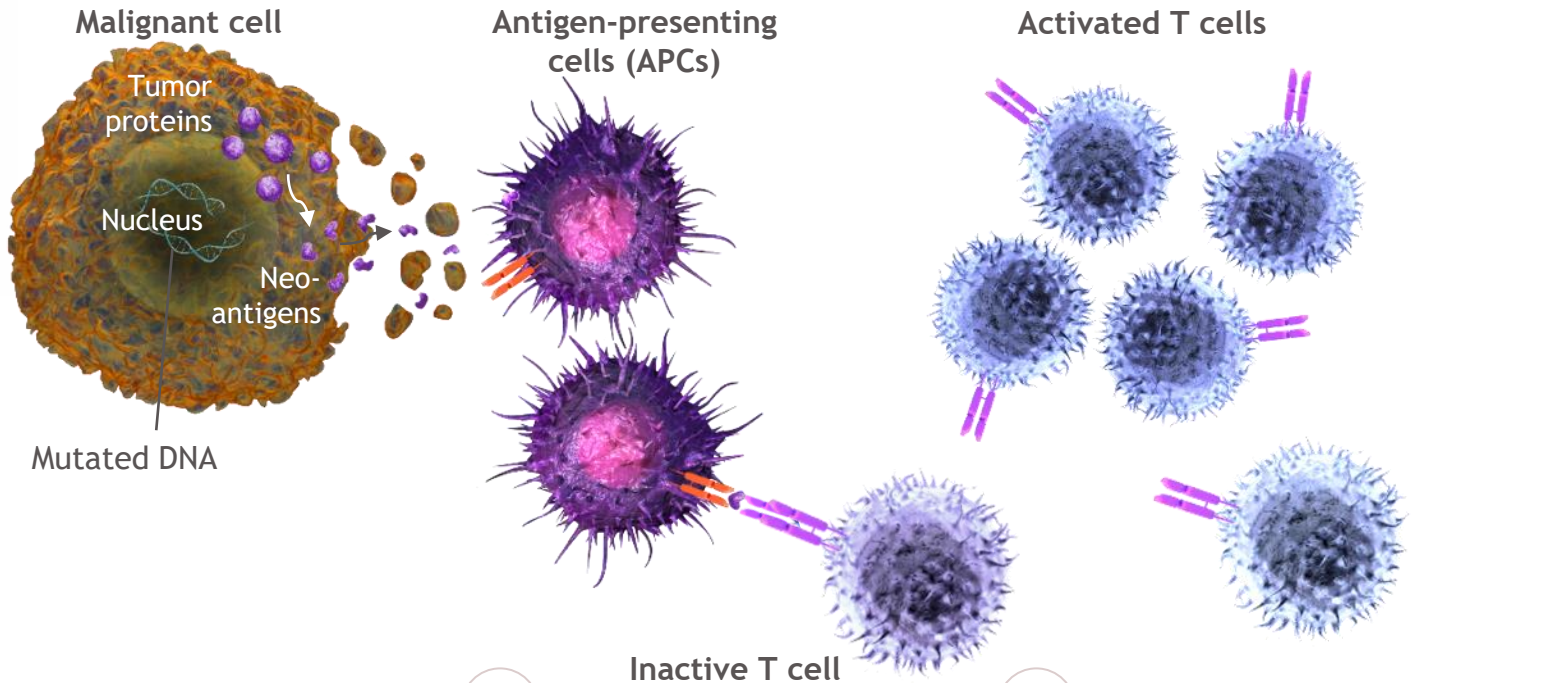
References: 1. Dranoff G. *Nat Rev Cancer*. 2004;4(1):11-22. **2.** Betts JG, et al. *Anatomy & Physiology*. 2nd ed. OpenStax, Rice University; 2017. Accessed May 21, 2021. https://openstax.org/details/books/anatomy-and-physiology **3.** Pavlasova G, et al. *Haematologica*. 2020;106(6):1494-1506. **4.** Wang K, et al. *Experimental Hematology & Oncology*. 2012, 1:36.

The Adaptive Immune System Plays a Fundamental Role in Protecting Against Cancer[1,2]

Occasionally, mutations may occur that cause hematopoiesis to become unregulated and cancerous. The cancerous cells can then become potential targets of immune attack[1]

The adaptive immune system[2]:

- Discerns "self" antigens from "nonself" antigens
- Generates pathogen-specific immunologic effector pathways to eliminate pathogen-infected or cancerous cells

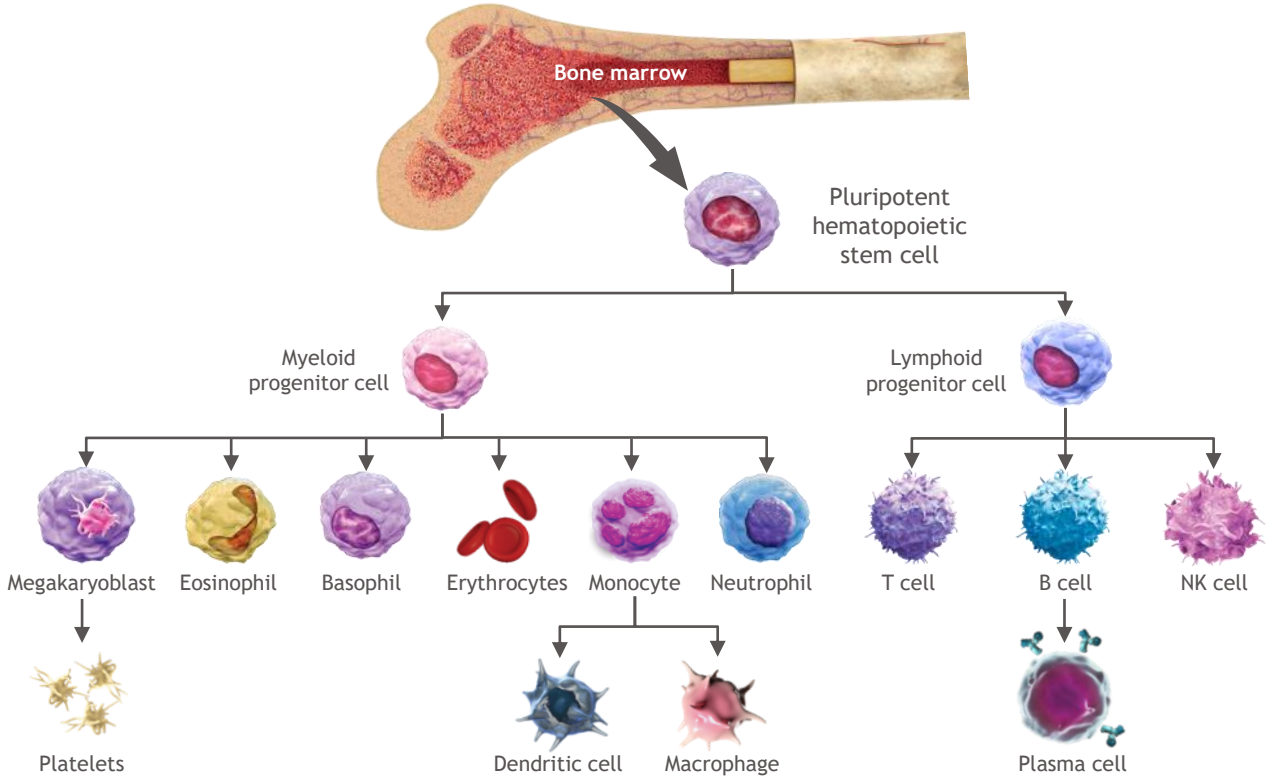


1. Tumor mutational burden leads to the production of neoantigen, a type of tumor antigen
2. Neoantigens are captured and processed by APCs
3. APCs present neoantigens to activate cytotoxic T cells, inducing cancer cell apoptosis

References: 1. Warrington R, et al. *Allergy Asthma Clin Immunol*. 2011;7:S1. **2.** Lu Y-C, et al. *Semin Immunol*. 2016;28:22-27.

