THE CAR-T CELL THERAPY INNOVATION DRIVERS: A YESCARTA CASE STUDY

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> Cancer randomly attacks people of all ages and forces its victims and their families to watch impotently as it grows and spreads. Cancer murders innocents. It is a holocaust.
>
> —Steven A. Rosenberg, National Cancer Institute[1]

I. INTRODUCTION

A highly effective treatment for cancer lies within our own bodies: our immune system. Chimeric antigen receptor (CAR)-T cell therapy harnesses patients' own immune cells to treat cancer. This Article explores the innovation drivers that spurred CAR-T cell therapy development.

From its inception, the United States sought to incentivize scientific innovation through various schemes. First, the Constitution drafters empowered Congress to create intellectual property rights for inventors—for example, patent protection.[2] Congress implemented these rights in several intellectual property schemes, including patent rights.[3] Later, the U.S. government developed additional innovation incentives: it created government research agencies (e.g., the National Cancer Institute), provided grants to researchers through its agencies (e.g., National Institutes of Health grants), and offered regulatory exclusivity to drug manufactures who successfully demonstrate innovative, safe, and efficacious drugs (e.g., biologic exclusivity).[4] This Article outlines the role of these and other innovation incentives in the successful development of CAR-T cells as cancer therapeutics.

1. Steven A. Rosenberg, *Immersion in the Search for Effective Cancer Immunotherapies*, 27 MOL. MED. 63, 2 (2021).

2. U.S. CONST. art. I, § 8, cl. 8.

3. *See, e.g.*, 35 U.S.C. §§ 1-390; Defend Trade Secrets Act, 18 U.S.C. § 1836.

4. *See, e.g.*, NATIONAL RESEARCH COUNCIL COMMITTEE ON ASSESSING THE VALUE OF RESEARCH IN ADVANCING NATIONAL GOALS, FURTHERING AMERICA'S RESEARCH ENTERPRISE 20–33 (Richard F. Celeste, Ann Griswold & Miron L. Straf eds., 2014).

Doctors have treated cancer, with varying degrees of success, for hundreds of years.[5] First, doctors attempted to remove cancer cells surgically.[6] Next, following X-ray technology development, doctors treated patients with radiation. Chemical warfare developed during World War II provided foundational research for the first chemotherapeutics.[7] More recent cancer therapeutics derive from advances in genetic engineering and understanding of the immune system. These recent therapeutics include anti-cancer monoclonal antibodies (i.e., engineered versions of natural proteins designed to bind to molecules associated with cancer cells), small molecules targeted to bind to proteins associated with cancer-causing genetic mutations, and CAR-T cells. Unlike earlier therapeutics, CAR-T cells are "living" therapeutics comprising engineered versions of patients' natural immune cells designed to target and kill cancer cells.[8]

CAR-T cell therapy innovation began with individual researchers driven by intrinsic and extrinsic motivations.[9] Researchers sought treatments with better results and reduced side effects relative to surgery and traditional chemotherapies. Because of rare but repeated reports of spontaneous cancer remission in patients with an activated immune system (e.g., due to an infection), the immune system seemed to hold the answer. Tenacity, curiosity, and grant funding fueled individual researchers' investigations into the immune system and its anti-cancer activity. New technology enabled researchers to understand immune system components, like B cells and T cells. Genetic engineering techniques allowed researchers to engineer B and T cells to perform new or modified functions.[10] CAR-T cell therapy involves engineering a patient's own T cells to produce a CAR protein, causing the T cell to attack the patient's cancer cells.

Researchers' efforts combined with pharmaceutical company investment and manufacturing expertise led to FDA approval of six CAR-T cell therapies starting in 2017.[11] In some instances, CAR-T cell therapies offer advantages over traditional chemotherapies including reduced treatment time (months vs. years), shorter-term and lesser side effects, and longer-lasting efficacy.[12] As of

5. *See, e.g.*, *Milestones in Cancer Research and Discovery*, NAT'L CANCER INST. (Aug. 31, 2020), https://www.cancer.gov/research/progress/250-years-milestones.

6. *See* discussion *infra* Sections II.A–II.C.

7. *See* discussion *infra* Section II.C.

8. *See* discussion *infra* Sections II.D–II.F.

9. *See* discussion *infra* Section IV.A.

10. *See* discussion *infra* Sections II.D–II.F, III.A.

11. *See* discussion *infra* Sections III.B–III.C.

12. *See, e.g.*, Zoom Interview with Dario Campana, Professor, Nat'l Univ. of Sing., Dep't of Paediatrics (Apr. 11, 2023) [hereinafter Campana Interview].

April 2024, all six FDA-approved therapies treat blood cancers, but researchers hope to expand CAR-T cell therapies to treat solid tumors in the future.[13]

This Article explores the innovation drivers that incentivized individuals and companies to advance CAR-T cells therapeutics from the bench to the bedside. First, this Article will explain the scientific background for CAR-T cell therapy development. Next, the Article will discuss the CAR-T cell therapy development from the researcher brainstorming phase through commercialization. Finally, the Article will identify individual researcher and corporate innovation drivers, including individual intrinsic motivations like curiosity and altruism and external incentives like patent rights, trade secret protection, and regulatory exclusivity.

II. BACKGROUND

Today, researchers understand the immune system as a complex system including two important cell types (B cells and T cells) that distinguish between the body's natural cells and materials and foreign materials. B cells secrete antibodies, specialized proteins designed to specifically bind to other, foreign proteins circulating in the body.[14] B cells' genetic material encodes the information required for the cells to create their proteins, including antibodies.[15] T cells recognize foreign materials differently. Instead of secreting antibodies, T cells have receptors on their cell surfaces designed to specifically bind foreign proteins.[16] T cell receptors (TCRs) are also proteins, encoded by T cells' genetic material. The portion of the TCR responsible for binding to the foreign protein is structurally similarly to the corresponding portion of an antibody.[17] However, unlike antibodies which bind to foreign proteins free in circulation, TCRs bind to foreign proteins displayed on the surface of other cells by a surface protein called the major histocompatibility complex (MHC).[18] Prior to the 1960s, scientists suspected the immune system's role in cancer suppression, but lacked this foundational understanding of B and T cell functioning.

13. *See* discussion *infra* Sections II.F, III.C.

14. Alex D. Waldman et al., *A Guide to Cancer Immunotherapy: From T Cell Basic Science to Clinical Practice*, 20 NATURE REVS. IMMUNOLOGY 651, 652 (2020).

15. *See, e.g.*, Caressa N. Tsai, *The Invention of Next-Generation Sequencing*, 39 BERKELEY TECH. L.J. 613, II.A (2024) (providing additional information on the translation of genetic information).

16. *Id.*

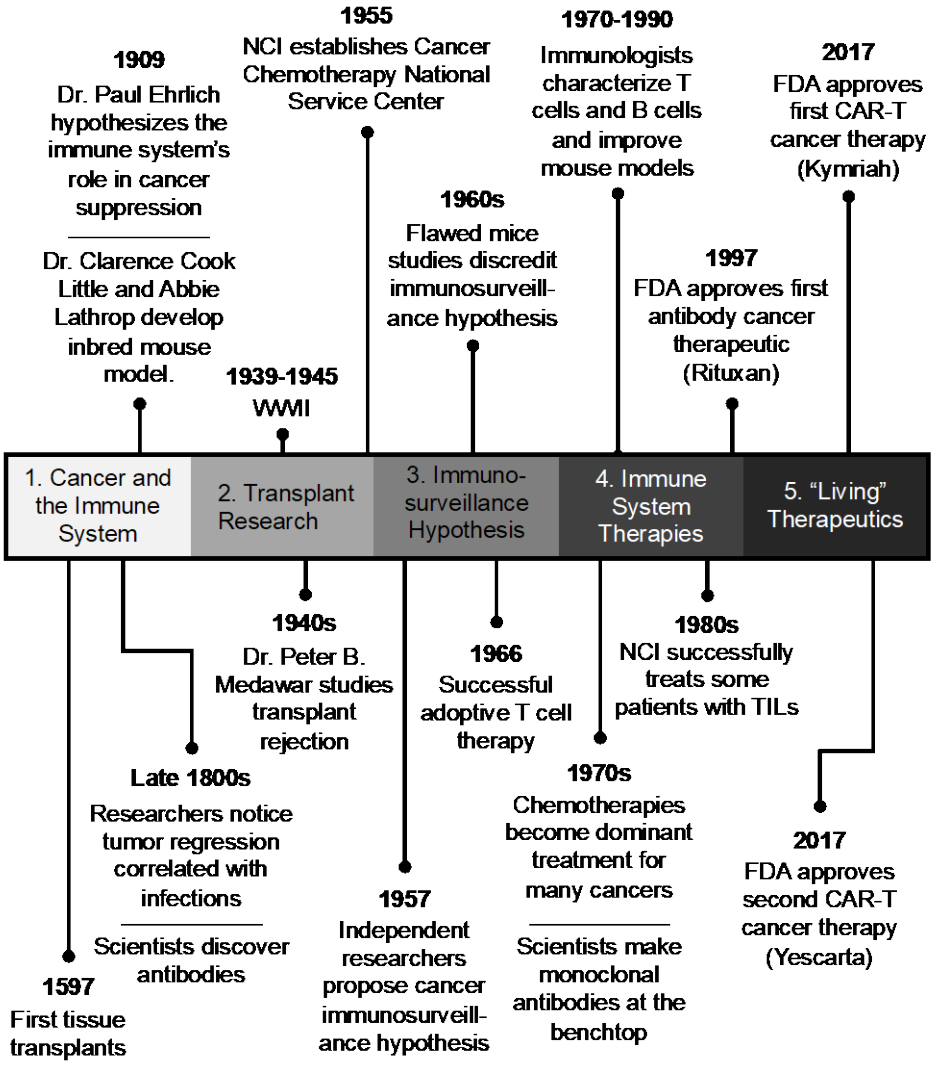
17. *See infra* Section III.A.

18. *Id.*

Yescarta harnesses a patient's own immune cells to treat their cancer.[19] The development of CAR-T cell therapies, like Yescarta, required advances in transplantation research (Section II.B), immune system and cancer biology understanding (Sections II.A, II.C–II.D), and genetic sequencing and editing techniques (Section II.E). This Section traces these scientific developments over the last century to provide context for the innovation of CAR-T cell therapy (Figure 1).

19. *CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers*, NAT'L CANCER INST. (Mar. 10, 2022), https://www.cancer.gov/about-cancer/treatment/research/car-t-cells (Mar. 10, 2022) [hereinafter NCI 2022].

Figure 1: Timeline of key events leading to the first CAR-T cancer therapeutics.



A. CANCER AND THE IMMUNE SYSTEM

Researchers have long suspected that the immune system naturally suppresses or mitigates cancer. In the late 1800s, Wilhelm Busch and Friedrich Fehleisen noticed tumor regression in human patients who had also developed a skin infection.[20] A few years later, New York physician William Coley injected his cancer patients with bacteria to spur an immune response.[21]

20. Waldman et al., *supra* note 14, at 651.
21. *Id.*

In 1909, one year after winning the Nobel Prize in Physiology or Medicine, German chemist and immunologist Paul Ehrlich hypothesized that the immune system might play a role in tumor suppression.[22] He observed that cancer occurred in families, but typically developed later in adulthood.[23] Therefore, he hypothesized, parents can pass on cancer to their children but the body has some defenses to suppress tumors for years.[24] However, without animal cancer models, scientists could not test this hypothesis.[25] Thus, in the early 20th century, most doctors treated cancer with surgery and localized radiation, even though both treatments frequently failed to eradicate all of the cancer cells.[26]

B. TRANSPLANTATION RESEARCH ELUCIDATES IMMUNE PROCESSES

Evidence from surgical transplantation research further supported Ehrlich's hypothesis that some bodily defenses could recognize harmful or foreign cells.[27] As early as 1597, surgeon Gaspare Tagliacozzi of Bologna noticed most successful tissue transplants (mostly skin grafts) occurred when the tissue came from the patient and not from a donor.[28] His work and that of other transplantation surgeons led tumor biologists to graft tumors into mice to study cancer and graft rejection.[29] However, mouse immune cells appeared to recognize the graft cells as foreign and reject them.[30] As both surgeons and tumor biologists continued to face non-self-transplant rejection, this research stalled.[31]

The need to treat burn victims from World War II renewed interest in transplant research. Many patients' injuries were too severe for them to act as their own tissue donors.[32] The British Medical Research Counsel assigned zoologist Peter B. Medawar to research transplantation in the 1940s.[33] By

22. Paul Ehrlich, *Ueber Den Jetzigen Stand Der Karzinomforschung*, 5 NED.TIJDSCHR. GENEESKD 273, 289–90 (1909); Stefan H. E. Kaufmann, *Immunology's Coming of Age*, 10 FRONTIERS IMMUNOLOGY 684, 685 (2019); Waldman et al., *supra* note 14, at 651.

23. Ehrlich, *supra* note 22, at 288–90.

24. *Id.*

25. *See* Gavin P. Dunn et al., *Cancer Immunoediting: From Immunosurveillance to Tumor Escape*, 2 NATURE IMMUNOLOGY 991, 991 (2002).

26. Vincent T. DeVita, Jr. & Edward Chu, *A History of Cancer Chemotherapy*, 68 CANCER RSCH. 8643, 8643 (2008).

27. *See* Dunn, *supra* note 25, at 991.

28. *See* Arthur M. Silverstein, *Transplantation and Immunogenetics*, *in* HISTORY OF IMMUNOLOGY 275, 276–78 (1989).

29. *See id.* at 279–83.

30. *Id.* at 278–82.

31. *Id.* at 283–85.

32. *Id.* at 285–91.

33. *Id.*

studying human patients with skin grafts, and later, transplant rejection in laboratory animals, Medawar and others confirmed that immune cells caused transplant rejection.[34] Their work caught the attention of the growing immunology field.[35]

C. THE CANCER IMMUNOSURVEILLANCE HYPOTHESIS

Medawar's work and the creation of reliable mouse models re-ignited research into the connection between cancer and the immune system. At the same time Ehrlich proposed his immune system cancer hypothesis, scientist Clarence Cook Little and mouse breeder Abbie Lathrop created the first inbred mouse model.[36] Inbred mouse models allow multiple generations of mice to have nearly identical genetic makeups.[37] The genetic similarity permitted tumor transplantation from one inbred mouse to another—an early animal cancer model. Further, in support of Ehrlich's hypothesis, researchers discovered they could train an inbred mouse's immune system to recognize a transplant from a genetically similar mouse as foreign.[38] This training involved inducing tumor formation (e.g., through exposure to a carcinogen), removing the tumor, and, after a period of time, re-transplanting the tumor back into the mouse.[39] This training research led scientists to hypothesize that the immune system recognized markers on the surface of tumor cells (i.e., "tumor-specific antigens").[40]

By 1957, two researchers had independently proposed the "cancer immunosurveillance" hypothesis.[41] The hypothesis is as follows: when cancer cells develop, either from inherited cancer-causing genes or from a cancer-causing genetic mutation, the cancer cells lose their "self" antigens or develop foreign antigens, and then provoke "an effective immunological reaction with regression of the tumor and no clinical hint of its existence."[42]

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34. *Id.*

35. *Id.*

36. Tom Clarke, *Mice Make Medical History*, NATURE (Dec. 5, 2002), https://www.nature.com/articles/news021202-10; *see also* Leila McNeill, *The History of Breeding Mice for Science Begins with a Woman in a Barn*, SMITHSONIAN MAG. (Mar. 20, 2018), https://www.smithsonianmag.com/science-nature/history-breeding-mice-science-leads-back-woman-barn-180968441/.

37. Clarke, *supra* note 36.

38. Lloyd J. Old & Edward A. Boyse, *Immunology of Experimental Tumors*, 15 ANN. REV. MED. 167, 173 (1964).

39. *Id.*

40. Dunn, *supra* note 25, at 991; *see also* Old & Boyse, *supra* note 38, at 167–69.

41. *See* Macfarlane Burnet, *Cancer – A Biological Approach*, 1 BRIT. MED. J. 841, 846 (1957); *see also* Dunn, *supra* note 25, at 991–92.

42. Burnet, *supra* note 41, at 846.

Nude mouse models, another advance in animal models, initially threw cold water on the cancer immunosurveillance hypothesis.[43] Nude mice have severely impaired immune systems, with different levels and types of impairment depending on the method scientists use to induce impairment.[44] In the 1960s, researchers developed an athymic nude mouse model, a genetically immunocompromised model lacking a thymus and most T cells.[45] Despite the severe immune impairment, the athymic mice showed no significant difference in spontaneous tumor formation compared to immunocompetent mice.[46] The cancer immunosurveillance hypothesis, and research on the immune system's role in suppressing cancer, thus fell into temporary disfavor.[47]

In addition to the initial nude mice experiment results, another class of cancer therapeutics distracted from cancer immunotherapy research. World War II kicked off intense research into the chemical components of poison gases called nitrogen mustards as cancer "chemotherapeutics."[48] These efforts eventually led Congress to provide $5 million to the National Cancer Institute to establish the Cancer Chemotherapy National Service Center.[49] After initial skepticism related to severe adverse reactions, improved chemotherapeutics became the dominant treatment for many blood cancers (including large B-cell lymphoma) by the 1970s.[50] Still in use today, these treatments prolong life expectancy, but often fail to cure patients and cause severe adverse reactions.[51]

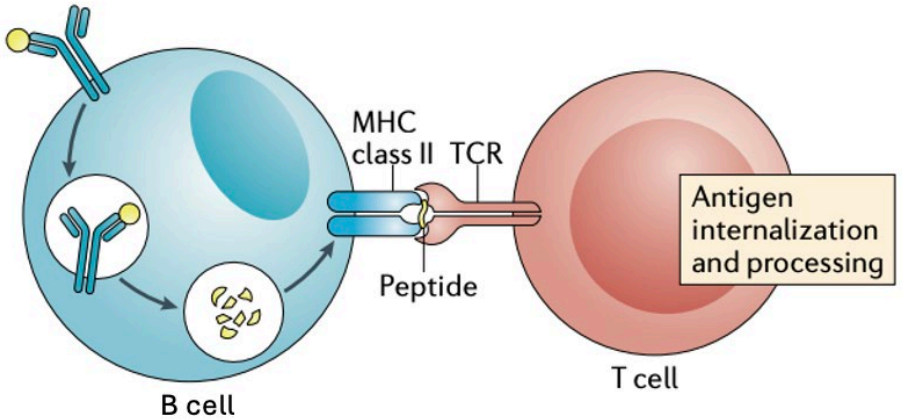
D. THE IMMUNE SYSTEM AS A THERAPEUTIC TOOL

Advances in immunology renewed focus on the cancer immunosurveillance hypothesis.[52] By the 1960s, immunologists identified the thymus and bone marrow as key tissues where immune cells arise.[53] Cells arising from the thymus became known as T cells; those arising from bone marrow became known as B cells.[54] During the 1970s and 1980s,

43. Dunn, *supra* note 25, at 992.
44. *Id.*
45. *Id.*
46. *Id.*
47. *Id.*; *see also* discussion *supra* Section II.D.
48. DeVita, Jr. & Chu, *supra* note 26, at 8643–47.
49. *Id.*
50. *Id.* at 8647–49.
51. *Id.* at 8647–52.
52. Kaufmann, *supra* note 22, at 7–8; Dunn, *supra* note 25, at 992–94.
53. Jacques F. A. P. Miller, *The Golden Anniversary of the Thymus*, 11 NATURE REVS. IMMUNOLOGY 489, 490 (2011).
54. *Id.* at 491.

immunologists learned that T cells and B cells work collaboratively.[55] A subclass of T cells ("helper T cells") help B cells to make antibodies.[56] T cells and B cells both possess surface receptors that bind to antigens (e.g., proteins) (Figure 2).[57] TCRs bind only to antigens displayed on cell surfaces by the MHC, an issue that would become relevant to early CAR-T cell designs.[58]

Figure 2: B cell receptors bind to free antigens (shown as a yellow circle) while TCRs bind to antigen fragments displayed by an MHC protein on another cell's surface, such as a B cell (edited from original source).[59]



The discovery of T cell and B cell receptors and their role in immune regulation revealed that earlier nude mice were not as immunodeficient as previously believed.[60] Studies with nude mice modified for additional immunosuppression supported the cancer surveillance hypothesis.[61] Nude mice with certain immunosuppressive modifications were more susceptible to tumors (induced and spontaneously generated) than unmodified nude mice.[62] The cancer surveillance hypothesis also appeared to hold up in humans.

55. *Id.*
56. *Id.*
57. *Id.* at 491–92; Yoshihisa Kuwana et al., *Expression of Chimeric Receptor Composed of Immunoglobulin-derived V Regions and T-Cell Receptor-Derived C Regions*, 149 BIOCHEMICAL & BIOPHYSICAL RSCH. COMMC'NS 960 (1987).
58. *See* sources cited *supra* note 57.
59. Munir Akkaya et al., *B Cell Memory: Building Two Walls of Protection Against Pathogens*, 20 NATURE REVS. IMMUNOLOGY 229, 233 (2020) (showing a portion of Figure 2).
60. Dunn, *supra* note 25, at 992–93.
61. *Id.*
62. *Id.*

Correlational data suggests immunosuppression correlates with increased cancer risk in humans.[63]

One of the first treatments developed from improved immunology knowledge was adoptive T cell therapy (ACT), a process where doctors infuse cancer patients with T cells (either their own or from a donor).[64] Doctors first saw promising results with ACT in 1966, when they noticed tumor regression in patients treated with a mixture of their own tumor cells and leukocytes (i.e., white blood cells, including T cells and B cells).[65] The National Cancer Institute built on these advances in the 1980s by treating patients with lymphocytes (i.e., a subset of leukocytes that includes T cells and B cells) isolated from their own tumor biopsies (tumor-infiltrating lymphocytes, TILs).[66] Patient response to ACT improved dramatically when patients underwent lymphodepletion, a process where doctors reduce patients' T cells, prior to treatment with TILs.[67] However, many patients' tumors lacked enough TILs for effective ACT.[68]

At the same time, scientists explored another strategy to harness the immune system to treat cancer: infusing patients with antibodies designed to target cancer cell antigens.[69] Scientists discovered antibodies in the 1890s.[70] By the 1970s, scientists understood the role of antibodies in the immune system and established a robust method to produce monoclonal antibodies (i.e., antibodies designed to target a single antigen).[71] Identification of a protein called CD20 on the surfaces of cancerous B cells associated with non-Hodgkin's lymphoma led to approval of rituximab, the first FDA-approved antibody to treat cancer.[72] Today, scientists continue to advance antibody

63. *Id.* at 994–95.

64. Waldman et al., *supra* note 14, at 658; M. Teresa Villanueva, *Engineering Armed T Cells for the Fight*, NATURE CANCER MILESTONES (Dec. 10, 2020), https://www.nature.com/articles/d42859-020-00077-6.

65. Chester M. Southam et al., *Effect of Leukocytes on Transplantability of Human Cancer*, 19 CANCER 1743 (1966); Waldman et al., *supra* note 14, at 658.

66. Waldman et al., *supra* note 14, at 658; Villanueva, *supra* note 64.

67. Waldman et al., *supra* note 14, at 658; *see also* Steven A. Rosenberg et al., *Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy*, 17 CLINICAL CANCER RSCH. 4550, 4556 (2011) (explaining several hypotheses for lymphodepletion's beneficial effects, including less competition with other T cells for the resources which promote T cell growth).

68. *See* sources cited *supra* note 67.

69. Paula Dobosz & Tomasz Dzieciątkowski, *The Intriguing History of Cancer Immunotherapy*, 10 FRONT. IMMUNOL. 2965, 3–4 (2019).

70. *Id.*

71. *Id.*

72. *Id.*

cancer therapeutics with positive clinical results.[73] For patients with cancer cells that display identifiable and targetable antigens, treatment with antibodies often enables better outcomes and reduced adverse reactions relative to chemotherapeutics.[74] However, some patients fail to respond or show minimal responses to antibody therapeutics.[75]

E. ENGINEERING T CELLS AS A "LIVING" THERAPEUTIC

By the 1990s, researchers hypothesized that T cells engineered to specifically target cancer antigens would combine the benefits of ACT, a "living" therapeutic, with the specificity and MHC-independence of antibody-based therapeutics.[76]

Substantial evidence now shows tumor cells persist because they evade the body's natural immune response.[77] Most proteins on the surface of tumor cells do not elicit a strong immune response because they appear on non-tumor cells as well (i.e., self antigens).[78] Even when one or more of a tumor cell's antigens can trigger an immune response, tumor cells may evade T cell detection by producing less of the antigen and/or MHC proteins and creating an immunosuppressive microenvironment.[79]

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73. *Id.* at 3–5.

74. Andrew M. Scott et al., *Antibody Therapy of Cancer*, 12 NATURE REVS. CANCER 278, 278, 281, 284 (2012); *see also* Ruei-Min Lu et al., *Development of Therapeutic Antibodies for the Treatment of Diseases*, 27 J. BIOMED. SCI. 1, 2–5 (2020) (listing in Table 1, FDA-approved monoclonal antibodies to-date as well as their target antigens).

75. *See, e.g.*, Esteban Cruz & Veysel Kayser, *Monoclonal Antibody Therapy of Solid Tumors: Clinical Limitations and Novel Strategies to Enhance Treatment Efficacy*, 13 BIOLOGICS: TARGETS & THERAPY 33, 33–34 (2019).

76. Lærke J. B. Brandt et al., *Emerging Approaches for Regulation and Control of CAR T Cells: A Mini Review*, 11 FRONTIERS IMMUNOLOGY 326, 1 (2020); Waldman et al., *supra* note 14, at 659; Helene M. Finney et al., *Activation of Resting Human Primary T Cells with Chimeric Receptors: Costimulation from CD28, Inducible Costimulator, CD134, and CD137 in Series with Signals from the TCRζ Chain*, 172 J. IMMUNOLOGY 104 (2004); Gideon Gross & Zelig Eshhar, *Endowing T Cells with Antibody Specificity Using Chimeric T Cell Receptors*, 6 FASEB J. 3370 (1992); Villanueva, *supra* note 64; Michel Sadelain et al., *The Promise and Potential Pitfalls of Chimeric Antigen Receptors*, 21 CURRENT OPINION IMMUNOLOGY 215 (2009); Kuwana, *supra* note 57, at 965–67.

77. U.S. Patent No. 7,446,190, at [1:17-19] (filed May 28, 2003) [hereinafter '190 patent]; *see also* Anat Globerson Levin et al., *CAR T Cells: Building on the CD19 Paradigm*, 51 EUR. J. IMMUNOLOGY 2151 (2021).

78. '190 patent, *supra* note 77, at [1:19-21]; *see also* Sadelain, *supra* note 76, at 217; John Maher et al., *Human T-lymphocyte Cytotoxicity and Proliferation Directed by a Single Chimeric TCRζ/CD28 Receptor*, 20 NATURE BIOTECHNOLOGY 70, 70 (2002).

79. '190 patent, *supra* note 77, at [1:21-29]; *see also* Levin, *supra* note 77, at 2151; Maher, *supra* note 78, at 70; Waldman et al., *supra* note 14, at 658–60; Federico Garrido et al., *The Urgent Need to Recover MHC Class I in Cancers for Effective Immunotherapy*, 39 CURRENT OPIN. IMMUNOLOGY 44, 48 (2016); Soldano Ferrone et al., *How Much Longer Will Tumour Cells Fool the Immune System?* 21 IMMUNOLOGY TODAY 70, 70–71 (2000).

CAR-T cell therapies avoid some tumor cell defenses by modifying the native TCR to act more like an antibody.[80] As explained *supra*, antibodies bind to antigens that are not displayed by MHC proteins on cell surfaces (e.g., circulating antigens or antigens displayed directly on cell surfaces without MHC proteins).[81] Despite this binding difference, antibodies and TCRs share many structural similarities.[82] With advances in DNA sequencing and gene editing technology, scientists leveraged TCRs' structural similarity with antibodies to modify the binding region of patients' native TCRs with a single chain version of an antibody binding domain ("scFv") targeting a particular cancer antigen.[83] Scientists dubbed these engineered T cells chimeric antigen receptor (CAR) T cells or CAR-T cells.[84] A chimera is a hybrid creature from Greek mythology (part lion, part goat, and part serpent); a CAR is a hybrid protein that contains part of an antibody binding region attached to part of a TCR (the intracellular portion)[85] (Figure 5). However, "first-generation" CAR-T cells failed to live up to their promise.[86] The CAR-T cells neither proliferated nor mounted a strong immune response to their target tumor antigen.[87]

F. CARs WITH CO-STIMULATORY DOMAINS ACHIEVE CLINICAL SUCCESS

The key insight that transformed CAR-T cells from benchtop hope to clinical success was that natural T cells require two binding events to activate an immune response: T cells must bind to both (1) the target antigen and (2) a "co-stimulatory" molecule, such as another protein on the cell surface like CD28.[88] Upon receiving signals from both binding events, the TCR intracellular portion (CD3ζ) signals the cell to multiply to create an army of T cells and to release chemical signals to recruit other immune cells to destroy

80. *See infra* Section III.A.

81. Maher, *supra* note 78, at 70.

82. *See infra* Secion III.A, Figure 5.

83. Gross & Eshhar, *supra* note 76, at 3372–73; Levin, *supra* note 77, at 2151; *see also* Waldman et al., *supra* note 14, at 659; Villanueva, *supra* note 64; Sadelain, *supra* note 76, at 215, 217–18.

84. Vicki Brower, *The CAR T-Cell Race*, SCIENTIST (Apr. 1, 2015), https://www.the-scientist.com/bio-business/the-car-t-cell-race-35701 (Fig. 2 illustrating first-, second-, and third-generation CAR technology differing primarily in the intracellular signaling domain)).

85. *See infra* Section III.A.

86. *Id.*

87. *Id.*

88. Ronald H. Schwartz, *T Cell Anergy*, SCI. AM. 62, 68 (1993); Maher, *supra* note 78, at 70, 74; Waldman et al., *supra* note 14, at 652, 659; Finney et al., *supra* note 76, at 104; Sadelain, *supra* note 76, at 215, 217–18; Kuwana, *supra* note 57, at 965; Villanueva, *supra* note 64.

target antigen-bearing cells.[89] When a T cell receives only one signal from binding to the target antigen, the T cell may fail to replicate and even initiate a programmed cell death pathway.[90]

"Second generation" CARs supplemented the native TCR intracellular signaling domain (CD3ζ) with a second, "costimulatory" signaling domain (e.g., CD28 or 4-1BB signaling domains).[91] The "costimulatory" domain causes the T cell to mount an immune response upon binding to *only* the target antigen (Figure 2).[92] With this modification, the first CAR-T cell therapies showed dramatic success in treating blood cancers.[93] The innovation underlying Yescarta's success is a second-generation CAR with an intracellular signaling domain comprising CD3ζ and portions of the CD28 signaling element (SEQ ID NO:6 in U.S. Pat. No. 7,446,190 ("the '190 patent"); Figure 3).[94]

89. Schwartz, *supra* note 88, at 62; Sadelain, *supra* note 76, at 217; Maher, *supra* note 78, at 70.

90. '190 patent, *supra* note 77, at [1:49-67]; *see also* Schwartz, *supra* note 88, at 66, 68; Sadelain, *supra* note 76, at 217; Maher, *supra* note 78, at 70–71, 74.