Hematologic Malignancies Arise From Disrupted Hematopoiesis

Hematologic cancers can be classified into three categories: leukemia, lymphoma, and myeloma[1]



1. **Leukemia** is a broad term for blood cell cancer, and may produce abnormal leukocytes (white blood cells)[2]

2. **Lymphoma** is a broad term for cancers originating in the lymphatic system that produce abnormal lymphocytes[2]

3. **Myeloma, or multiple myeloma,** is a cancer of plasma cells[3]

Leukemia, lymphoma, and myeloma account for about 9.8% of all new cancer diagnoses annually[4]

References: 1. Center for Disease Control (CDC). Accessed June 30, 2023. https://www.cdc.gov/cancer/uscs/about/data-briefs/no30-hematologic-incidence-surv-prev.html **2.** Betts JG, et al. *Anatomy & Physiology*. 2nd ed. OpenStax, Rice University; 2017. Accessed May 21, 2021. https://openstax.org/details/books/anatomy-and-physiology **3.** American Cancer Society (ACS). Accessed June 23, 2023. https://www.cancer.org/cancer/types/multiple-myeloma/about/what-is-multiple-myeloma.html **4.** National Cancer Institute (NCI). 2018. Accessed August 7, 2023. https://seer.cancer.gov/archive/csr/1975_2018/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.01

Lymphoma Is the Most Prevalent Hematologic Malignancy

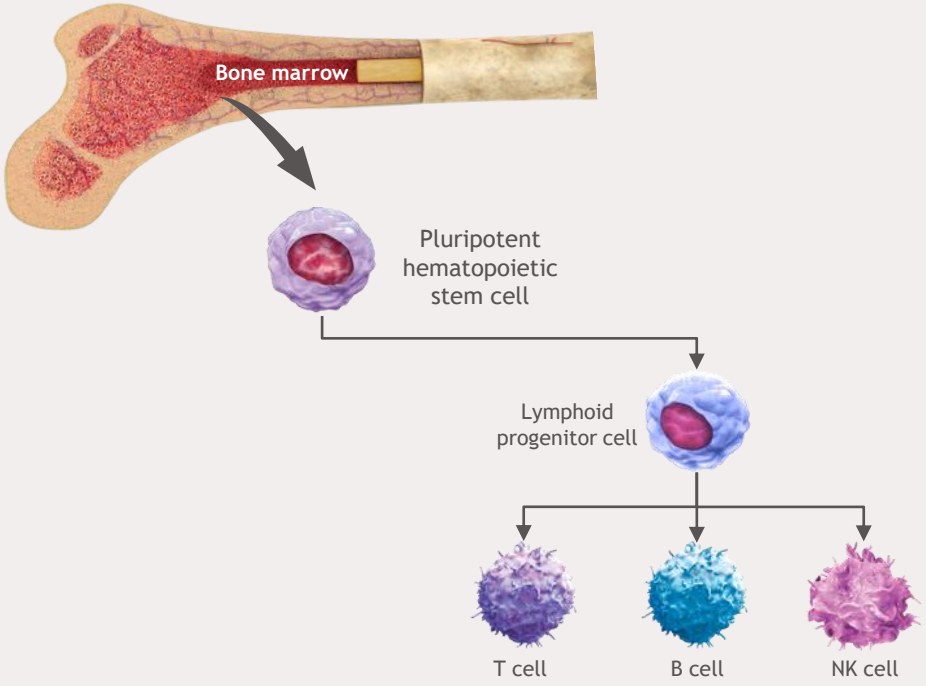
According to the National Cancer Institute SEER data, **lymphoma accounts for an estimated 4.8% of new cancer cases in the US**[1,a]

There are two main categories of lymphoma:

1. **Hodgkin lymphoma (HL)** is a curable cancer that typically spreads in an orderly manner from one group of lymph nodes to another. HL is identified by the presence of Reed-Sternberg cells and is significantly less common than other lymphomas[1,2]

2. **Non-Hodgkin lymphoma (NHL)** represents a diverse group of diseases distinguished by the characteristics of the cancer cells associated with each disease type[3]
   - Most patients with NHL have a B-cell subtype (~90%), while others have a T-cell type or an NK cell type of lymphoma[4]

Lymphoma affects cells in the lymphoid lineage[5]



[a]Estimate based on 2003-2017 registry data (N=1,898,160).
SEER, Surveillance, Epidemiology, and End Results.

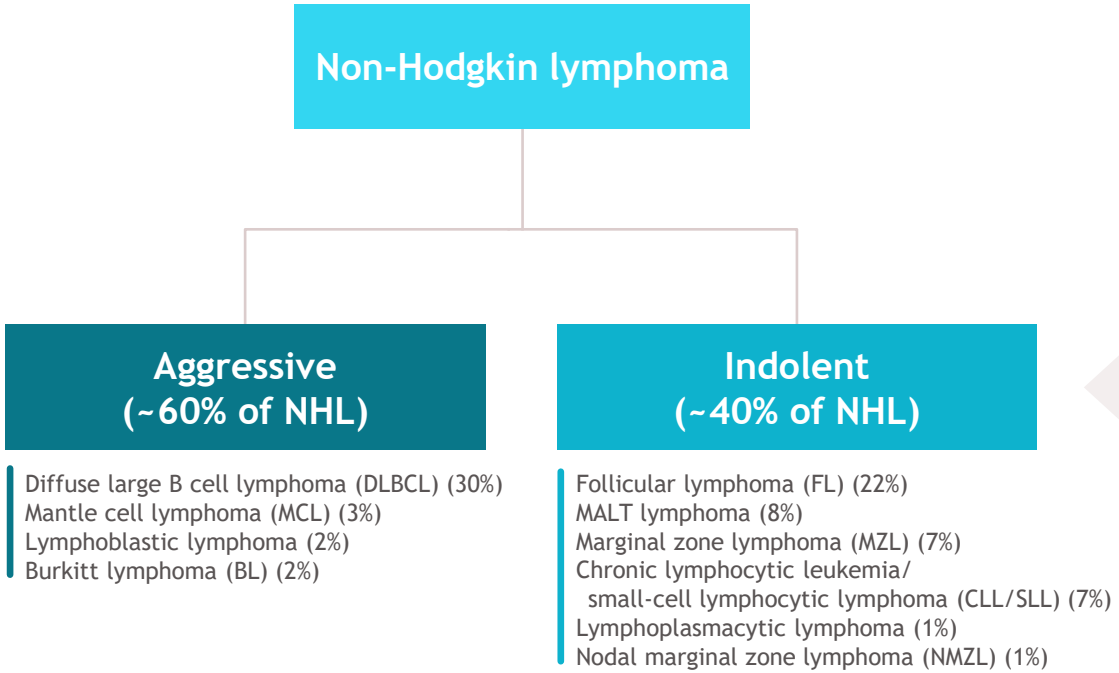
References: 1. National Cancer Institute (NCI). 2018. Accessed August 7, 2023. https://seer.cancer.gov/archive/csr/1975_2018/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.01 **2.** American Cancer Society (ACS). Accessed June 23, 2023. https://www.cancer.org/cancer/types/hodgkin-lymphoma/about/what-is-hodgkin-disease.html **3.** American Cancer Society (ACS). Accessed June 23, 2023. https://www.cancer.org/cancer/types/non-hodgkin-lymphoma/about/what-is-non-hodgkin-lymphoma.html **4.** Hashmi H, et al. *Hematol Oncol Stem Cell Ther*. 2021;16(1). **5.** Betts JG, et al. *Anatomy & Physiology*. 2nd ed. OpenStax, Rice University; 2017. Accessed June 23, 2023. https://openstax.org/details/books/anatomy-and-physiology