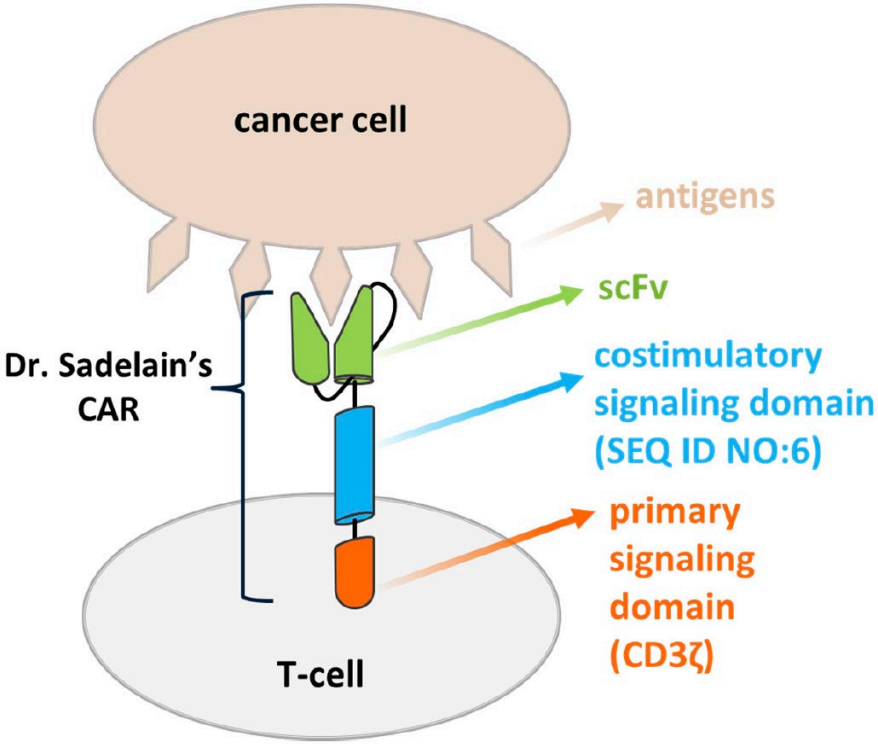
91. Petition for Writ of Certiorari, at 2–3, 10–11, Juno Therapeutics, Inc. v. Kite Pharma, Inc., 143 S. Ct. 402, *reh'g denied*, 143 S. Ct. 631 (2023); *see also* Donald B. Kohn et al., *CARS on Track in the Clinic*, 19 MOLECULAR THERAPEUTICS 432, 432, 434 (2011).

92. *See* sources cited *supra* note 91.

93. Waldman et al., *supra* note 14, at 660.

94. Maher, *supra* note 78, at 70, 74; Juno Therapeutics, Inc. v. Kite Pharma, Inc. (*Juno v. Kite I*), No. 2:17-cv-07639 SJO-KS, 2020 WL 10460622, at *9 (C.D. Cal. Mar. 24, 2020) ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 [p]atent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 [p]atent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 [p]atent."), *rev'd*, 10 F.4th 1330 (Fed. Cir. 2021) (appealing only on invalidity arguments (not non-infringement)); *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14 ("Kite stipulated that Yescarta literally infringes the ['190] patent" with only one independent claim reciting SEQ ID NO:6).

Figure 3: The Yescarta co-stimulatory domain comprises CD3ζ and portions of CD28 (including '190 patent SEQ ID NO: 6).[95]



Blood cancers made for a promising first target for CAR-T cell therapies because scientists had already identified antigens to target on blood cancer cells (e.g., rituximab targeted the CD20 marker on B cells), doctors can easily monitor cell counts, and T cells easily access the location of these cancers (e.g., blood, bone marrow, and lymph nodes); now the field aims to expand to solid tumors.[96]

CAR-T cell therapeutics differ from off-the-shelf small-molecule therapeutics; the cells are highly personalized, engineered versions of each patient's own T cells (i.e., "autologous" T cells).[97] To make a CAR-T cell

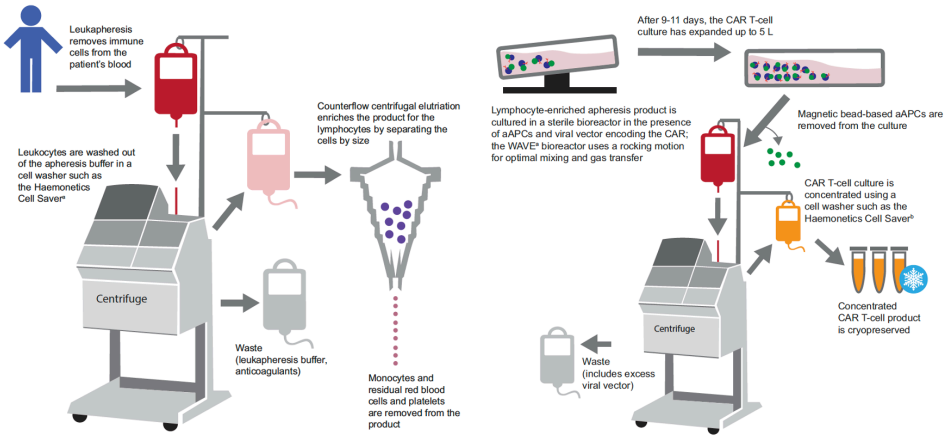
95. Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 12.

96. *See* Marcela V. Maus et al., *Antibody-Modified T Cells: CARs Take the Front Seat for Hematologic Malignancies*, 123 BLOOD 2625 (2014); NCI 2022, *supra* note 19; Waldman et al., *supra* note 14, at 660.

97. *See* Daniel Hollyman et al., *Manufacturing Validation of Biologically Functional T Cells Targeted to CD19 Antigen for Autologous Adoptive Cell Therapy*, 32 J. IMMUNOTHERAPY 169, 169–70 (2009).

therapy for a single patient, researchers withdraw the patient's blood, separate T cells from red blood cells and other white blood cells, introduce genetic material encoding the CAR gene, and multiply the engineered T cells to a sufficient quantity to achieve therapeutic effect (Figure 4).[98]

Figure 4: Patient-specific CAR-T cell manufacturing process.[99]



III. DEVELOPMENT HISTORY OF INVENTION

Yescarta and other CAR-T cell therapy development occurred in three phases. First, researchers identified effective co-stimulatory domains.[100] Next, hospitals with research facilities developed small-scale manufacturing techniques to transform patients' own T cells into cancer-fighting CAR-T cells in small, Phase I clinical studies.[101] Finally, both start-up and established

98. Bruce L. Levine et al., *Global Manufacturing of CAR T Cell Therapy*, 4 MOLECULAR THERAPY – METHODS & CLINICAL DEV. 92, 92–93 (2017); *see also* Hollyman, *supra* note 97, at 170–72.

99. One complexity of CAR-T cell therapy manufacturing is that each patient requires their own unique dose. The process starts when doctors withdraw a patient's own T cells. Then, scientists engineer these cells to express a CAR targeted to a particular antigen. Eventually, doctors administer the engineered cells back to the patient. Levine, *supra* note 98, at 93–94 (Figures 2 and 3). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Figure reproduced from Levine, *supra* note 98, at 93-94.

100. *See infra* Section III.A.

101. *See infra* Section III.B.

pharmaceutical companies provided funding and expertise to expand CAR-T cell manufacturing for Phase II and III clinical studies.[102]

A. FINDING THE RIGHT CAR CONSTRUCT

Researchers hypothesized that substitution of the TCR binding domain for the antibody binding domain would permit TCRs to bind to antigens without also binding to MHC proteins, as discussed in Section II.E, *supra*.[103] Antibodies and TCRs share many functional and structural features.[104] Functionally, antibodies and TCRs include a region capable of binding specifically to an antigen.[105] Structurally, the binding regions of both proteins comprise two peptide chains covalently bound together (Figure 5).[106] One key difference is that antibodies bind to free antigens, while TCRs bind to antigens attached to MHC proteins on cells' surfaces.[107] Early efforts by Zelig Eshhar's team at the Weizmann Institute of Science, and others, struggled to test this hypothesis due to low yields of this chimeric protein.[108] One reason for the low yields related to the antibody binding domain structure.[109] Natively, two peptide chains must bind to form each arm of the antibody binding domain.[110] In 1990, Eshhar took a one-year sabbatical to collaborate with Steven Rosenberg at NIH's National Cancer Institute (NCI) on CAR-T cells targeted to human melanoma.[111]

By 1993, Eshhar's team overcame the two peptide chain challenge by implementing a "single chain" antibody binding domain, called a single chain variable region (scFv).[112] A scFv includes a "linker" to connect the two

102. *See infra* Section III.C.

103. *See, e.g.*, Nicholas R. J. Gascoigne et al., *Secretion of a Chimeric T-Cell Receptor-Immunoglobulin Protein*, 84 PROC. NAT'L. ACAD. SCIS. 2936 (1987); Kuwana, *supra* note 57, at 960–61; Peter Braendstrup et al., *The Long Road to the First FDA-Approved Gene Therapy: Chimeric Antigen Receptor T Cells Targeting CD19*, 22 CYTOTHERAPY 57, 58–59 (2020); Gideon Gross et al., *Expression of Immunoglobulin-T-Cell Receptor Chimeric Molecules as Functional Receptors with Antibody-Type Specificity*, 86 PROC. NAT'L ACAD. SCIS. 10024 (1989).

104. Gross, *supra* note 103, at 10024.

105. *Id.*

106. *Id.*

107. *Id.*

108. Kuwana, *supra* note 57, at 966–67; Zelig Eshhar et al., *Specific Activation and Targeting of Cytotoxic Lymphocytes Through Chimeric Single Chains Consisting of Antibody-Binding Domains and the γ or ζ Subunits of the Immunoglobulin and T-Cell Receptors*, 90 PROC. NAT'L ACAD. SCIS. 720, 720–21 (1993).

109. *See* sources cited *supra* note 108.

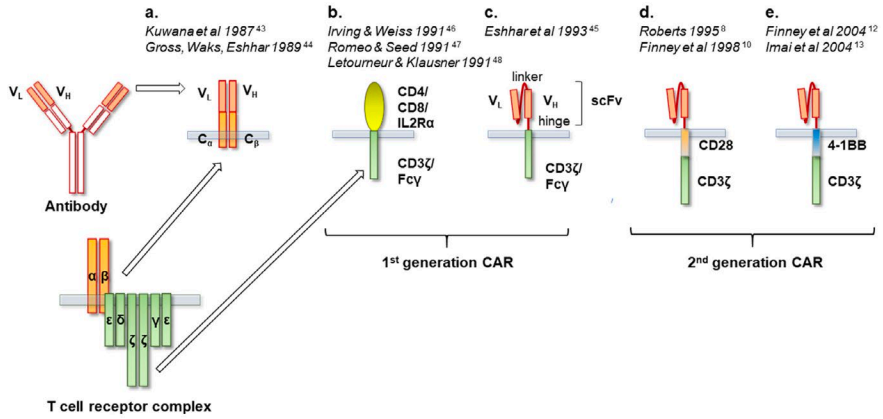
110. *Id.*

111. Brower, *supra* note 84.

112. Eshhar, *supra* note 108, at 723; Brower, *supra* note 84; Braendstrup, *supra* note 103, at 58; Villanueva, *supra* note 64; Sadelain, *supra* note 76, at 215.

antibody binding domain peptide chains (Figure 5(a) shows an antibody binding domain with two, unconnected peptide chains (V_L and V_H); Figure 5(c) shows an antibody binding domain (orange) with peptide chains chemically connected with a "linker" (red)).[113] Eshhar created the "first-generation" CAR when his team connected this scFv to TCR's native, intracellular signaling domain, CD3ζ (Figure 5(c)).[114]

Figure 5: Structural evolution of CARs from dual peptide (a) to single peptide (b–e) and from first-generation (b–c) to second-generation (d–e).[115]



In 1988, following the excitement around recent, successful biotech IPOs (e.g., Genentech, Amgen), medical researchers and entrepreneurs founded Cell Genesys to develop therapies based on gene editing, specifically cancer therapeutics and vaccines.[116] Stephen Sherwin served as Cell Genesys's first CEO following his work at Genentech (1983–1990) and NCI (pre-1983).[117] Margo Roberts, principal scientist and director of Immune and Cell Therapy at Cell Genesys, and her collaborators created a "first-generation" CAR targeting HIV antigens.[118] Their research led to the first CAR-T cell clinical

113. *See* sources cited *supra* note 112.

114. *Id.*

115. Braendstrup, *supra* note 103, at 59 (Figure 2).

116. Bernadette Tansey, *Drug Trial Halted; Cell Genesys Shares Plummet*, SFGATE (Aug. 28, 2008), https://www.sfgate.com/business/article/Drug-trial-halted-Cell-Genesys-shares-plummet-3198009.php; Cell Genesys, Inc., Annual Report (Form 10-K), at 3 (Mar. 31, 2001).

117. *Stephen A. Sherwin, MD*, PARKER INST. CANCER IMMUNOTHERAPY, https://www.parkerici.org/person/stephen-a-sherwin-md/ (last visited Sept. 24, 2023).

118. Margo R. Roberts et al., *Targeting of Human Immunodeficiency Virus-Infected Cells by CD8+ T Lymphocytes Armed with Universal T-Cell Receptors*, 84 BLOOD 2878 (1994); *Margo Roberts, PhD*,

trials in 1994 in collaboration with Carl June at the University of Pennsylvania (who was already investigating cell-based therapies).[119] When these clinical studies showed only limited efficacy and HIV antiviral treatments proved effective, Cell Genesys shifted focus to cancer vaccines and prostate cancer.[120] Despite limited clinical efficacy, these studies progressed CAR-T cell manufacturing techniques and evidenced the importance of "co-stimulation" to trigger robust CAR-T cell activation.[121] T cells naturally require "co-stimulation" to activate.[122]

In February 1995, Roberts solved the co-stimulation problem by adding a "co-stimulatory" domain to the first-generation CAR, inventing a "second-generation" CAR (Figure 5(d); Figure 6).[123] This second-generation CAR's signaling domain included portions of two native, T cell stimulating receptors: the TCR CD3ζ signaling domain and the CD28 signaling domain. Cell Genesys patented the invention in U.S. Patent No. 5,712,149 ("the '149 patent"). As late as 2002, Cell Genesys continued to protect their chimeric receptor intellectual property, pursing interference or opposition proceedings to ensure patent rights.[124] However, in 2005, Cell Genesys restructured to focus resources on their "most advanced and most promising development

UNITY BIOTECHNOLOGY, https://unitybiotechnology.com/team/margo-roberts/ (last visited Sept. 24, 2023) [hereinafter Roberts Bio].

119. *Cells Genesys Gains NIAID AIDS Researcher Hoth*, PINK SHEET (July 5, 1993), https://pink.pharmaintelligence.informa.com/PS022870/CELLS-GENESYS-GAINS-NIAID-AIDS-RESEARCHER-HOTH; Steven G. Deeks et al., *A Phase II Randomized Study of HIV-Specific T-Cell Gene Therapy in Subjects with Undetectable Plasma Viremia on Combination Antiretroviral Therapy*, 5 MOLECULAR THERAPY 788, 796 (2002) (using CD28 stimulation); Ronald T. Mitsuyasu et al., *Prolonged Survival and Tissue Trafficking Following Adoptive Transfer of CD4ζ Gene-Modified Autologous CD4+ and CD8+ T Cells in Human Immunodeficiency Virus-Infected Subjects*, 96 BLOOD 785 (2000); Robert E. Walker et al., *Long-Term In Vivo Survival of Receptor-Modified Syngenic T Cells in Patients with Human Immunodeficiency Virus Infection*, 96 BLOOD 467 (2000); Braendstrup, *supra* note 103, at 59; J. L. Macpherson & J. E. J. Rasko, *Clinical Potential of Gene Therapy: Towards Meeting the Demand*, 44 INTERNAL MED. J. 224, 229–30 (2014).

120. Gloria B. Kim et al., *CAR Talk: How Cancer-Specific CAR T Cells Can Instruct How to Build CAR T Cells to Cure HIV*, 10 FRONTIERS IMMUNOLOGY 2310, 2310–12 (2019); Braendstrup, *supra* note 103, at 59; Macpherson & Rasko, *supra* note 119, at 229–30; Ron Leuty, *Inside a Big Pharma Cancer Drug Approval with Roots in a Small Bay Area Biotech*, SAN FRANCISCO BUS. TIMES (June 1, 2021), https://www.bizjournals.com/sanfrancisco/news/2021/06/01/bristol-myers-squibb-car-t-abecma-multiple-myeloma.html.

121. Kim, *supra* note 120, at 2310–12; Braendstrup, *supra* note 103, at 59; Macpherson & Rasko, *supra* note 119, at 229–30.

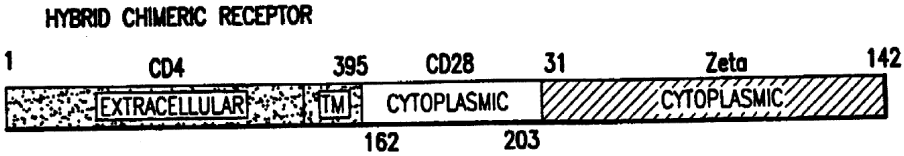
122. *See supra* Section II.F.

123. U.S. Patent No. 5,712,149 at [4:60-5:50] (filed Feb. 3, 1995) [hereinafter '149 patent]; Braendstrup, *supra* note 103, at 60.

124. Cell Genesys, Inc., Annual Report (Form 10-K), at 10, 21 (Mar. 31, 2001); Cell Genesys, Inc., Annual Report (Form 10-K), at 11, 23 (Mar. 31, 2002); Cell Genesys, Inc., Annual Report (Form 10-K), at 10, 23 (Mar. 31, 2003).

programs," primarily their cancer vaccines and not CAR-T cell therapies.[125] Cell Genesys merged with another pharmaceutical company after terminating their vaccine clinical studies due to safety issues in 2008.[126] Later, Kite Pharma, Inc. ("Kite"), the company that makes Yescarta, acquired Cell Genesys's CAR patents.[127]

Figure 6: One of Roberts's second-generation CARs including CD3ζ and CD28 costimulatory domains.[128]



To compete with the U.S. biotechnology industry, the British government funded biotechnology initiatives which led to the founding of Celltech Group Limited in 1980 to develop antibody-derived drugs.[129] Helene Finney and colleagues at Celltech also created a CD28-based second-generation CAR and filed a patent application on December 23, 1996.[130] Faced with repeated rejections over the '149 patent (and other prior art), Celltech abandoned their U.S. application.[131] In 2001, Finney (and, later, independent researchers at St. Jude Children's Research Hospital) invented a different second-generation CAR with the 4-1BB signaling domain in place of the CD28 domain (4-1BB-

125. Cell Genesys, Inc., Annual Report (Form 10-K), at 6 (Mar. 13, 2006).

126. Cell Genesys, Inc., Annual Report (Form 10-K), at 6–7 (Mar. 9, 2009); *BioSante, Cell Genesys Merge in $38M Deals*, FIERCE BIOTECH (June 30, 2009), https://www.fiercebiotech.com/biotech/biosante-cell-genesys-merge-38m-deals.

127. Kite Pharma, Inc., Registration Statement (Form S-1), at 79 (May 19, 2014).

128. '149 patent, *supra* note 123, at Fig. 1D.

129. Celltech Group PLC, Annual Report (Form 20-F), at 11 (June 30, 2003); *see also* Tim Harris, *A British Biotech Biopedia: Early Days in the U.K.*, GENETIC ENG'G & BIOTECHNOLOGY NEWS (Oct. 4, 2021), https://www.genengnews.com/commentary/a-british-biotech-biopedia-early-days-in-the-u-k/ (explaining the National Enterprise Board, among others, provided initial Series A funding for Celltech).

130. Helene M. Finney et al., *Chimeric Receptors Providing Both Primary and Costimulatory Signaling in T Cells from a Single Gene Product*, 161 J. IMMUNOLOGY 2791, 2791–92 (1998); Braendstrup, *supra* note 103, at 60.

131. Braendstrup, *supra* note 103, at 60; *see* Mar. 21, 2000 Office Action, File History of U.S. Patent Application No. 2003/0077249, at 15 [hereinafter '249 application]; Feb. 27, 2003 Office Action, File History of '249 application, at 3–8; July 9, 2004 Abandonment, File History of '294 application.

CD3ζ)(Figure 5(d–e)).[132] Celltech continued to develop antibody-derived and small-molecule therapeutics until 2004, when they were acquired by UCB S.A., but never focused on cell-based therapies.[133]

Michel Sadelain and colleagues at Memorial Sloan Kettering Cancer Center (MSKCC) improved early second-generation CD28-based CARs by implementing a longer CD28 co-stimulatory domain in 2002.[134] Their second-generation CAR-T cells not only killed cancer cells, but also underwent "multiple rounds of expansion and continue[d] to specifically kill tumor cells, even after withdrawal and re-exposure to the target antigen."[135] The longer CD28 domain included a thirty-nine amino acid portion of CD28's *extracellular* domain (in addition to earlier second-generation CARs use of CD28 intracellular and transmembrane domains).[136] Although they did not yet know the mechanism, Sadelain and colleagues were the first to recognize that extracellular portions of CD28 acted not merely as inert spacers, but as CAR functionality modulators.[137]

In addition to an effective signaling portion, researchers sought an extracellular binding region specific to therapeutically relevant targets. By the early 2000s, researchers identified the CD19 protein as an attractive target for CAR-T cells.[138] First, the CD19 protein specifically exists on the surface of a

132. WO 2002/033101 (filed Oct. 16, 2001); Finney et al., *supra* note 76, at 104–6; Chihaya Imai et al., *Chimeric Receptors with 4-1BB Signaling Capacity Provoke Potent Cytotoxicity Against Acute Lymphoblastic Leukemia*, 18 LEUKEMIA 676 (2004) (Figure 2 showing second generation CAR constructs incorporate a co-stimulatory domain, often CD28 or 4-1BB).

133. *See* Celltech Group PLC, Annual Report (Form 20-F), at 11–24 (June 25, 2004).

134. Maher, *supra* note 78, at 70; '190 patent, *supra* note 77; Villanueva, *supra* note 64; Sadelain, *supra* note 76, at 215; Juno Therapeutics, Inc. v. Kite Pharma (*Juno v. Kite IPR Appeal*), No. 17-cv-07639 SJO-RAO, 2018 WL 1470594, at *1 (C.D. Cal. Mar. 8, 2018); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 12.

135. Patent Owner Response, at 1, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016) [hereinafter Patent Owner Response].

136. *Id.* at 1–2; Maher, *supra* note 78, at 70; Brower, *supra* note 84 ("'Ultimately, we needed 20 years to learn how to supercharge these cells to deliver anticancer activity,' says Arie Belldegrun, president and CEO of Kite Pharma in Santa Monica, California, which is assessing CAR T cells in six trials for B cell leukemia and lymphomas, and glioblastoma.").

137. Patent Owner Response, *supra* note 135, at 1–2; *see also* Maher, *supra* note 78, at 73 (proposing several hypotheses for improved CAR-T cell functionality due to CD28 region); Yangbing Zhao et al., *A Herceptin-Based Chimeric Antigen Receptor with Modified Signalling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity*, 183 J. IMMUNOL. 5563, 5563–64 (2009) (describing a collaboration of Drs. Sadelain, Eshhar, and Rosenberg, citing Maher, *supra* note 78, for creating effective second-generation CAR with CD28-CD3ζ co-stimulatory domain).

138. Braendstrup, *supra* note 103, at 60; Juno Therapeutics, Inc., Registration Statement (Form S-1), at 99 (Nov. 17, 2014); Michel Sadelain et al., *The Basic Principles of Chimeric Antigen*

particular subset of cells found in the blood, B cells, and is not present on other cell types.[139] Second, most types of B cell cancers express the CD19 antigen.[140] Third, patients tolerate loss of healthy B cells (i.e., an off-target effect of CD19-targeting CAR-T cell therapy).[141] And, as discussed in Section II.E *supra*, blood cancer therapeutics benefit from the relative ease of reaching tumor cells.

These advances resulted in the CAR protein key to Yescarta's clinical success.[142] The primary funding for this foundational CAR research came from government grants, charitable organizations, and private investment (Table 1).

Receptor Design 3 CANCER DISCOV. 388, 393 (2013); Junru Lu & Guan Jiang, *The Journey of CAR-T Therapy in Hematological Malignancies*, 21 MOL. CANCER 194, 4 (2022).

139. Sadelain, *supra* note 138, at 393; *see also* Pier Luigi Zinzani & Giorgio Minotti, *Anti-CD19 Monoclonal Antibodies for the Treatment of Relapsed or Refractory B-Cell Malignancies: A Narrative Review with Focus on Diffuse Large B-Cell Lymphoma* 148 J. CANCER RSCH & CLINICAL ONCOLOGY 177, 178 (2021); Hollyman, *supra* note 97, at 169.

140. Sadelain, *supra* note 138, at 393; *see also* Zinzani, *supra* note 139, at 178.

141. James N. Kochenderfer et al., *Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor*, 32 J. IMMUNOTHERAPY 689, 689–90 (2009).

142. *See* '190 patent, *supra* note 77, at [1:13-2:36]; *see also Juno v. Kite I*, *supra* note 94, at *9 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 [p]atent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 [p]atent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 Patent."); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14 ("Kite stipulated that Yescarta literally infringes the ['190] [p]atent" with only one independent claim reciting SEQ ID NO:6).

Table 1: Government, charitable funds, and corporate collaborations funded early CAR construct invention (selected).

Inventor	CAR Construct	Funding
Zelig Eshhar (Weizmann Institute of Science)[143]	CD3ζ	Charitable Funds (Crown Endowment Fund for Immunological Research)
Margo Roberts (Cell Genesys, Inc.)[144]	CD28-CD3ζ	Corporate (Cell Genesys, Inc.)
Helene Finney and collaborators (Celltech Therapeutics Ltd.)[145]	CD28-CD3ζ 4-1BB- CD3ζ	Corporate (Celltech Therapeutics Ltd.)
Michel Sadelain[146] (MSKCC)	CD28-CD3ζ	Government grants (NIH) Charitable Funds (CaP CURE Association, Cure for Lymphoma Foundation) Individual investigator grants (Jean Shanks Clinical Research Fellowship)
Dario Campana, Chihaya Imai (St. Jude Children's Research Hospital)[147]	4-1BB- CD3ζ	Government grants (NCI, Center of Excellence grant from the State of Tennessee) Charitable Funds (American Lebanese Syrian Associated Charities) Individual investigator grants (FM Kirby Clinical Research Professor of the American Cancer Society)

B. EARLY, SINGLE-CENTER CLINICAL STUDIES

Manufacturing challenges posed the next major barrier to commercializing CAR-T cell therapies. By the early 2000s, researchers could make small numbers of CAR-T cells at the benchtop, but clinical trials required significantly more cells.[148]

Research institutions with a hospital arm like MSKCC, NCI, and the University of Pennsylvania harnessed their combined clinical and research capabilities to bring CAR-T cells from the benchtop to the bedside. In

143. Eshhar, *supra* note 108, at 724.
144. '149 patent, *supra* note 123.
145. Finney, *supra* note 130, at 2791; Finney et al., *supra* note 76, at 104.
146. Maher, *supra* note 78, at 75.
147. Imai, *supra* note 132, at 683.
148. Hollyman, *supra* note 97, at 169–70, 173, 179; Levine, *supra* note 98, at 93–99.

collaboration with NCI, MSKCC initiated the first clinical study of a second-generation (CD28-CD3ζ) CAR-T cell therapy in 2007.[149] This Phase I study evaluated CAR-T safety in eight patients with relapsed purine analog-refractory chronic lymphocytic leukemia (CLL) at a single center, MSKCC.[150] MSKCC and NCI soon initiated a second Phase I study in two patients with $CD19^+$ B-cell acute lymphoblastic leukemia (B-ALL).[151] MSKCC relied on their research facilities to rapidly (within two to three weeks) engineer and scale-up personalized CAR-T cells for each patient in their trials.[152] Soon after, NCI (led by Rosenberg) developed their own manufacturing methods for CAR-T cells based on a different co-stimulatory design (4-1BB-CD3ζ) and initiated another Phase I clinical trial.[153] Carl June at the University of Pennsylvania tested a similar co-stimulatory design (4-1BB-CD3ζ) in another small Phase I clinical study.[154] The 4-1BB-CD3ζ design ultimately became the

149. *Treatment of Relapsed or Chemotherapy Refractory Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma Using Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT00466531?id=NCT00466531&draw=2&rank=1 (last visited Sept. 24, 2023); Renier J. Brentjens et al., *Safety and Persistence of Adoptively Transferred Autologous CD19-Targeted T Cells in Patients with Relapsed or Chemotherapy Refractory B-Cell Leukemias*, 118 BLOOD 4817 (2011); Levin, *supra* note 77, at 2152; Braendstrup, *supra* note 103, at 60; James N. Kochenderfer et al., *Eradication of B-Lineage Cells and Regression of Lymphoma in a Patient Treated with Autologous T Cells Genetically Engineered to Recognize CD19*, 116 BLOOD 4099 (2010) (reporting study results).

150. Brentjens, *supra* note 149, at 4817; *see also* Levin, *supra* note 77, at 2152; Braendstrup, *supra* note 103, at 60; Kochenderfer, *supra* note 149, at 4099. Relapsed CLL patients received but did not respond well to earlier "purine analog" treatment.

151. *Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated With Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT01044069?id=NCT01044069&draw=2&rank=1 (last visited Sept. 24, 2023); Brentjens, *supra* note 149, at 4817–18; Renier J. Brentjens et al., *CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia*, 5 SCI. TRANSLATIONAL MED. 177ra38, 1–2 (2013).