Treatment Options and Outcomes Vary According to Aggressive and Indolent Disease and Subtype

NHL can be broadly categorized into two subtypes: aggressive and indolent disease

Aggressive lymphomas tend to progress quickly and therefore require immediate intervention[1,2]

- Typically, treatment begins immediately after diagnosis with intensive multidrug chemotherapy regimens, such as R-CHOP[2]
  - Some patients with fast-growing NHL can be cured[2]



Indolent lymphomas tend to be slow-growing and therefore have a longer clinical course[1,3,a]

- Front-line treatment may vary from observation to chemotherapy. Patients with indolent lymphoma are often seen in the community setting[4,5]
  - Indolent lymphomas are considered to be incurable, and have multiple treatment options including chemotherapy and immunotherapy[3,6]

[a]Some indolent lymphoma cases can transform into aggressive lymphomas.
MALT, mucosa-associated lymphoid tissue; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

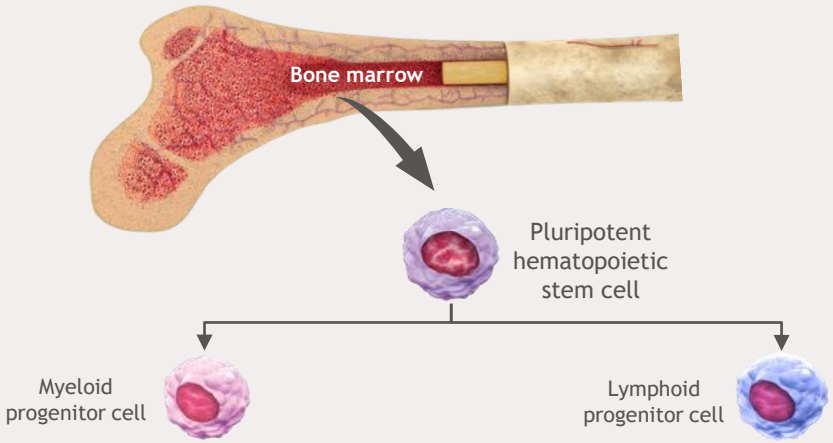
References: 1. Leukemia & Lymphoma Society (LLS). Accessed June 23, 2023. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes **2**. Leukemia & Lymphoma Society (LLS). Accessed June 30, 2023. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes/treatment-aggressive-nhl-subtypes **3.** Jeong SH. *Blood Research*. 2022;57(S1). **4**. Leukemia & Lymphoma Society (LLS). Accessed June 30, 2023. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes/treatment-indolent-nhl-subtypes **5.** Nooka AK, et al. *Ann Oncol*. 2013;24(2):441-448. **6.** Smith S, et al. *Haematologica*. 2022;107(1):4-6.

Leukemia Is the Second Most Prevalent Hematologic Malignancy

According to the National Cancer Institute SEER data, **leukemia accounts for an estimated 3.2% of new cancer cases in the US annually**[1,a]

- Leukemia is caused by the production of dysfunctional progenitor cells. These abnormal cells are not able to fight infection and impair the ability of the bone marrow to produce healthy red blood cells and platelets[2-4]
- Leukemias can be categorized by the rapidity of cell proliferation and the lineage of origin. For example[2,3]:
  - **Acute myeloid leukemia (AML)** is the most common and aggressive acute leukemia in adults and characterized by the percentage of myeloid blasts
  - **Acute lymphocytic leukemia (ALL),** while not a common type of leukemia in adults, is a disease of lymphocytes that can progress quickly and be fatal within a few months if not treated
- Treatment options for leukemias are determined by subtype and disease stage, but typically include chemotherapy and targeted drug therapies[4,5]

Leukemia can affect cells in the lymphoid or myeloid lineage[1,7]



- Acute myeloid leukemia (AML) (33%)[b]
- Chronic myeloid leukemia (CML) (15%)[b]
- Acute lymphocytic leukemia (ALL) (9%)[b]

[a]Estimate based on 2003-2017 registry data (N=1,898,160). [b]Estimated number of new leukemia cases (N=61,090).

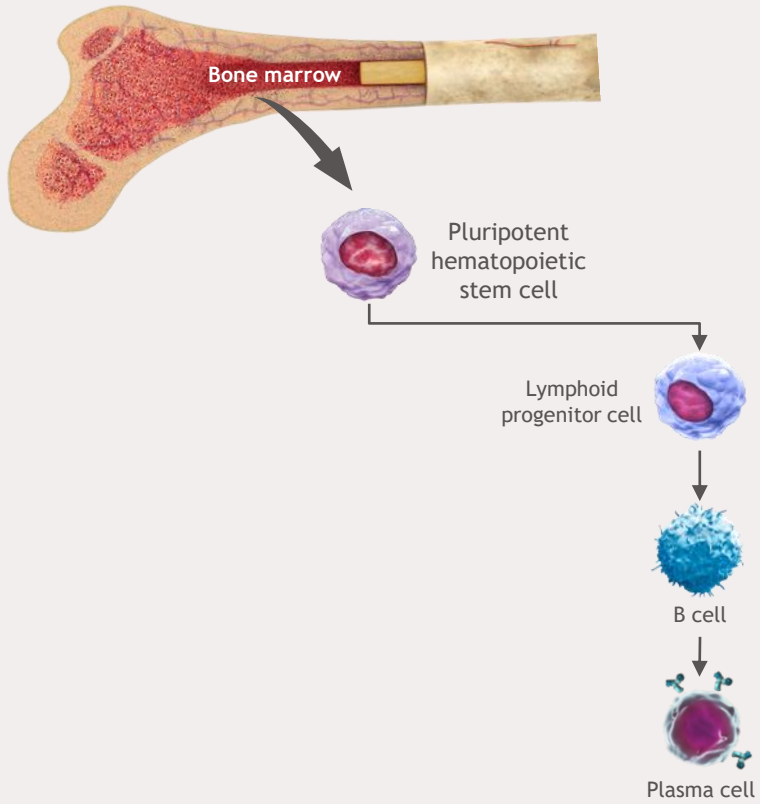
References: 1. National Cancer Institute (NCI). Accessed June 22, 2023. https://seer.cancer.gov/archive/csr/1975_2018/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.01 **2.** Chennamadhavuni A, et al. Updated January 17, 2023. In:StatPearls[Internet]. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560490 **3.** American Cancer Society (ACS) Accessed July 24, 2023. https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/about/what-is-all.html **4.** Leukemia & Lymphoma Society (LLS). Accessed July 24, 2023. https://www.lls.org/leukemia/acute-myeloid-leukemia/treatment **5.** Leukemia & Lymphoma Society (LLS). Accessed July 24, 2023. https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/treatment **6.** National Cancer Institute (NCI). 2018. Accessed August 7, 2023. https://seer.cancer.gov/archive/csr/1975_2018/results_merged/topic_apxcount.pdf **7.** Betts JG, et al. *Anatomy & Physiology*. 2nd ed. OpenStax, Rice University; 2017. Accessed June 23, 2023. https://openstax.org/details/books/anatomy-and-physiology