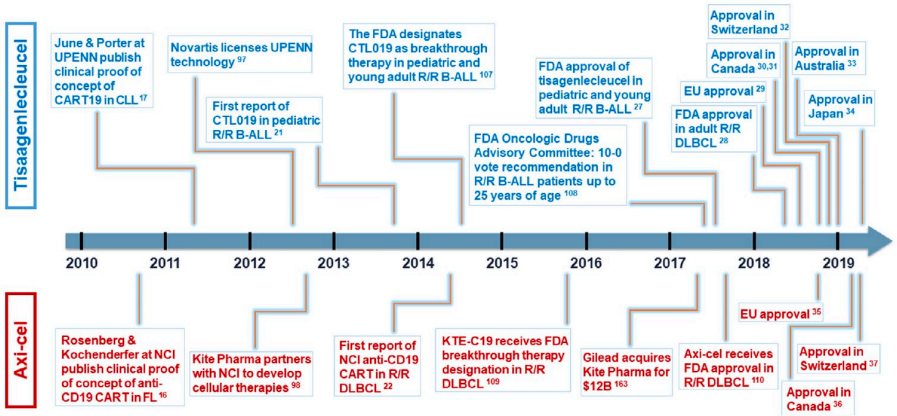
152. Brentjens, *supra* note 149, at 4818; Hollyman, *supra* note 97, at 169–70, 173, 179.

153. *CAR T Cell Receptor Immunotherapy for Patients With B-cell Lymphoma*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT00924326?id=NCT00924326&draw=2&rank=1 (last visited Sept. 24, 2023); Kochenderfer, *supra* note 141, at 689–90.

154. *CART19 to Treat B-Cell Leukemia or Lymphoma That Are Resistant or Refractory to Chemotherapy*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT01029366?id=NCT01029366&draw=2&rank=1 (last visited Sept. 24, 2023); Stephan A. Grupp et al., *Chimeric Antigen Receptor-Modified T Cells for Acute Lymphoid Leukemia*, 368 NEW ENGLAND J. MED. 1509, 1509–10 (2013); Shannon L. Maude et al., *Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia*, 371 NEW ENGLAND J. MED. 1507, 1507–8 (2014); David L. Porter et al., *Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia*, 365 NEW ENGLAND J. MED. 725, 731, 733 (2011); Michael Kalos et al., *T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia*, 3 SCI. TRANSLATIONAL MED. 95ra73, 1–2 (2011).

first CAR-T therapeutic approved by the FDA (Kymriah, tisagenlecleucel; Figure 7).[155]

Figure 7: Timeline showing key events leading to regulatory approval of first two CAR-T cancer therapeutics.[156]



In addition to reporting promising results, these studies established the feasibility of small-scale clinical CAR-T cell manufacturing.[157] Other institutions with research and hospital arms followed suit.[158]

Funding of these studies relied primarily on government and charitable foundation grants (Table 2).

155. Braendstrup, *supra* note 103, at 60–61; Brower, *supra* note 84.

156. Braendstrup, *supra* note 103, at 58 (Figure 1).

157. Brentjens, *supra* note 149, at 4818; Hollyman, *supra* note 97, at 169–70, 173, 179; Kochenderfer, *supra* note 141, at 689–90; James N. Kochenderfer et al., *B-Cell Depletion and Remissions of Malignancy Along with Cytokine-Associated Toxicity in a Clinical Trial of Anti-CD19 Chimeric-Antigen-Receptor-Transduced T Cells*, 119 BLOOD 2709 (2012); Brentjens, *supra* note 151, at 1–2; Kalos et al., *supra* note 154, at 2.

158. Kohn, *supra* note 91, at 433; James N. Kochenderfer & Steven A. Rosenberg, *Treating B-Cell Cancer with T Cells Expressing Anti-CD19 Chimeric Antigen Receptors*, 10 NAT'L REV. CLINICAL ONCOLOGY 267, 269–74 (2013) (Tables 1 and 3 showing multiple combined hospitals and research sites initiated early, single-site clinical studies of second-generation CAR-T cell therapies (as of publication on April 2, 2013)).

Table 2: Government, charitable funds, and corporate collaborations funded early CAR-T clinical studies (selected) (continued on the next page).

Study Details	Funding
Institution MSKCC (with NCI) CAR Construct CD28-CD3ζ Clinical Study NCT00466531[159] Initiation Date 4/27/2007	**Government grants** (NIH, NCI, National Center for Advancing Translational Sciences) **Charitable Funds** (e.g., The Annual Terry Fox Run for Cancer Research, Lymphoma Research Foundation) **Individual investigator grants** (e.g., ASCO Conquer Cancer Foundation Young Investigator Award, American Society of Hematology Scholar Clinical Fellow Award, Leukemia and Lymphoma Society Career Development Grant)
Institution MSKCC (with NCI) CAR Construct CD28-CD3ζ Clinical Study NCT01044069[160] Initiation Date 1/7/2010	**Government grants** (NIH, NCI, National Center for Advancing Translational Sciences) **Charitable Funds** (e.g., The Annual Terry Fox Run for Cancer Research, Lymphoma Research Foundation, Carson Family Charitable Trust) **Individual investigator grants** (e.g., ASCO Conquer Cancer Foundation Young Investigator Award, American Society of Hematology Scholar Clinical Fellow Award, Leukemia and Lymphoma Society Career Development Grant)

159. Brentjens, *supra* note 149, at 4817, 4827; Mark B. Geyer et al., *Safety and Tolerability of Conditioning Chemotherapy Followed by CD19-Targeted CAR T Cells for Relapsed/Refractory CLL*, 4 JCI INSIGHT e122627 1, 15 (2019).

160. Brentjens, *supra* note 149, at 4817, 4827; Brentjens, *supra* note 151, at 7, 9.

Institution NCI CAR Construct 4-1BB- CD3ζ Clinical Study NCT00924326[161] NCT01087294[162] Initiation Date 6/18/2009 3/16/2010	**Government grants** (NCI, NIH) **Corporate collaboration** (Kite Pharma, Inc.)
Institution University of Pennsylvania CAR Construct 4-1BB- CD3ζ Clinical Study NCT01029366[163] Initiation Date 12/10/2009	**Government grants** (NIH, Pennsylvania Department of Health) **Charitable Funds** (e.g., Leukemia and Lymphoma Society, Jeffrey Jay Weinberg Memorial Foundation, Alliance for Cancer Gene Therapy) **Individual investigator grants** (e.g., St. Baldrick's Foundation Scholar Award, Research Scholar Grant from the American Cancer Society) **Corporate collaboration** (Novartis)

As of 2012, the biggest challenge facing CAR-T cell therapeutics was a lack of financial investment and expertise to scale CAR-T cell manufacturing sufficiently to progress the candidates from small-scale single-center clinical

161. James N. Kochenderfer et al., *Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated with High Serum Interleukin-15 Levels*, 35 J. CLINICAL ONCOLOGY 1803, 1803–13 (2017).

162. James N. Kochenderfer et al., *Donor-Derived CD19-Targeted T Cells Cause Regression of Malignancy Persisting After Allogeneic Hematopoietic Stem Cell Transplantation*, 122 BLOOD 4129, 4129–38 (2013).

163. Maude et al., *supra* note 154, at 1507, 1516; Porter et al., *supra* note 154, at 726, 733; Kalos et al., *supra* note 154 at 9, 11.

studies to large-scale multi-center studies and, eventually, to commercialize successful candidates.[164]

C. INDUSTRY GETS INVOLVED

Institutions with successful results from early clinical studies partnered with companies to fund larger clinical studies (Figure 8). The initial CAR-T cell therapeutics targeted CD19, but recent approvals target a B cell maturation antigen (BCMA) (Table 3). As of April 2024, the FDA has approved six CAR-T cell therapies.[165]

The University of Pennsylvania partnered with Novartis in August 2012 resulting in FDA approval of Kymriah (tisagenlecleucel) in 2017 (Table 3).[166] The partnership followed a publication that detailed promising results from a single patient enrolled in a three-patient Phase I clinical study.[167]

Arie Belldegrun, a surgeon and former mentee of Rosenberg at NCI, founded Kite in 2009 to develop cancer immunotherapies.[168] NCI partnered with Kite and Gilead in 2012 (Gilead later acquired Kite in 2019 for $11.9B) resulting in FDA approval of Yescarta (axicabtagene ciloleucel) on October 18, 2017.[169] Roberts, formerly with Cell Genesys (discussed *supra*), led Kite's

164. Carl June et al., *T-Cell Therapy at the Threshold*, 30 NAT'L BIOTECHNOLOGY 611, 614 (2012); Kohn, *supra* note 91, at 432; Brower, *supra* note 84; Braendstrup, *supra* note 103, at 60; Deborah Bach, *Three Cancer Research Powerhouses Form Immunotherapy Startup*, FRED HUTCH CANCER CTR. (Dec. 3, 2013), https://www.fredhutch.org/en/news/center-news/2013/11/cancer-research-powerhouses-form-juno-therapeutics.html.

165. NCI 2022, *supra* note 19.

166. *University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients*, PENN MED. NEWS (Aug. 6, 2012), https://www.pennmedicine.org/news/news-releases/2012/august/university-of-pennsylvania-and; *University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients*, FIERCE PHARMA (Aug. 6, 2012), https://www.fiercepharma.com/pharma/university-of-pennsylvania-and-novartis-form-alliance-to-expand-use-of-personalized-t-cell; Braendstrup, *supra* note 103, at 60–61; Brower, *supra* note 84; Novartis 2014 Complaint at ¶ 11, *Tr. of the Univ. of Pennsylvania v. St. Jude Child.'s Research Hosp.*, No. 2:13-cv-01502 SD, 2014 WL 12610149 (2014).

167. Porter, *supra* note 154, at 725–26.

168. *Aya Jakobovits, Ph.D., Named President and CEO of Kite Pharma, Inc.*, GILEAD (Sept. 16, 2010), https://www.gilead.com/news-and-press/press-room/press-releases/2010/9/aya-jakobovits-phd-named-president-and-ceo-of-kite-pharma-inc; *Eight Lessons from Arie Belldegrun (Kite/Allogene)*, AXIAL (Feb. 7, 2021), https://medium.com/@axialxyz/eight-lessons-from-arie-belldegrun-kite-allogene-7bf09c504f19.

169. Braendstrup, *supra* note 103, at 60–61; Brower, *supra* note 84; Kite Pharma, Inc., Registration Statement (Form S-1) at 12 (May 19, 2014); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14; *Gilead Sciences to Acquire Kite Pharma for $11.9 Billion*, BUSINESSWIRE (Aug. 28, 2017), https://www.businesswire.com/news/home/20170828005415/en/;

Yescarta team as Kite's Chief Scientific Officer from 2013 to 2014.[170] Yescarta received regulatory approval in the European Union in 2018, in Canada and Switzerland in 2019, and in Australia and Japan in 2021 for various blood cancers.[171]

MSKCC inventors together with other researchers founded Juno Therapeutics ("Juno") to commercialize their CAR-T technology.[172] Celgene partnered with Juno to develop CAR-T cell therapies, and then acquired Juno in 2018.[173] Bristol-Myers Squibb (BMS) acquired Celgene in 2019, largely for their CAR-T cell portfolio.[174] Juno (within BMS) received approval for their first CAR-T cell therapeutic, Breyanzi, in 2021.[175]

YESCARTA (axicabtagene ciloleuce), U.S. FOOD & DRUG ADMIN. (Oct. 18, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel.

170. Roberts Bio, *supra* note 118; *Kite Pharma Expands Leadership Team and Announces Senior Management Promotions*, GILEAD (Apr. 14, 2014), https://www.gilead.com/news-and-press/press-room/press-releases/2014/4/kite-pharma-expands-leadership-team-and-announces-senior-management-promotions.

171. Braendstrup, *supra* note 103, at 61; *Kite's Yescarta® (Axicabtagene Ciloleucel) CAR T-Cell Therapy Now Widely Available and Publicly Funded For Patients in Australia with Four Types of Aggressive Non-Hodgkin Lymphoma*, KITE THERAPEUTICS (Aug. 5, 2021), https://www.kitepharma.com/news/company-statements/kite-yescarta-axicabtagene-ciloleucel-car-t-cell-therapy-now-widely-available-and-publicly-funded-for-patients-in-australia-with-four-types-of-aggressive-non-hodgkin-lymphoma; *Daiichi Sankyo Authorizes the First YESCARTA® (Axicabtagene Ciloleucel) CAR T-cell Therapy Treatment Site in Japan*, GILEAD (Dec. 16, 2021), https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/daiichi-sankyo-authorizes-the-first-yescarta-axicabtagene-ciloleucel-car-tcell-therapy-treatment-site-in-japan.

172. Christina Pernambuco-Holsten, *New Biotech Startup Will Pit the Immune System Against Cancer*, MEMORIAL SLOAN KETTERING CANCER CTR. (Dec. 6, 2013); Bach, *supra* note 164.

173. *Celgene Corporation to Acquire Juno Therapeutics, Inc.*, CELGENE (Jan. 22, 2018), https://www.celgene.com/newsroom/cellular-immunotherapies/celgene-corporation-to-acquire-juno-therapeutics-inc/#:~:text=About%20the%20Juno%2DCelgene%20Collaboration,CAR%20T%20and%20TCR%20technologies.

174. *Bristol-Myers Drives into CAR-T Therapies*, ECONOMIST INTELLIGENCE UNIT (Feb. 18, 2019), https://www.eiu.com/industry/article/817665265/bristol-myers-drives-into-car-t-therapies/2019-02-18. *But see* Carl H. June et al., *CAR T Cell Immunotherapy for Human Cancer*, 359 SCI. 1361, 1364 (2018) (noting that Juno terminated clinical development of JCAR015 in Mar 2017 because of five deaths related to cerebral edema using "the CD19 CAR originally developed by Brentjens and colleagues").

175. Steve Brachmann, *Supreme Court's Denial of Juno Therapeutics is Another Blow to the Life Science Patent Industry*, IPWATCHDOG (Nov. 8, 2022), https://ipwatchdog.com/2022/11/08/supreme-courts-denial-juno-therapeutics-another-blow-life-science-patent-industry/id=152655/.

Figure 8: Corporate investment in CAR-T cell therapy commercialization occurred through start-ups and partnerships with established pharmaceutical companies.[176]

CAR-T Cell Company IPOs		
Company	**Date**	**Value**
Kite Pharma	2014	$134.1M
Bellicum Pharmaceuticals	2014	$160M
Juno Therapeutics	2014	$264.6M
Cellectis	2015	$228M

CAR-T Cell Corporate Deals		
Institution/Company	**Partner**	**Date**
University of Pennsylvania	Novartis	2012
Celgene	Bluebird Bio, Baylor College of Medicine	2013
Cellectis	Pfizer	2014
Cellectis	Ohio State University	2015
Kite Pharma	Amgen	2015
MD Anderson Cancer Center	Ziopharm, Intrexon	2015

Table 3: As of April 2024, the FDA has approved six CAR-T cell therapies; most target CD19, but the two most recently approved therapies target BCMA; and most use the 4-1BB construct, but Kite uses the CD28 construct.

Product	**Sponsor**	**First Approval Date**	**First Approved Indication**
Kymriah[177] (tisagenlecleucel) Target CD19 Co-Stimulation Domain 4-1BB	Novartis Pharmaceuticals, Inc.	Aug. 30, 2017	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

176. Brower, *supra* note 84.

177. *Package Insert – KYMRIAH*, U.S. FOOD & DRUG ADMIN. 1, 22, 29 (May 2022), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel; *Approval Letter – KYMRIAH*, U.S. FOOD & DRUG ADMIN. 1 (Aug. 30, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel.

Yescarta[178] (axicabtagene ciloleucel) Target CD19 Co-Stimulation Domain CD28	Kite Pharma, Inc.	Oct. 18, 2017	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Tecartus[179] (brexucabtagene autoleucel) Target CD19 Co-Stimulation Domain CD28	Kite Pharma, Inc.	July 24, 2020	Adult patients with relapsed/refractory mantle cell lymphoma
Breyanzi[180] (lisocabtagene maraleucel) Target CD19 Co-Stimulation Domain 4-1BB	Juno Therapeutics, a Bristol-Myers Squibb Company	Feb. 5, 2021	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

178. *Package Insert – YESCARTA*, U.S. FOOD & DRUG ADMIN. 2, 22, 32 (Mar. 2024), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel; *Approval Letter – YESCARTA*, U.S. FOOD & DRUG ADMIN. 1 (Oct. 18, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel.