Multiple Myeloma Is the Third Most Prevalent Hematologic Malignancy

According to the National Cancer Institute SEER data, **multiple myeloma accounts for an estimated 1.8% of new cancer cases in the US annually**[1,a]

- When B cells respond to an infection, they become plasma cells[2]
  - Normal plasma cells secrete antibodies to fight infections
- **Myeloma cells are cancerous plasma cells**[2]
  - They secrete an abnormal antibody, called "monoclonal protein," which cannot properly fight infections
- Multiple myeloma is currently incurable, though the current standard of care options aim to slow disease progression and maintain and/or improve QoL[3]
  - Some of these treatments include IMiDs, PIs, and anti-CD38 antibodies[4]
- Despite available treatments, almost all patients with multiple myeloma relapse and may go on to receive 5+ lines of therapy during the course of the disease[4]

Multiple myeloma affects the lymphoid lineage, specifically plasma cells[2,5]



[a]Estimate based on 2003-2017 registry data (N=1,898,160).
CD, cluster of differentiation; IMiD, immunomodulatory imide drug; PI, proteosome inhibitor.

References: 1. National Cancer Institute (NCI). Accessed June 22, 2023. https://seer.cancer.gov/archive/csr/1975_2018/browse_csr.php?sectionSEL=1&pageSEL=sect_01_table.01 **2.** American Cancer Society (ACS). Accessed June 23, 2023. https://www.cancer.org/cancer/types/multiple-myeloma/about/what-is-multiple-myeloma.html **3.** Leukemia & Lymphoma Society (LLS). Accessed July 24, 2023. https://www.lls.org/myeloma/treatment **4.** Rajkumar SV, et al. *Blood Cancer J.* 2020;10(9):94. **5.** Betts JG, et al. *Anatomy & Physiology*. 2nd ed. OpenStax, Rice University; 2017. Accessed June 23, 2023. https://openstax.org/details/books/anatomy-and-physiology

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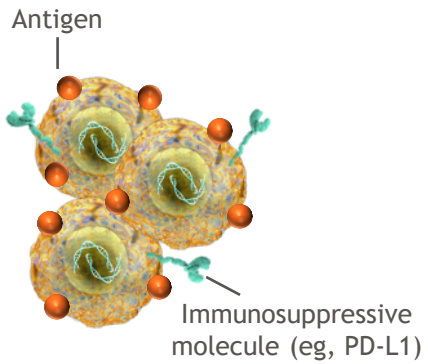
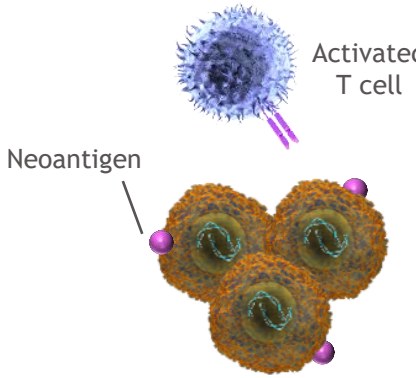
Malignant Cells Can Acquire Mechanisms to Evade Attack by the Immune System



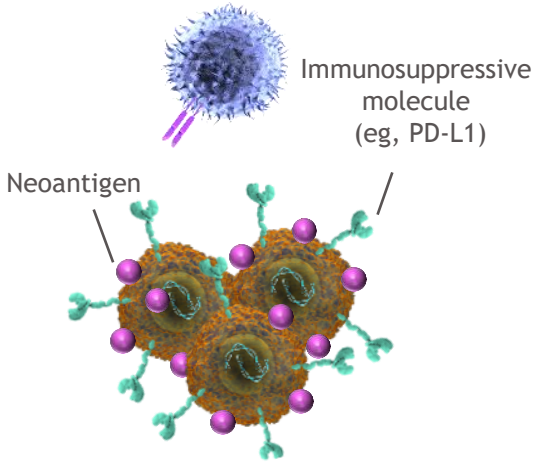
Healthy Cells[1,2]

Healthy cells exhibit normal levels of antigens and some immunosuppressive molecules



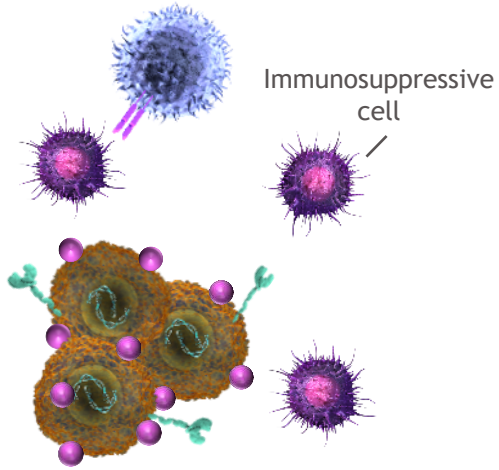
Loss of Antigenicity[1]

Malignant cells can acquire defects in antigen processing or presentation, or lose expression of immunogenic neoantigens



Loss of Immunogenicity[1]

Malignant cells can exhibit increased expression of immune checkpoint proteins (eg, PD-L1) or increased secretion of suppressive cytokines (eg, IL-10)



Immunosuppressive Microenvironment[1,3]

Increased local infiltration of immunosuppressive cells (eg, MDSCs, TAMs, Tregs) can occur, and in turn, downregulate cytotoxic T cell activity

Note that tumors can acquire additional mechanisms of immune evasion beyond those shown here[4]

IL-10, interleukin 10; MDSC, myeloid-derived suppressor cells; PD-L1, programmed cell death ligand 1; TAM, tumor-associated macrophage; Treg, regulatory T cell.

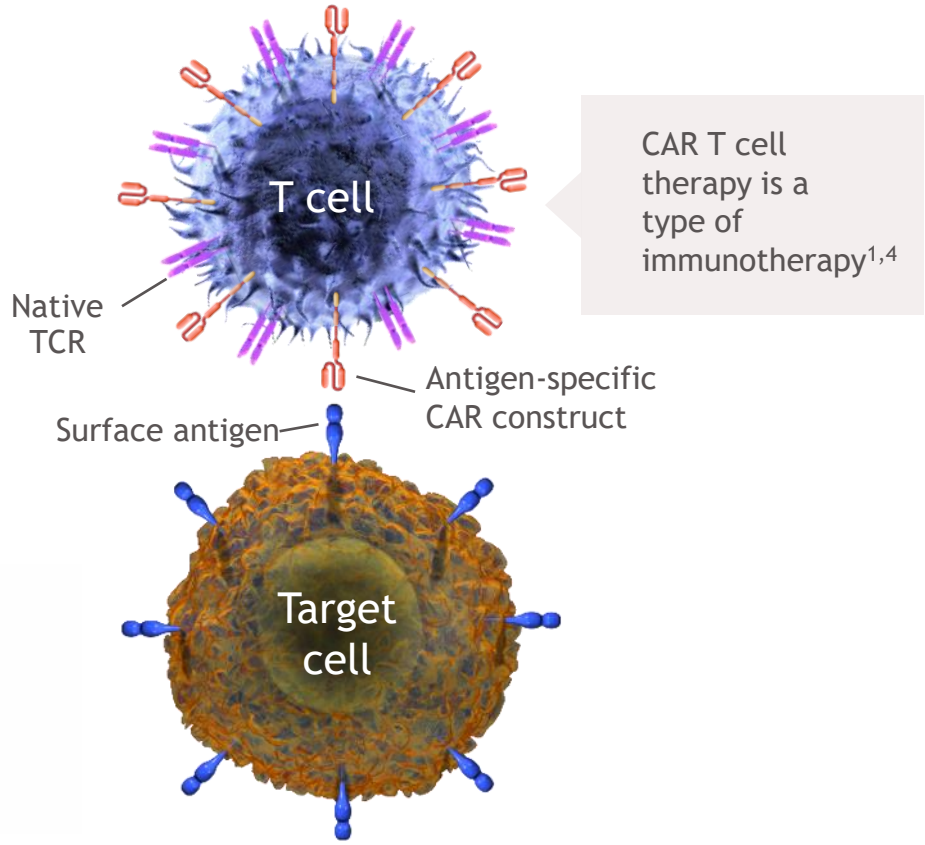
References: 1. Beatty GL, et al. *Clin Cancer Res*. 2015;21:687-692. **2.** Davis AA, Patel VG. *J Immunother Cancer*. 2019;7(1):278. **3.** Sterner RC, et al. *Blood Cancer J*. 2021;11(4):69. **4.** Vinay DS, et al. *Semin Cancer Biol*. 2015;35:S185-S198.

CAR T Cell Therapy May Bypass the Evasion Mechanisms of Malignant Cells by Leveraging Inherent T Cell Abilities

Chimeric antigen receptor (CAR) T cell therapy is a type of immunotherapy that leverages the ability of T cells to detect and target specific antigen-expressing cells, which may include both cancer cells and normal cells[1]

Gene transfer technology is used to express CARs on T cells, conferring antigen specificity[2]

- CAR T cells can be directed to a specific surface antigen found on target cells[2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells by binding target cells in an antigen-dependent manner[2]



CAR T Cell Persistence

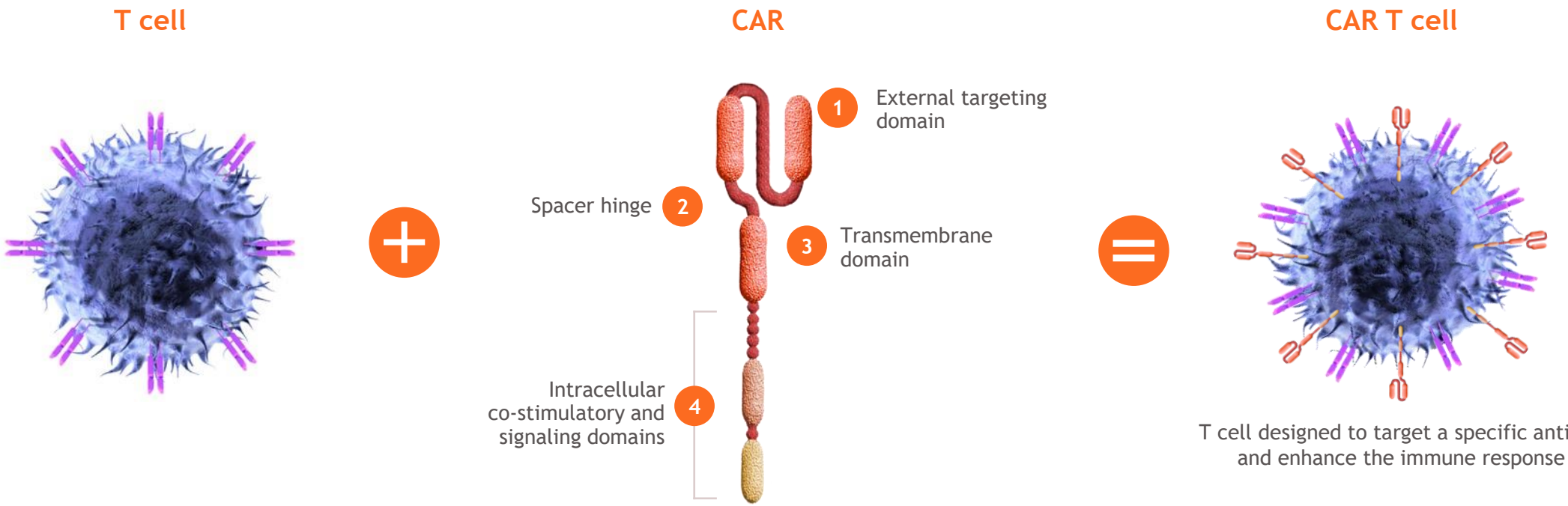
- CAR T cells may also expand and persist, providing T cell memory for a period of time[2]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]

TCR, T cell receptor.

References: 1. Leukemia & Lymphoma Society. Accessed August 1, 2022. https://www.lls.org/sites/default/files/2022-07/FSHP1_HCP_CART_revjune22.pdf **2.** Oluwole OO, et al. *J Leukoc Biol*. 2016;100:1265-1272. **3**. McLellan AD, et al. *Immunol Cell Biol*. 2019;97(7):664-674. **4**. Leukemia & Lymphoma Society. Accessed August 1, 2022. https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Components of a CAR T Cell

Autologous CAR T cell therapy helps equip a patient's T cells with the ability to detect and destroy target cells, including malignant cells, by combining the specificity of an antibody with the cytotoxic and memory capabilities of a T cell[1,2]



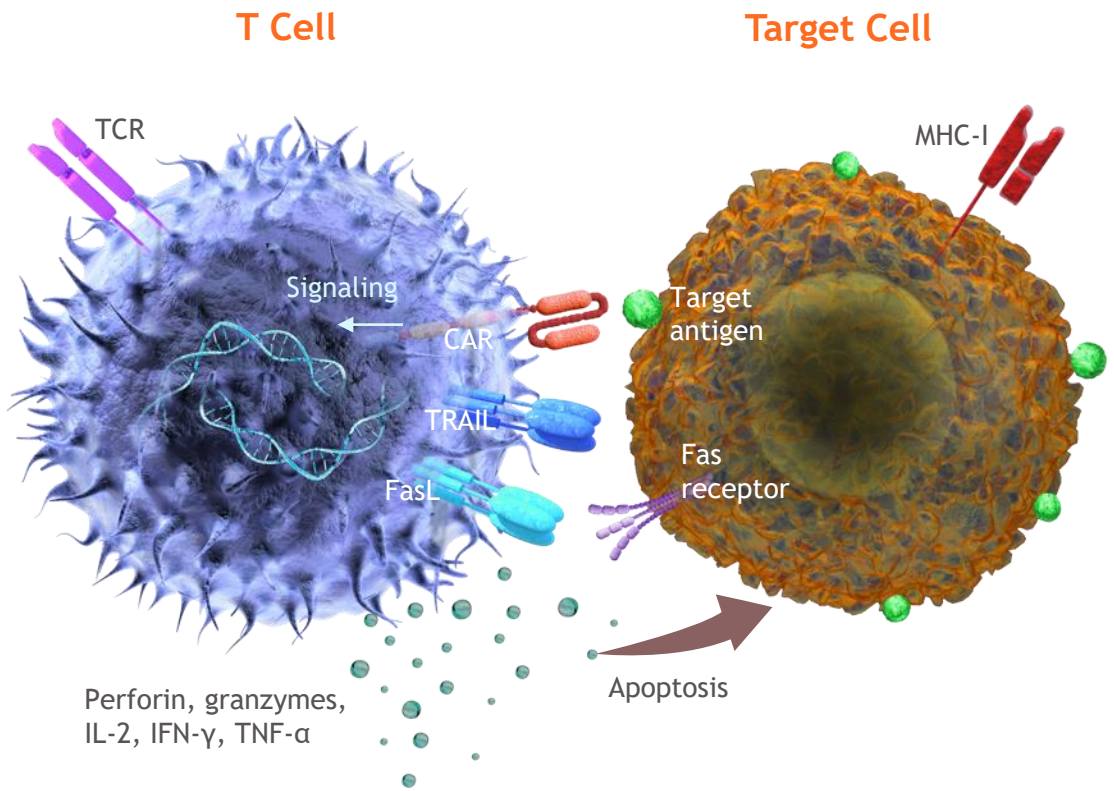
References: 1. Leukemia & Lymphoma Society. Accessed August 1, 2022. https://www.lls.org/sites/default/files/2022-07/FSHP1_HCP_CART_revjune22.pdf **2.** Maus MV, et al. *Oncologist*. 2016;21:608-617. **3.** Jayaraman J, et al. *EBioMedicine*. 2020;58:102931.