179. *Package Insert – TECARTUS*, U.S. FOOD & DRUG ADMIN. 2, 21, 30 (Oct. 2021), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel; *Approval Letter – TECARTUS*, U.S. FOOD & DRUG ADMIN. 1 (July 24, 2020), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel.

180. *Package Insert – BREYANZI*, U.S. FOOD & DRUG ADMIN. 29, 38 (June 2022), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel; *Approval Letter – BREYANZI*, U.S. FOOD & DRUG ADMIN. 1 (Feb. 5, 2021), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel.

Abecma[181] (idecabtagene vicleucel) Target BCMA Co-Stimulation Domain 4-1BB	Celgene Corporation, a Bristol-Myers Squibb Company	Mar. 26, 2021	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
Carvykti[182] (ciltacabtagene autoleucel) Target BCMA Co-Stimulation Domain 4-1BB	Janssen Biotech, Inc.	Feb. 28, 2022	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody

IV. ANALYSIS OF INNOVATION DRIVERS

CAR-T cell therapy development followed a familiar pharmaceutical development pattern. Researchers at academic institutions and pharmaceutical companies conceived of the CAR constructs and conducted the early clinical studies to show their therapeutic promise.[183] These researchers were driven by financial rewards (e.g., compensation, grants, commercialization), professional recognition (e.g., papers, awards), and intrinsic motivations (e.g., curiosity, altruism). For inventions to reach patients, clinical study data must show they

181. *Package Insert – ABECMA*, U.S. FOOD & DRUG ADMIN. 2, 23, 34 (Mar. 2021), https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel; *Approval Letter – ABECMA*, U.S. FOOD & DRUG ADMIN. 1 (Mar. 26, 2021), https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel.

182. *Package Insert – CARVYKTI*, U.S. FOOD & DRUG ADMIN. 1, 24, 33 (Feb. 2023), https://www.fda.gov/vaccines-blood-biologics/carvykti; *Approval Letter – CARVYKTI*, U.S. FOOD & DRUG ADMIN. 1 (Feb. 28, 2022), https://www.fda.gov/vaccines-blood-biologics/carvykti.

183. *See infra* Section IV.A.

are safe and effective.[184] Grants and charitable donations provided sufficient funding to perform early, single-site clinical studies, but not the large, multi-site clinical studies necessary for regulatory approval.[185] Promising results from early studies enticed private sector funding for the large, multi-center clinical studies.[186] These actors were driven primarily by profit maximization, often via market exclusivity—in the form of patent protection, trade secret protection, and regulatory exclusivity.[187] CAR-T cell therapy is now one of the most promising cancer therapy research areas with academic and industry projects in the pipeline.[188] Intellectual property and regulatory exclusivity continue to play a prominent and growing role in CAR-T cell therapy development.[189]

A. CURIOSITY, SERENDIPITY, TENACITY, ALTRUISM, AND PATENT RIGHTS

Individual researchers, like the early CAR-T cell therapy inventors, often pursue research for personal and professional reasons.[190] Eshhar's, Sadelain's, Rosenberg's, Campana's, and June's experiences illustrate these innovation

184. *See The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD & DRUG ADMIN. (Nov. 24, 2017), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

185. *See supra* Section III.A, III.B; *see also* Bach, *supra* note 164 ("In an era of shrinking federal funding, the Hutch's president and director reasoned, the center needed a bold new strategy – one that would allow it to freely pursue innovation without being slowed down by a grants process that, while useful in providing pilot data, would not be large enough to enroll and follow the number of patients required to develop an adequate clinical profile for a novel cancer therapy.").

186. *See supra* Section III.B–III.C; *infra* Section IV.B–IV.C.

187. *See* sources cited, *supra* note 186; Olga Gurgula, *Strategic Patenting by Pharmaceutical Companies – Should Competition Law Intervene?*, 51 IIC INT'L REV. INDUS. PROP. COPYRIGHT LAW 1062, 1066 (2020); *see also* William T. Allen et al., *Commentaries and Cases on the Law of Business Organization* 311 (Rachel E. Barkow et al. eds., 6th ed. 2021) (explaining that U.S. corporations act under the shareholder primacy norm where maximizing profits for shareholders motivates business decisions).

188. *See supra* Section III.C.

189. *See Price Declines After Branded Medicines Lose Exclusivity in the U.S.*, IMS INST. FOR HEALTHCARE INFORMATICS 2, 4 (2016), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf; Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of New Medicines*, 20 YALE L.J. & TECH. 1, 6–23 (2018); Matthew J. Higgins et al., *The Role of Assets in Place: Loss of Market Exclusivity and Investment*, Nat'l Bureau of Econ. Rsch. Working Paper No. 27588 25–27 (2020); Gurgula, *supra* note 187, at 1066.

190. *See* Alice Lam, *What Motivates Academic Scientists to Engage in Research Commercialization: 'Gold', 'Ribbon' or 'Puzzle'?*, 40 RSCH. POL'Y 1354 (2011).

drivers for CAR-T cell therapies.[191] For Eshhar—who routinely lacked grant funding—curiosity, tenacity, and revenues from patent royalties represent the primary innovation drivers. For Rosenberg, Sadelain, and Campana, who received adequate funding through grants and institutional support, curiosity and altruism represent the primary innovation drivers. For June, altruism and personal tragedy represent primary innovation drivers. For all five, the timing of their early professional lives serendipitously coincided with renewed interest in cancer immunotherapies.

1. Eshhar

Curiosity, serendipity, professional awards, tenacity, a flash of genius, altruism, and patent rights drove Eshhar's CAR-T cell therapy innovations.

Eshhar's scientific story begins with curiosity. While serving in the Israeli military, Eshhar saw a presentation by researchers from Weismann Institute of Science on molecular biology.[192] In his words: "My jaw dropped. Immediately I wanted to translate all the wonders I'd come to know into molecules."[193]

Serendipity and professional prizes also drove Eshhar's innovation. He chose TCRs as the subject for his doctoral research in the 1960s, just as interest in the cancer immunosurveillance hypothesis renewed.[194] Eshhar chose to work with a series of renowned researchers who went on to receive top scientific awards shortly after mentoring Eshhar.[195] At the time, he viewed TCR research as "totally basic science" and he had "no concept or pretention that a day would come when that knowledge would serve [him] in devising a treatment for cancer."[196] His research resulted in identifying the native TCR structure and amino acid code.[197] When Eshhar decided to pursue post-doctoral research, his advisor dissuaded him from a school in New York and, "on the spot", called a friend at Harvard to secure Eshhar a place in more

191. Finney declined an interview for this research. Roberts, Sadelain, and June did not respond to an interview request. Information about Eshhar's, Rosenberg's, Sadelain's, and June's experiences comes from publicly available interviews and articles. Information about Campana's experience comes from an interview with the author.

192. *See* Smadar Reisfeld, *The Story Behind an Israeli Immunologist's Cancer-Fighting Breakthrough*, HAARETZ (Nov. 10, 2017), https://www.haaretz.com/science-and-health/2017-11-10/ty-article-magazine/.premium/the-scientist-who-paved-the-way-for-a-chimeric-cancer-therapy/0000017f-e6e1-da9b-a1ff-eeefeac70000.

193. *Id.*

194. *See id.*

195. *See id.* (explaining Eshhar selected advisors "simply because they were the best in the field").

196. *See id.*

197. *See id.*

family-friendly Boston.[198] Eshhar's post-doctoral advisor, Baruj Benacerraf, received the Nobel Prize in Physiology or Medicine in 1980 for his T cell research, just four years after Eshhar left.[199] Benacerraf directed Eshhar to engineer T cells to target "a distinctive molecule that characterizes the cancerous cells" Benacerraf recently discovered.[200] In 1976, his last year at Harvard, Eshhar heard a lecture about a method to produce antibodies by fusing a B cell with a cancer cell.[201]

Tenacity and a flash of genius drove Eshhar to combine his serendipitous knowledge of TCRs and antibodies into a cancer-fighting CAR-T cell therapy. After the 1976 antibody lecture, Eshhar showed up, unannounced, to work in the inventor's lab—the Milstein lab in Cambridge, England.[202] According to Eshhar's recollection, Milstein rejected Eshhar, asking why he failed to contact the lab before showing up.[203] Eshhar replied: "I was impassioned, and I was certain we would work something out."[204] When Milstein did not relent, Eshhar sought out a different inventor, Georges Kohler in Switzerland, to learn the antibody manufacturing method.[205] While implementing the method in his own lab at the Weismann Institute, Eshhar thought:

> Why not take the best of both worlds? In principle, a T cell is capable of eradicating a cancerous cell, thanks to its killer mechanism, but it's not good at identifying the target. An antibody, in contrast, is an expert in identifying targets but it has no killer mechanism. What if the capabilities are combined? We'll create a hybrid, a chimera – the monster in Greek mythology that had the head of a lion, the body of a goat and the tail of a dragon or snake. On the one hand, it will have the antibody's excellent binding ability, and on the other, the T cell's killer ability. We named the chimera the "T-body," a kind of verbal hybrid of antibody and T cell.[206]

Eshhar conceived of this idea with his graduate students, including Gideon Gross.[207] Shortly after, in 1990, Eshhar spent a year on sabbatical with Rosenberg at the NIH and initiated his first clinical study with human cancer

198. *See id.* (explaining Eshhar had three children at the time and his advisor believed Boston would be a better city to raise his family).
199. *See id.*
200. *See id.*
201. *See id.*
202. *See id.*
203. *See id.*
204. *See id.*
205. *See id.*
206. *See id.*
207. *See id.*

patients.[208] The NIH results failed to show clinical efficacy and Eshhar returned home.[209]

Because Eshhar failed to receive sufficient grants to fund his research, he "constantly registered patents in order to use the money from the royalties."[210] For example, when Eshhar learned of a United Nations initiative offering large grants to prevent drug abuse, he pitched an idea to a Swedish company to develop an antibody-based opium sensor.[211] The company licensed Eshhar's patented idea.[212] He similarly patented his CAR technology.[213] When the Weismann Institute, the original assignee, refused to continue maintenance payments, Eshhar and his co-inventors bought the patent rights from the Institute.[214] When Kite eventually licensed Eshhar's patent, Eshhar and his co-inventors personally received royalties from their invention.[215]

In addition to other innovation drivers, Eshhar's motivation is also altruistic—he receives great satisfaction when he "happen[s] to meet someone whose life was saved by the treatment."[216] According to him, "there's nothing greater than that."[217]

2. Sadelain

Serendipity, tenacity, curiosity, and altruism drove Sadelain's innovations.

Serendipity placed Sadelain at the start of his career in the 1980s when ACT and other immune-based approaches began to show clinical promise for cancer therapy.[218] Like Eshhar, Sadelain's doctoral research focused on T cells.[219] Sadelain selected the Massachusetts Institute of Technology for his post-doctoral research because it was one of "only a handful of institutions in the world" beginning to insert foreign genes into cells.[220] To his new colleagues' surprise, he selected an "esoteric purpose" for genetic engineering—modifying T cells.[221] In fact, his "official" project focused on

208. *See id.*
209. *See* Rosenberg, *supra* note 1, at 15.
210. *See* Reisfeld, *supra* note 192.
211. *See id.*
212. *See id.*
213. *See id.*
214. *See id.*
215. *See id.*
216. *See id.*
217. *See id.*
218. *See* Jennifer E. Adair, *An Interview with Michel Sadelain, MD, PhD*, 29 HUM. GENE THERAPY 530 (2018).
219. *See id.* at 531.
220. *See id.*
221. *See id.*

genetically engineering different cells.[222] After two to three years of failed experiments, Sadelain genetically modified a T cell to express a foreign gene in 1992.[223] He presented the result at the World Congress of Immunology where "it elicited absolutely zero interest."[224] Serendipitously, Eshhar published his first CAR-T cell paper just one year later.[225]

Curiosity and altruism drove Sadelain to persist. He applied to permanent positions at institutions which "understood clinical trials and getting treatments to patients."[226] Sadelain joined MSKCC because it ranked highly in Investigational New Drug holdings.[227] There, Sadelain engineered T cells to target blood cancers (particularly directed to cell surface markers CD19, CD20, and CD22) because of MSKCC colleagues' experience with bone marrow transplants.[228] Serendipity struck again when Sadelain identified a CAR construction with improved co-stimulatory properties through an unknown mechanism.[229] Sadelain, with his collaborator Isabelle Rivière, set out to "pave the way" for CAR-T cell therapies to reach patients.[230] Over a decade, Sadelain's team developed capacity to manufacture and test CAR-T cell therapies on MSKCC patients. To spur adoption of new CAR-T cell therapies, Sadelain coordinated with NCI and the University of Pennsylvania to publish the "provocative data" from the first clinical studies.[231]

Commercialization did not initially drive Sadelain's research. Because CAR-T cell therapy was "both a cell therapy and a genetic therapy," Sadelain knew his work "was not the kind of thing [he] could take to a company for clinical development."[232] Instead he and Rivière leveraged MSKCC's resources to develop a facility following Good Manufacturing Practices in-house.[233] With just three rooms, Sadelain and Rivière treated over 250 patients with more than

222. *See id.*

223. *See* Katrina Altersitz, *'A Moment of Marvel' in Manhattan Brings a Revolution in CAR T-Cell Therapy*, HEALIO (May 24, 2019), https://www.healio.com/news/hematology-oncology/20190522/a-moment-of-marvel-in-manhattan-brings-a-revolution-in-car-tcell-therapy.

224. *See id.*

225. *See* Eshhar, *supra* note 108.

226. *See* Altersitz, *supra* note 223.

227. *See id.*

228. *See id.*

229. *See* Maher, *supra* note 78, at 73 (proposing several hypotheses for improved CAR-T cell functionality due to CD28 region).

230. *See* Altersitz, *supra* note 223.

231. *See id.*

232. *See id.*

233. *See id.*

350 different CAR-T cell products.[234] Positive results from this work enabled them to expand to thirteen rooms.[235]

While grants and charitable donations provided sufficient funds for initial, small-scale clinical studies, these resources could not fund the large-scale clinical studies required for CAR-T cell therapies to receive FDA approval and reach patients more broadly.[236] Sadelain and his collaborators founded Juno to accelerate widespread access to CAR-T therapies through collaboration and private sector funding.[237]

3. Rosenberg

Rosenberg's cancer immunotherapy innovations arose from altruism, curiosity, and stubbornness as well as serendipity; to him, commercialization represented only a pathway to bring his breakthroughs to more patients.

As early as high school, Rosenberg recognized that "[c]ancer randomly attacks people of all ages and forces its victims and their families to watch impotently as it grows and spreads" and decided he wanted to "stop everyone's suffering."[238] In addition to altruistic motivations, Rosenberg found cell biology "thrill[ing]."[239] Rosenberg's experiences as a surgical resident piqued his curiosity about the immune system's regulation of cancer.[240] He encountered a patient who experienced "one of the rarest events in medicine," a stomach cancer diagnosis which underwent complete, spontaneous remission.[241] His interests piqued at just the right time—Rosenberg initiated research into cancer immunotherapies in the late 1960s and early 1970s at the NIH, just as interest in the cancer immunosurveillance hypothesis re-ignited.[242]

Pursuing cancer immunotherapy research required Rosenberg to persevere through skepticism as many researchers feared "there was no such thing as an immune response to spontaneous cancers in humans."[243] A serendipitous 1976 research article detailing a method to permit scientists to grow human T cells

234. *See id.*

235. *See id.*

236. *See* Andrew Pollack, *Setting the Body's 'Serial Killers' Loose on Cancer*, N.Y. TIMES (Aug. 1, 2016), https://www.nytimes.com/2016/08/02/health/cancer-cell-therapy-immune-system.html; *see also* Bach, *supra* note 164.

237. *See Fred Hutchinson, Memorial Sloan-Kettering Team Up to Launch Juno Therapeutics*, CENTERWATCH (Dec. 5, 2013), https://cms.centerwatch.com/articles/18926; *see also* Bach, *supra* note 164.

238. *See* Rosenberg, *supra* note 1, at 2–3.

239. *See id.* at 2.

240. *See id.*

241. *See id.*

242. *See id.* at 2; *see also supra* Section II.E.

243. *See* Rosenberg, *supra* note 1, at 3.

in the laboratory through exposure to a T cell growth factor called interleukin-2 (IL-2) enabled Rosenberg to make crucial progress in ACT.[244] "Intuitively," Rosenberg selected lymphocytes harvested from within the tumor (i.e., TILs) as the "most likely site to find T-cells reactive against" the tumor and found some tumor-killing ability *in vitro*.[245] Despite these successes in the late 1970s, Rosenberg's innovation required more stubborn determination to prevail. In the first seventy-six patients Rosenberg treated with various immunotherapies, none showed anti-tumor effects.[246] His first clinical successes came from treating patients directly with IL-2.[247] Rosenberg published these results in a 1985 study with data on "the first patients to develop reproducible tumor shrinkages from any immunotherapy."[248] Shortly after, Rosenberg published results showing successful clinical outcomes for patients treated with TILs; these studies were enabled, in part, by IL-2's ability to grow large numbers of TILs.[249]

Motivated by curiosity and altruism to improve TILs' cancer-targeting abilities, Rosenberg pursued strategies to modify TIL receptors in the late 1980s. Regulatory and ethical concerns about treating patients with cells engineered to express "foreign genes" represented a hurdle to his research.[250] However, after a year negotiating with various NIH review bodies, the NIH approved a study and, in 1990, Rosenberg demonstrated treatment with genetically-modified human cells could be safe.[251] In the early 1990s, Rosenberg learned of Eshhar's CAR work and "quickly invited" him to collaborate.[252] By 2010, Rosenberg's group demonstrated clinical success with anti-CD19 CAR-T cell therapy.[253]

Commercialization and profit did not drive Rosenberg's experimentation and discovery. In the 1980s, when Rosenberg sought IL-2 in large quantities from corporate suppliers for his experiments, he attended a conference by IL-2 manufacturer Cetus.[254] Rather than agree to keep conference research confidential, Rosenberg "sat in a side room unable to hear their discussion" because he found "secrecy in medicine" to be "unseemly when one was trying

244. *See id.*
245. *See id.* at 4.
246. *See id.* at 5–6.
247. *See id.* at 6–7.
248. *See id.* at 6.
249. *See id.* at 9.
250. *See id.* at 9–11.
251. *See id.* at 11.
252. *See id.* at 15.
253. *See id.* at 17.
254. *See id.* at 5.

to develop treatments for desperate cancer patients."[255] When Rosenberg achieved clinical success with a CAR-T cell therapy, Belldegrun, one of Rosenberg's former colleagues and, at the time, a UCLA urology professor, contacted him.[256] Belldegrun wanted to commercialize the CAR-T cell therapy through a new company, Kite.[257] NCI transferred the CAR-T cell therapy technology to Kite under a Cooperative Research and Development Agreement.[258]

4. Campana

Campana's innovations arose from serendipity, professional achievement, altruism, stubbornness, and curiosity.

Serendipity and professional achievement led Campana to specialize in hematology, especially in children.[259] After medical school, students chose a specialty department.[260] Campana meant to choose clinical medicine, but, by chance, "showed up in the wrong department."[261] He bumped into a professor, Federico Caligaris-Cappio, who encouraged Campana to pursue hematology.[262] This chance encounter and curiosity led Campana to a career in hematology, a field that permitted him to pursue both research and clinical work.[263] After graduation, Campana accepted a position in England first as a visiting researcher and then as a professor in immunology.[264] Campana moved to St. Jude Children's Research Hospital because he knew of its strong clinical and research reputation.[265] This position drew Campana to childhood oncology, St. Jude's focus, and to the most common childhood cancer—acute lymphocytic leukemia (ALL).[266]

Altruism and curiosity motivated Campana to research improved cancer treatments.[267] From the beginning of his medical education, Campana focused on translational, rather than basic, research.[268] He quickly realized current drugs had reached a plateau in treatment efficacy, especially for children, at

255. *See id.*
256. *See id.* at 17–18.
257. *See id.*
258. *See id.*
259. Campana Interview, *supra* note 12.
260. *See id.*
261. *See id.*
262. *See id.*
263. *See id.*
264. *See id.*
265. *See id.*
266. *See id.*
267. *See id.*
268. *See id.*

about 90% efficacy.[269] Although highly effective, the treatments pose significant time and quality of life challenges for patients—the drugs produce toxic side effects, require years of treatment, and often leave long term side effects.[270] Doctors could not increase patients' doses due to drug toxicity.[271] At St. Jude's, Campana researched the interaction between leukemia cells and the bone marrow microenvironment and sensitive methods to detect leukemia cells.[272] He leveraged this expertise to develop new blood cancer treatments.[273] In the late 1990s, Campana attended a presentation by Shimon Slavin about a technique called donor lymphocyte infusion showing one child with leukemia in remission due to the treatment.[274] Although some patients, like this child, responded well to donor lymphocyte infusion, the treatment was not effective for many children.[275] Campana sought methods to increase the treatment's success rate and implement it to treat ALL.[276] Around this time, Campana and his post-doctoral researcher, Chihaya Imai, learned about Eshhar's CAR research.[277] They hypothesized a CD19-targeting antibody would target ALL.[278] Heddy Zola provided a CD19-targeting antibody scFv.[279] Imai used the CD19-targeting scFv to create a CAR with the CD3ζ domain.[280] Imai and Campana knew about the co-stimulation issue with first-generation CARs and learned of Sadelain's work with the CD28 co-stimulatory region.[281] They also knew, from St. Jude's ALL database, that few cancer cells naturally expressed co-stimulatory proteins.[282] This challenge motivated them to screen CAR constructs with CD28 and other co-stimulatory regions in different configurations (e.g., CD3ζ followed by 4-1BB vs. 4-1BB followed by CD3ζ) against ALL cells.[283] Their most promising results stemmed from a 4-1BB co-stimulatory domain.[284] Campana and Imai were "amazed": "You could see your target cells just dying in front of you. You sit at the microscope and it's kind of mesmerizing. You just don't want to leave. You just watch the action

269. *See id.*
270. *See id.*
271. *See id.*
272. *See id.*
273. *See id.*
274. *See id.*
275. *See id.*
276. *See id.*
277. *See id.*
278. *See id.*
279. *See id.*
280. *See id.*
281. *See id.*
282. *See id.*
283. *See id.*
284. *See id.*

happening in front of your eyes." Despite their excitement about the results, their publication initially received rejections "almost everywhere" and the community had "no interest at all" in their technology.[285]

Stubbornness and altruism fueled the next stages of Campana's CAR-T cell therapy development. In addition to facing publication rejection, the team also faced challenges getting their new CAR-T cell treatment to patients.[286] Only a few "visionary" physicians would attempt to treat patients with the untested therapy.[287] The 90% efficacy rate with current treatments further disincentivized physicians from trying new therapies.[288] Campana also expected pharmaceutical companies would not be interested without clinical data, especially for a therapy more complex and "far-fetched" than traditional small-molecule drugs.[289] Despite these challenges, Campana and Imai sought to patent their invention because it was "an invention worth protecting."[290] The breakthrough came when Imai presented the results from their publication at the American Society of Hematology (ASH) meeting in the early 2000s to a session attended by only ten to fifteen people.[291] Luckily, June was one of those who attended Imai's presentation.[292] Campana and Imai provided their construct to June.[293] June treated patients and found promising results.[294] After June published results, the community and pharmaceutical companies started to pay attention to CAR-T cell therapies.[295]

Campana's experience with CAR-T cell therapies changed his view of commercialization.[296] While previously uninterested, he realized commercialization could provide the funds and resources required to bring a therapeutic candidate from proof-of-concept to the clinic.[297] Now, he sees commercialization as the route "to reach as many patients as possible."[298]

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285. *See id.*; *see also* Imai, *supra* note 132.
286. *See* Campana Interview, *supra* note 259.
287. *See id.*
288. *See id.*
289. *See id.*
290. *See id.* ("St. Jude is not very commercially-oriented so we were working there, we were not really that interested in starting companies, neither me nor my colleagues . . . and also St. Jude itself is . . . entirely dependent on . . . philanthropy so it is not really that kind of institute that wants to generate a lot of revenues from patents.").
291. *See id.* ("Although you know ASH is attended by typically 20,000 hematologists . . . it just shows you how little interest there was in that kind of technology at that time.").
292. *See id.*
293. *See id.*
294. *See id.*
295. *See id.*; *see also infra* Section IV.A.5.
296. *See* Campana Interview, *supra* note 259.
297. *See id.*
298. *See id.*

5. June

Serendipity, altruism, and tenacity drove June's CAR-T cell therapy innovations.

Serendipitously, June's research career began with the Navy in the 1970s, a time when the Navy sought treatments for patients exposed to radiation.[299] June researched one such treatment, bone marrow transplantation, during his last year of medical school at the World Health Organization.[300] In 1983, the Navy sent June to continue his bone marrow transplantation research at Fred Hutchinson Cancer Center.[301] June arrived at Fred Hutchinson just as his mentors realized bone marrow transplantation did more than replace immune cells following cancer treatment.[302] They discovered transplanted cells contributed to an immune response against cancer cells and laid the foundation for ACT.[303] By the mid-1980s, June had focused his research on methods to grow T cells in a lab.[304] This T cell research led to a collaboration with Cell Genesys to develop a therapy for HIV.[305]

Altruism and personal tragedy re-directed June's research to focus on T cell-based cancer therapies. In 2001, June's wife passed away from ovarian cancer, despite treatment with June's own "primitive immune therapies."[306] Motivated by a desire to advance cell therapies to cancer patients, June transitioned from treating patients to a full-time researcher position at the University of Pennsylvania.[307] Two years after his wife's passing, June attended a presentation on CAR-T cell therapy by Campana.[308] June requested a sample of Campana's CAR, implemented the CAR design into T cells, and secured one of the first grants from the Alliance for Cancer Gene Therapy, a non-profit, to fund a three-person clinical study to treat leukemia with the CAR-T

299. *See* Pollack, *supra* note 236.

300. *See* Mary Engel, *Dr. Carl June Weaves Together HIV and Cancer Research to Advance Cures for Both*, FRED HUTCH CANCER CTR. NEWS STORIES (Aug. 17, 2017), https://www.fredhutch.org/en/news/center-news/2017/08/carl-june-weaves-together-hiv-and-cancer-research-to-advance-cures-for-both.html.

301. *See id.*

302. *See id.*

303. *See id.*

304. *See* Pollack, *supra* note 236.

305. *See id.*

306. *See id.*

307. *See id.*

308. *See id.*

cell therapy.[309] Two of his three patients went into complete remission.[310] But, June's grant money ran out after this small clinical trial completed.[311] June decided to publish the study results to spur interest in CAR-T cell therapies.[312] The publication drew interest from patients with similar diagnoses, as well as large pharmaceutical companies and start-up investors interested in commercializing a treatment.[313] June's team selected Novartis as their commercialization partner because they believed a large pharmaceutical company could advance the therapy faster than the alternatives.[314] According to June, working with Novartis

> was an ethical decision. Speed to market was important because it was not a question of whether it would work, which it often is. By going to a pharma, there was no delay in building bricks and mortar and hiring people. They had a salesforce in place. We just had to teach their people to manufacture a cell therapy.[315]

Interestingly, for June's subsequent therapeutic candidates, he pivoted to start-up partners.[316] In his view, "[i]f you have a company that's singularly focused, it can be more nimble, and that's what I learned from the Kite versus Novartis experiments. Novartis has this huge portfolio and decision makers in Switzerland and Massachusetts. It just can't keep up with a highly focused team."[317]

B. INTELLECTUAL PROPERTY EXCLUSIVITY

The Yescarta manufacturer (Kite) and other CAR-T cell therapy manufacturers rely primarily on patents and trade secrets for intellectual property exclusivity. Historically, pharmaceutical companies have relied on patent exclusivity to ensure recovery of their substantial research and development (R&D) and clinical investment.[318] CAR-T cell therapy developers similarly relied on patents, even in the early CAR construct development

309. *See id.*; *see also* Antonio Regalado, *T-Cell Pioneer Carl June Acknowledges Key Ingredient Wasn't His*, MIT TECH. REV. (Mar. 14, 2016), https://www.technologyreview.com/2016/03/14/161592/t-cell-pioneer-carl-june-acknowledges-key-ingredient-wasnt-his/.

310. *See* Pollack, *supra* note 236.

311. *See* Ben Fidler, *CAR-T Pioneer Carl June on Founding Startups and Cell Therapy's Next Act*, BIOPHARMA DIVE (Oct. 18, 2022), https://www.biopharmadive.com/news/carl-june-in-vivo-car-t-capstan-tmunity/633980/.

312. *See id.*

313. *Id.*

314. *Id.*

315. *Id.*

316. *Id.*

317. *Id.*

318. *See* Halabi, *supra* note 189, at 6.

stage.[319] However, recent patent litigation created uncertainty on the validity of a particular class of patent claims important to therapeutics manufacturers: composition claims.[320]

Trade secret protection affords additional exclusivity protection for CAR-T cell manufacturers. Because CAR-T cell therapeutics require a complex manufacturing process, manufacturing conditions are critical to therapeutic success, and competitors cannot easily (if at all) determine important know-how (like cell culture conditions) based on the product alone, CAR-T cell manufacturing processes are strong candidates for trade secret protection.[321]

1. Patents

Patent claims to compositions of matter tend to afford the strongest protection for pharmaceutical products because they typically withstand validity challenges.[322] The next strongest claims for pharmaceutical products include methods of manufacturing and methods of treatment (e.g., covering new dosing regimens or indications).[323] Pharmaceutical companies often rely on one or more of these types of patent claims to maintain exclusivity for their products.[324]

a) CAR-T Cell Therapy Composition Patent Landscape

Early CAR-T cell therapy innovators sought patent protection (Table 4). Eshhar acquired multiple patents covering first-generation CAR constructions, including U.S. Pat. No. 7,741,465 ("the '465 patent") claiming "chimeric DNA" encoding an antibody-derived binding region connected to an "endogenous" signaling protein, including CD3.[325] Finney and Roberts, and their respective employers, also sought patent protection for their second-generation CAR constructs.[326] Sadelain acquired patent claims covering the

319. *See*, *e.g.*, '149 patent, *supra* note 123; '249 application, *supra* note 131; U.S. Patent No. 7,741,465 (filed July 2, 1993) [hereinafter '465 patent]; '190 patent, *supra* note 77.

320. *See* Juno Therapeutics, Inc. v. Kite Pharma, Inc. (*Juno v. Kite II*), 10 F.4th 1330, 1335–41 (Fed. Cir. 2021), *cert. denied*, Juno Therapeutics, Inc. v. Kite Pharma, Inc. (*Juno v. Kite III*), 143 S. Ct. 402, (2022), *reh'g denied*, 143 S. Ct. 631, (2023).