CAR T Cell Mechanism of Action

Current Understanding of the Mechanism

1. When a CAR binds to a specific antigen on the target cell, a signaling cascade is induced, leading to activation of the CAR T cell[1]
2. Once activated, the T cell[1]:
   - Induces cytotoxic activities
   - Expresses proapoptotic-molecules (eg, FasL and TRAIL) to induce apoptosis of the target cell
   - Secretes pro-inflammatory cytokines to activate other tumor-infiltrating immune cells

Target Cell Killing by CAR T Cells[1-3]



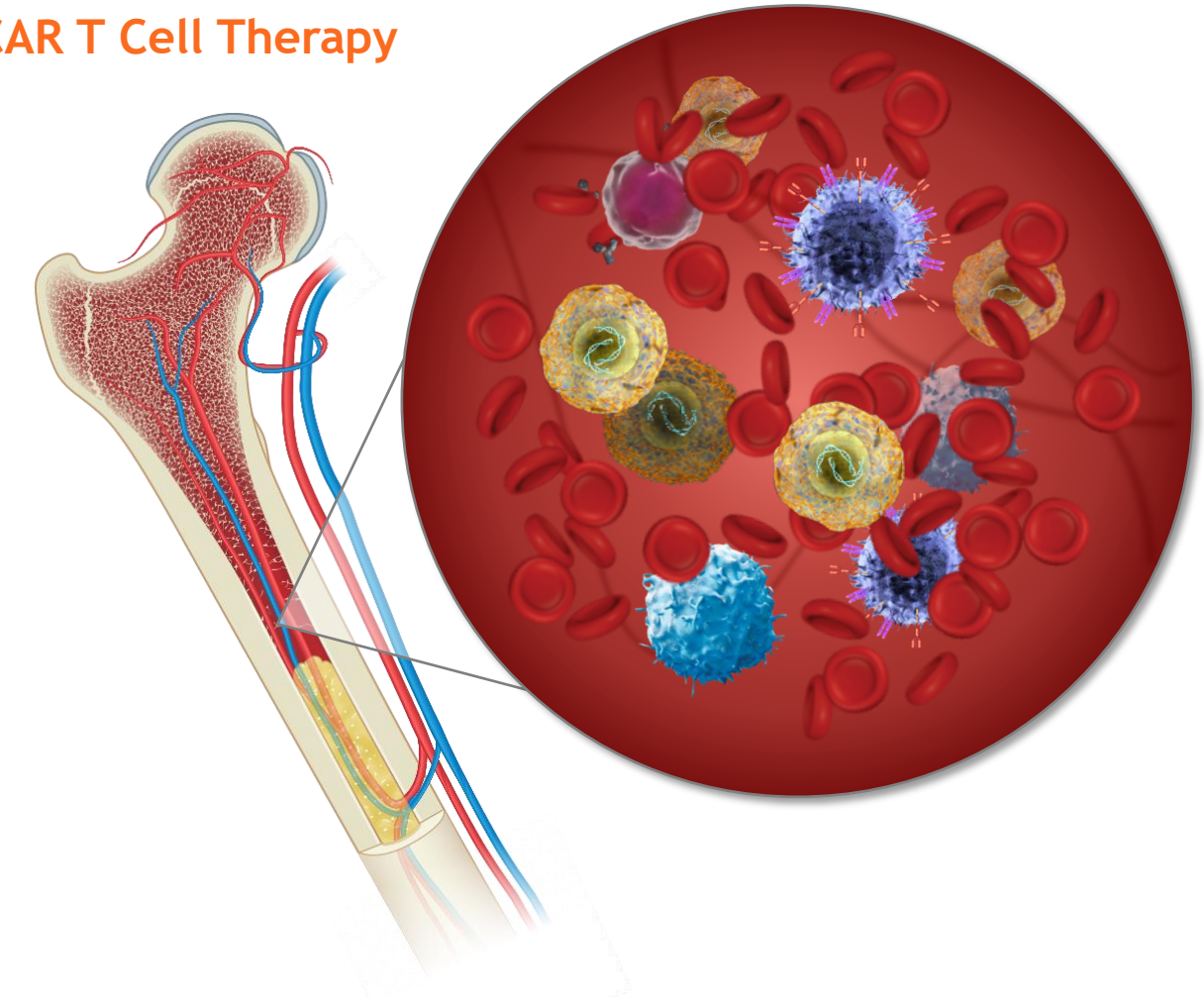
FasL, Fas ligand; IFN, interferon; IL-2, interleukin-2; MHC, major histocompatibility complex; TCR, T cell receptor; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; TNF, tumor necrosis factor.

References: 1. Cartellieri M, et al. *J Biomed Biotechnol*. 2010;2010:956304. **2.** Maus MV, et al. *Oncologist*. 2016;21:608-617. **3.** Benmebarek MR, et al. *Int J Mol Sci*. 2019;20(6).

CAR T Cell Therapy in Hematologic Malignancies[1,2]

Features of Hematologic Malignancies Utilized for CAR T Cell Therapy

- Antigen expression is specific to target cells[3,4]
- Hematologic malignancies do not have the same physical barriers or immunosuppressive microenvironments of solid tumors[4]
- Hematologic malignancies typically reside in the same locations as migrating T cells (eg, peripheral blood, lymph nodes, bone marrow)[4]



References: 1. Miliotou AN, et al. *Curr Pharm Biotechnol*. 2018;19:5-18. **2.** Ogba N, et al. *J Natl Compr Canc Netw*. 2018;16:1092-1106. **3.** June CH, et al. *Science*. 2018;359:1361-1365. **4.** Filley AC, et al. *Front Oncol*. 2018;8(OCT):1-19.

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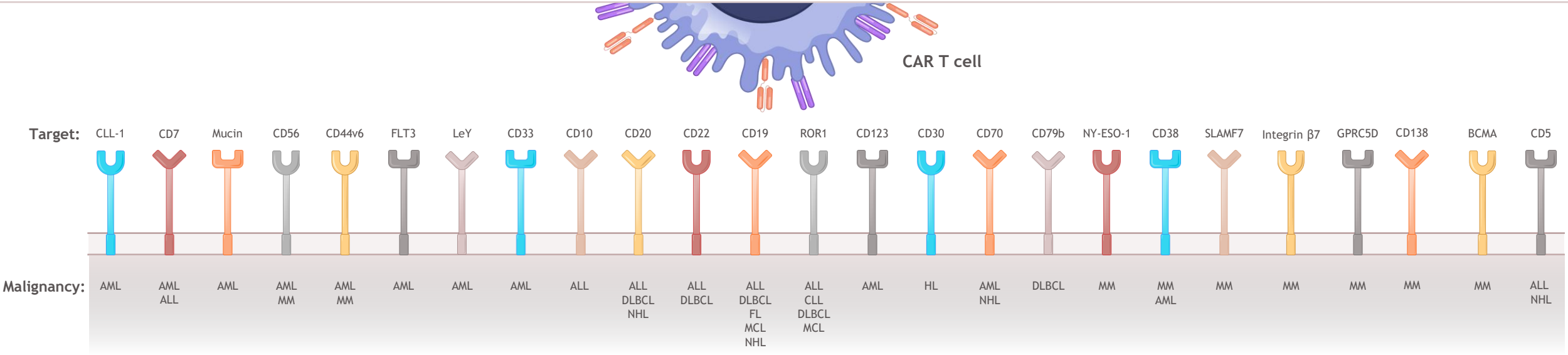
Cancer Cells Express Potential Targets That Could Be Leveraged for CAR T Cell Therapy Approaches[1-8,a]

Target Antigens Across Hematologic Malignancies

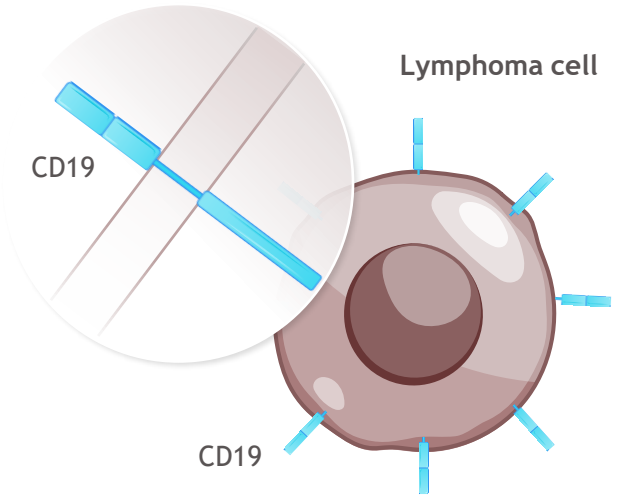


Additionally, **CAR T cell therapy is under investigation for other diseases,** including solid tumor cancers and non-cancerous diseases[9,10]

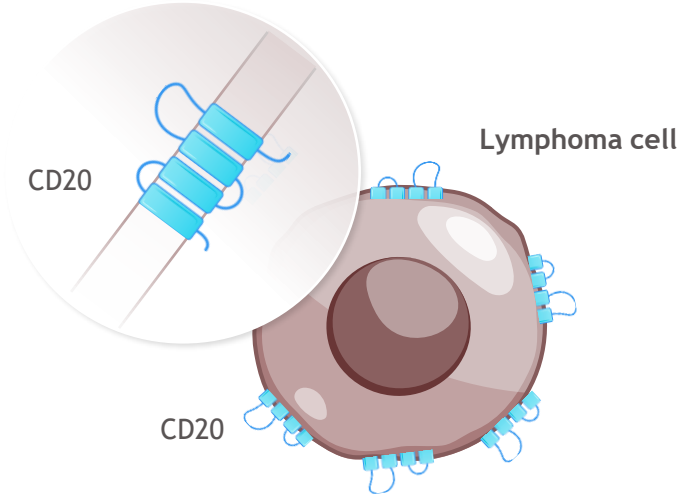
[a] This list may not be comprehensive as investigation for new targets and diseases is ongoing.
AML, acute myeloid leukemia; BCMA, B cell maturation antigen; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; FLT3, fms-like tyrosine kinase 3; GPRC5D, G protein-coupled receptor class C group 5 member D; LeY, Lewis Y; MCL, mantle cell lymphoma; MM, multiple myeloma; NY-ESO-1, New York squamous cell carcinoma-1; ROR1, receptor tyrosine kinase-like orphan receptor 1; SLAMF7, surface antigen CD319.

References: **1.** Zhang X, et al. *Front Immunol*. 2022;13:927153. **2.** Dagar G, et al. *J Transl Med*. 2023;21:449. **3.** Schorr C, et al. *Front Immunol*. 2022;13:1085978. **4.** Kozani P, et al. *Translational Oncology*. 2021;14(7):101079. **5.** Rodrigues-Lobato L, et al. Front Oncol. 2020;10:1243. **6.** Osorio-Rodriguez D, et al. *Front Med*. 2023;10:1121020. **7.** Marofi F, et al. *Front Immunol*. 2021;12:681984. **8.** Mitwasi N, et al. *Int J Mol Sci*. 2022;23:4920. **9.** Marofi F, et al. *Stem Cell Research and Therapy*. 2021;12:81. **10.** Mougiakakos D, et al. *NEJM*. 2021;385;6.

Target Antigens for NHLs Include CD19 and CD20, Which Are Expressed on the Surface of Lymphoma Cells[1,2]



- **CD19** is a transmembrane glycoprotein critical for B cell signaling[1]
  - CD19 expression is highly regulated during B-cell development and maturation, until expression is lost during plasma cell differentiation[1]
  - CD19 plays a role in antigen-independent development and immunoglobulin-induced activation of B cells and is thus vital for mounting an optimal immune response[1]
  - CD19 is an appealing target for CAR T cell therapy because it is evenly expressed by a majority of B cell malignancies[1,3]
    - CD19-targeted CAR T cell treatment has shown efficacy in B cell malignancies, including lymphomas. Additionally, CD19-targeted CAR T cell therapy for CLL is under investigation[4]

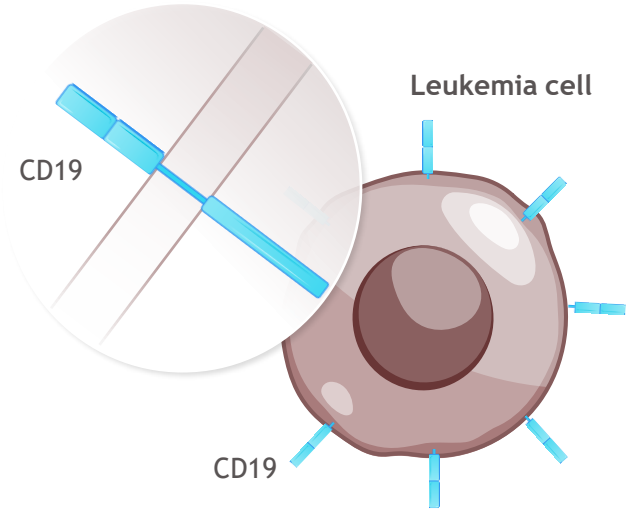


- **CD20** is a non-glycosylated transmembrane protein, and is thought to be physiologically directly required for efficient BCR signaling in B cells[2]
  - CD20 is not expressed in early pro-B lymphocytes, but is expressed in late pre-B lymphocytes until the cells become terminally differentiated plasma cells[2]
  - CD20 presents in most B cell lymphomas, making it an appealing target molecule for the treatment of NHL[5]

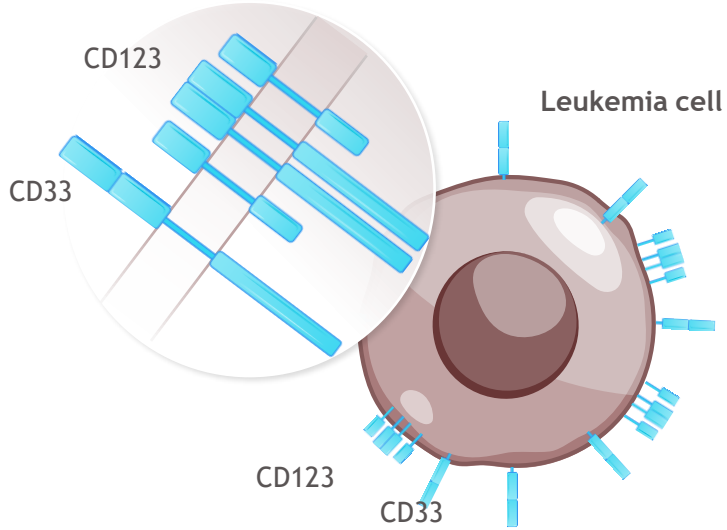
BCR, B cell receptor.

References: 1. Wang K, et al. *Experimental Hematology & Oncology*. 2012, 1:36. **2.** Pavlasova G, et al. *Haematologica*. 2020;106(6):1494-1506. **3.** Kochenderfer J, et al. *Nat Rev Clin Oncol*. 2013;10(5):267-276. **4.** Iovino L, et al. *Clin Adv Hematol Oncol*. 2023;21(3). **5.** Tan Su Yin E, et al. *Immuno Medicine*. 2022;2:e1039.

CD19 Expression Is Highly Conserved in Most B Cell Cancers, Including Leukemias[1]



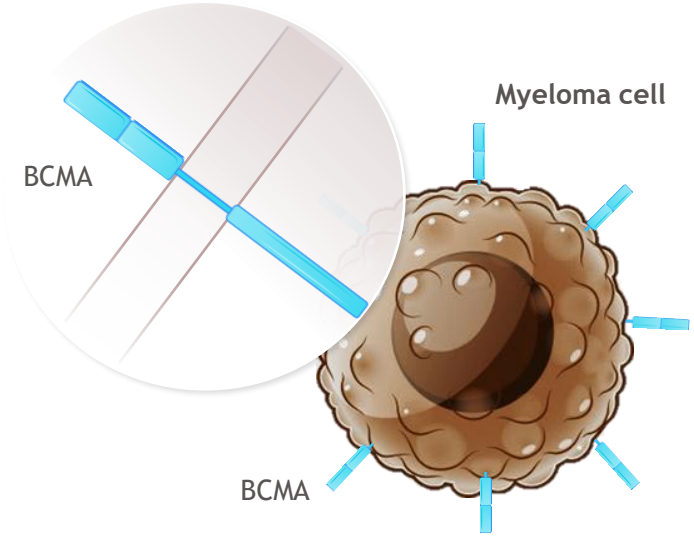
- Leukemic cells can also be derived from B cells, making **CD19** a prime target antigen for the treatment of leukemia[1]
- Current CAR T cell therapies for leukemias target CD19[2,3]
  - In ALL, patients treated with CD19-directed therapy have achieved responses[3]



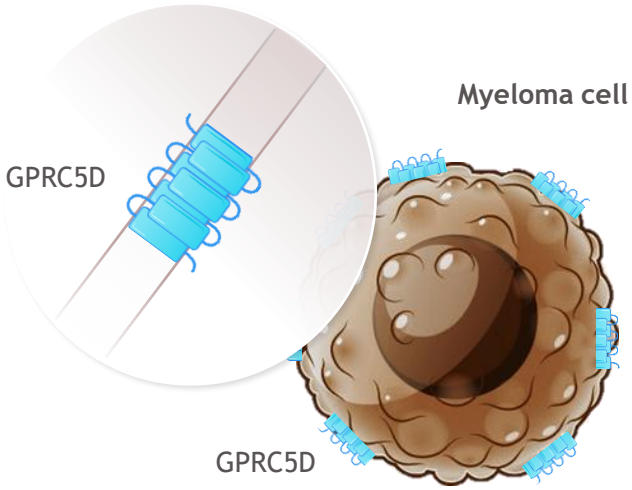
- Other target antigens expressed on leukemic cells are under investigation for CAR T-based intervention/therapy, including **CD33** and **CD123**[4]
  - Both CD33 and CD123 are involved in cell signaling and growth[5,6]
  - CD123 expression is upregulated in leukemic stem cells which could make it a useful target for CAR T cell therapy[6]

References: **1**. Wang K, et al. *Experimental Hematology & Oncology*. 2012, 1:36. **2**. Iovino L, et al. *Clin Adv Hematol Oncol*. 2023;21(3). **3**. Zhang X, et al. *Front Immunol*. 2022;13:927153. **4**. Vishwasrao P, et al. *Cancers*. 2022, 14:1241. **5**. National Cancer Institute (NCI). Accessed July 3, 2023. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cd33-positive **6**. El Achi H, et al. *Cancers*. 2020, 12(11):3087.

BCMA and GPRC5D Are Preferentially Expressed by Plasma and Myeloma Cells[1,2]



- **BCMA** is a protein that plays a key role in the proliferation, maturation, and differentiation of B cells into plasma cells and is important for plasma cell survival[3]
  - BCMA is elevated in MM and plays a role in promoting MM pathogenesis1[3,4]
  - Several BCMA-targeted CAR T cell therapies have shown efficacy in MM, and more are in development[1,5]



- **GPRC5D** typically present only in hair follicles, is abnormally expressed in the bone marrow of patients with MM[2]
  - Because GPRC5D expression is excluded from nearly all healthy tissue and is consistently expressed in MM cells, GPRC5D is a promising target for CAR T cell therapy[2]
  - GPRC5D expression is independent of BCMA expression, which could suggest that GPRC5D is a suitable target for CAR T cell therapy in patients who relapse after BCMA-directed therapies[2,6]

References: 1. Cho SF, et al. *Front Immunol*. 2018;9:1821. **2.** Smith EL, et al. *Science Transl Med*. 2019;11:7746. **3.** Dogan A, et al. *Blood Cancer Journal*. 2020;10:73. **4.** Tai Y-T, et al. *Blood*. 2016;127(25):3225-3236. **5.** Roex G, et al. *J Hematol Oncol*. 2020; 13:164. **6.** Mailankody S, et al. *NEJM*. 2022;387(13):1196-206.

Summary

The adaptive immune system plays a fundamental role in protecting against cancer by utilizing specific receptors that bind target antigens and strategically mount an immune response[1,2]

However, cancer cells develop mechanisms to evade the immune system, including a loss of antigenicity and immunogenicity[3]

CAR T cell therapy leverages the power of the immune system to fight cancer by modifying T cells to recognize and eliminate target cells expressing a specific antigen[4,5]

- Once the CAR T cell recognizes the target antigen on a cell, it causes cell lysis of the target cell

Several CAR T cell therapies are already approved, and a number are currently under investigation with novel targets. Targets are malignancy-specific, for example[6]:

- CD19 and CD20 for lymphomas and leukemias
- BCMA and GPRC5D for myeloma

References: 1. Warrington R, et al. *Allergy Asthma Clin Immunol*. 2011;7:S1. **2.** Dranoff G. *Nat Rev Cancer*. 2004;4(1):11-22. **3.** Beatty GL, et al. *Clin Cancer Res*. 2015;21:687-692. **4.** Maus MV, et al. *Oncologist*. 2016;21:608-617. **5.** Cartellieri M, et al. *J Biomed Biotechnol*. 2010;2010:956304. **6.** Zhang X, et al. *Front Immunol*. 2022;13:927153.

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