321. *See* Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 545–47 (2010).

322. *See* N. Nicole Stakleff, *A Drug Life: The Chemistry of Patent and Regulatory Exclusivity for Pharmceuticals*, 16 FLA. COASTAL L. REV. 27, 53–54, 61–62 (2014); Gurgula, *supra* note 187, at 1067–68.

323. *See* sources cited, *supra* note 322.

324. *See id.*

325. *See* Kite Pharma, Inc., Registration Statement (Form S-1) at Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on December 12, 2013); '465 patent, *supra* note 319, claims 1, 6.

326. *See, e.g.*, '249 application, *supra* note 131; '149 patent, *supra* note 123.

sequence of his improved second-generation CAR in U.S. Pat. No. 7,446,190, including a sequence used in the Yescarta CAR.[327] Eshhar and Sadelain licensed their patents to start-up companies Kite and Juno, respectively, which leveraged the patent assets to attract investors to fund additional clinical studies.[328]

Patent exclusivity was key to Kite's business strategy from the outset. Kite's registration statement identified patents as important to competing in the market.[329] One of Kite's first corporate acts was to license Eshhar's CAR patents (including the '465 patent) from his licensing company, Cabaret Biotech Ltd.[330] Kite also licensed Cell Genesys patents.[331] Kite's '465 patent family includes applications filed in Europe, Canada, Japan, and Australia.[332] Kite applied Yescarta's patent term extension to the '465 patent.[333] Further, Kite invested in a re-examination proceeding at the U.S. Patent and Trademark Office (USPTO) for the '465 patent and acquired new claims in 2016.[334] With

327. *See Juno v. Kite I*, at *9–10 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 [p]atent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 [p]atent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 [p]atent."); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14 ("Kite stipulated that Yescarta literally infringes the ['190] patent" with only one independent claim reciting SEQ ID NO:6).

328. *See* CLAUDE BARFIELD & JOHN E. CALFEE, TECHNOLOGY AND THE PATENT SYSTEM: BALANCING INNOVATION AND PROPERTY RIGHTS 27 (2007) (explaining that patents are typically "crucial" for startup biotechnology companies because they serve as stable assets to attract investment); *see also* Kite Pharma, Inc., Registration Statement (Form S-1), *supra* note 138, at Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on December 12, 2013); Bach, *supra* note 164; Brendan Doherty, *Cell Genesys Transforms Patents Into Gold Mines*, S.F. BUS TIMES (June 16, 2002), https://www.bizjournals.com/sanfrancisco/stories/2002/06/17/newscolumn1.html.

329. Kite Pharma, Inc., Registration Statement (Form S-1), *supra* note 138, at 31.

330. *Id.* at 86 (indicating that Cabaret patents and not NCI patents cover KTE-C19); *see also id.* at 2–5, 30–31, Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on December 12, 2013); Complaint at ¶¶ 23–24, Cabaret Biotech Ltd. v. Kite Pharma, Inc., No. 1:19-cv-01732 LPS, 2020 WL 8265236 (2019) [hereinafter Cabaret Complaint].

331. Kite Pharma, Inc., Registration Statement (Form S-1) at 79 (May 19, 2014).

332. *See* WO 93/19163; AU668156; EP0638119; CA2132349; JP3643590.

333. Cabaret Complaint, *supra* note 330 at ¶¶ 32–36; *Applications for Patent Term Extension And Patent Terms Extended Under 35 U.S.C. § 156*, U.S.P.T.O., https://www.uspto.gov/patents/laws/patent-term-extension/patent-terms-extended-under-35-usc-156 (last accessed Nov. 11, 2022).

334. Reexamination Request 90/013,790.

the exception of a 2019 dispute, Kite (and later Gilead) continuously paid and continues to pay royalties on Eshhar's patents.[335]

Like Kite, Juno similarly relied on patent rights. Researchers affiliated with Fred Hutchinson Cancer Research Center, MSKCC, and Seattle Children's Research Institute founded Juno to commercialize cancer immunotherapies including the technology claimed in Sadelain's '190 patent.[336] Juno's registration statement also identifies patents as key to its ability to compete in the market.[337] Several of Juno's first corporate actions involved licensing agreements with various research organizations, including MSKCC, Fred Hutchinson Cancer Research Center, Seattle Children's Research Institute, and St. Jude Children's Research Hospital.[338] In 2014, Juno sued the University of Pennsylvania and Novartis to enforce patent rights over the CD3ζ-4-1BB CAR design (voluntarily settled in 2015).[339]

335. Cabaret Complaint, *supra* note 330, at ¶ 31 (Kite paid licensing fees to Cabaret from December 2013 to October 2018); *Id.* at ¶¶ 31, 37–40 (Gilead pushed back and eventually stopped paying licensing fees from 2017 to 2019); *Id.* at ¶ 61 (Cabaret sued Kite/Gilead for declaratory judgment that '465 patent valid and Yescarta® infringes in 2019); Joint Claim Construction Brief, Cabaret Biotech Ltd. v. Kite Pharma, Inc., No. 1:19-cv-01732 LPS, 2020 WL 8265236 (2019) (filed July 13, 2020); Stipulation of Dismissal, Cabaret Biotech Ltd. v. Kite Pharma, Inc., No. 1:19-cv-01732 LPS, 2020 WL 8265236 (2019) (parties settled in December 2020).

336. *See* Bach, *supra* note 164. Strikingly, the '190 patent lacks international counterparts.

337. Juno Therapeutics, Inc., Registration Statement (Form S-1) at 108 (Nov. 17, 2014).

338. *See id.* at 71, 110–16.

339. *See* Trustees of the Univ. of Pennsylvania v. St. Jude Children's Rsch. Hosp., 2014 WL 12610149 (E.D. Pa. Mar. 13, 2014) (voluntarily dismissed); *see also* Juno Therapeutics, Inc., Registration Statement (Form S-1), *supra* note 138, at 53 (Nov. 17, 2014).

Table 4: CAR-T inventors sought patent protection for two key signaling constructs (exemplary patents).

U.S. Patent No. / Appl. No.	CAR Construct	Earliest Priority Year	Inventor	Initial Assignee	Current Assignee
7,741,465	CD3ζ	1993	Eshhar & others	Yeda Research and Development Co. Ltd.	Eshhar (Licensed to Kite)[340]
5,712,149	CD28-CD3ζ	1995	Roberts	Cell Genesys	Cabaret Biotech Ltd. (Licensed to Kite)[341]
09/091,608	CD28-CD3ζ	1996	Finney & others	Celltech	N/A
10/399,364	4-1BB-CD3ζ	2001	Finney & others	Celltech	N/A
7,446,190 (60/383,872)	CD28-CD3ζ	2002	Sadelain & others	MSK	MSK (Licensed to Juno)[342]
8,399,645 (60/517,507)	4-1BB-CD3ζ	2003	Campana & Imai	St. Jude Children's Research Hospital	St. Jude Children's Research Hospital (Licensed to Juno, Novartis)[343]

Despite inventors' interest in patent protection, CAR-T cell therapy manufacturers face acute patent challenges beyond those commonly faced in the pharmaceutical field: (1) manufacturing technological complexity; (2) composition patent expiration near regulatory approval; and (3) disclosure requirement uncertainty, especially for composition claims. Composition claim challenges suggest other exclusivity schemes continue to incentivize pharmaceutical companies to commercialize CAR-T therapies, including trade secret protection[344] and regulatory exclusivity.[345]

340. Kite Pharma, Inc., Registration Statement (Form S-1) at Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on Dec. 12, 2013).

341. *Id.*

342. Second Amended Complaint at ¶ 15, *Juno v. Kite I,* 2020 WL 10460622 (C.D. Cal. Mar. 24, 2020), *rev'd*, 10 F.4th 1330 (Fed. Cir. 2021).

343. Juno Therapeutics, Inc., Annual Report (Form 10-K) at 82 (Feb. 29, 2016).

344. *See infra* Section IV.B.2.

345. *See infra* Section IV.C.

b) Collaborative Licensing Model

Pharmaceutical companies frequently license patents and trade secrets from innovators. Because CAR-T cell therapies require complex manufacturing processes, initial licensing agreements often followed an innovative, collaborative model. Juno referred to its model as "ongoing technology transfer."[346] While technology transfer from academic institutions to companies often ends with a licensing agreement, Juno sought to involve the innovators in its scientific strategy, as co-founders and as collaborators.[347] Indeed, Juno brought together academics from multiple academic institutions with expertise in cell therapy: MSKCC, Seattle Children's Research Institute, and Fred Hutchinson Cancer Center.[348]

c) Composition Patent Expiration

CAR-T cell therapy composition claims provide limited exclusivity to manufacturers because the claims likely expired before or will expire soon after manufacturers receive regulatory approval to market the new therapies.

For patents filed on or after June 8, 1995, exclusivity extends approximately twenty years from the earliest utility application priority date.[349] For patents filed before June 8, 1995, the exclusivity term is the greater of approximately twenty years from the earliest utility application priority date and seventeen years from the date the patent issued.[350]

Because the early CAR-T composition patents' priority dates range from 1993-2003 and the FDA approved the first CAR-T therapies in 2017, composition claims (e.g., those directed to CAR constructs) expired before or soon after the FDA first approved CAR-T therapies (Table 3).

d) Composition Claim Disclosure Uncertainty: *Juno v. Kite* and the Written Description Requirement Example

Even assuming the composition claims remain in force, recent precedent interpreting 35 U.S.C. § 112 creates uncertainty about the validity of

346. *See* Charlotte Schubert, *Juno's Lasting Legacy: How the Cell Therapy Juggernaut Influenced Biotech in Seattle and Beyond*, GEEKWIRE (Feb. 8, 2022), https://www.geekwire.com/2022/junos-lasting-legacy-how-the-cell-therapy-juggernaut-influenced-biotech-in-seattle-and-beyond/.

347. *See id.*; *see also Q&A: Carl June on CAR T-cell Therapy*, 1 BLOOD CANCER DISCOVERY 8 (2020).

348. *See* Bach, *supra* note 164; *see also* Matthew Herper, *Why One Cancer Company Has Raised $300 Million in 12 Months Without an IPO*, FORBES (Aug. 5, 2014), https://www.forbes.com/sites/matthewherper/2014/08/05/why-this-cancer-fighting-company-has-raised-300-million-in-just-12-months/?sh=149b353650d5.

349. *See* MPEP 2701 (citing 35 U.S.C. § 154(a)(2)) (9th ed. Rev. Feb. 2023).

350. *See id.* (citing 35 U.S.C. § 154(c)).

biotechnology composition claims for insufficient written description and lack of enablement.[351] For example, Juno's '190 patent created substantial freedom-to-operate risk for Yescarta, so Kite invested substantially in invalidating it. Although Kite ultimately succeeded, the Federal Circuit's invalidity decision may leave Kite's own composition claims and similarly situated companies' composition claims vulnerable.[352]

The dispute at the heart of *Juno v. Kite* arose from a research collaboration. Sadelain and co-inventors at MSKCC filed a patent application in 2003 leading to the grant of the '190 patent in 2008.[353] Sadelain shared this invention with Rosenberg at NCI.[354] Later, Kite established a collaboration with NCI "for the development and commercialization of novel engineered peripheral blood autologous T cell therapeutics (eACT) for the treatment of multiple cancer indications."[355] The collaboration provided Kite with "exclusive access to the current and future clinical product pipeline of autologous peripheral blood T cells, engineered with the NCI's proprietary tumor-specific TCRs and Chimeric Antigen Receptors (CARs), directed to multiple hematological and solid tumor types."[356] Rosenberg shared Sadelain's invention with Kite without MSKCC's permission; Kite developed this technology into Yescarta.[357]

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351. *See Juno v. Kite II* at 1338 ("To satisfy written description, however, the inventors needed to convey that they possessed the claimed invention, which encompasses all scFvs, *known and unknown*, as part of the claimed CAR that bind to a selected target.") (emphasis added).

352. Juno Therapeutics, Inc., Registration Statement (Form S-1) at 50 (Nov. 17, 2014) (even before *Juno v. Kite II*, biotech patent strength was "uncertain" due to complexities of patent law); *see also* Tam, *supra* note 321, at 535, 545–47; Jonathan B. Fitzgerald & Jeffrey D. Morton, *Juno v. Kite Case Implications for Functionally Claimed Biological Compositions*, Outsourced Pharma (Nov. 12, 2021), https://www.outsourcedpharma.com/doc/juno-v-kite-case-implications-for-functionally-claimed-biological-compositions-0001; Brachmann, *supra* note 175 (describing § 112 written description interpretation as "ridiculous," "nearly impossible for life sciences inventors to properly meet," and "greatly increase[ing] . . . validity risks for the entire life sciences sector.").

353. *Juno v. Kite IPR Appeal* at *1; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 12.

354. *See* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 13.

355. *Kite Pharma Partners with the National Cancer Institute to Develop Novel Cellular Immunotherapy Clinical Products*, Kite Pharma (Oct. 16, 2012), https://web.archive.org/web/20160303211144/http://amda-2v2xoy.client.shareholder.com/releasedetail.cfm?ReleaseID=852506.

356. *Id.*

357. *See Juno v. Kite I* at *9–10 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 Patent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was

Kite attempted several strategies to mitigate the '190 patent freedom-to-operate issue. First, Kite challenged the validity of the '190 patent in an *inter partes* review (IPR) petition filed on August 13, 2015.[358] Kite's petition asserted that the '190 patent was invalid on three § 102 and § 103 grounds.[359] The Patent Trial and Appeal Board (PTAB) instituted the IPR on all three grounds.[360] On December 16, 2016, the PTAB found for Juno, declining to find the '190 patent invalid.[361] Kite appealed the PTAB's decision to the Federal Circuit, which affirmed the '190 patent's validity in 2018.[362] After Kite failed to invalidate Sadelain's patent, Kite attempted to license it.[363] MSKCC refused to license Sadelain's patent, choosing instead to found Juno to commercialize it.[364]

Upon FDA approval of Yescarta, Juno sued Kite in district court for infringing the '190 patent.[365] A jury unanimously held for Juno on December 13, 2019—finding the '190 patent valid, willfully infringed by Kite, and awarding Juno $585M upfront payment plus 27.6% royalty on future sales.[366] The district court judge rejected Kite's motions for judgment as a matter of law and new trial.[367] Kite appealed to the Federal Circuit, arguing the '190

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so desperate to pursue a license to the '190 Patent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 Patent.") (emphasis added), *rev'd*, 10 F.4th 1330 (Fed. Cir. 2021) (reversing on other grounds); *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 13.

358. *Juno v. Kite I* at *2; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

359. Inter Partes Review Petition at 16, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016).

360. Institution Decision at 5, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016).

361. Final Written Decision at 3, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016); *see also Juno v. Kite IPR Appeal* at *2; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

362. *Juno v. Kite IPR Appeal* at *2; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

363. *Juno v. Kite I* at *9–10 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 Patent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 Patent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 Patent.") (emphasis added); *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 13.

364. *See Juno v. Kite IPR Appeal* at *2; *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

365. *Juno v. Kite I*.

366. *Id.* at *2.

367. *Id.* at *21.

patent was invalid (and admitting infringement).[368] The Federal Circuit found the '190 patent invalid for insufficient written description to support the claims (§ 112) and reversed the jury verdict.[369] In 2022, the Supreme Court denied certiorari leaving the '190 patent invalid.[370]

Although Kite won and avoided massive damages, *Juno v. Kite* leaves biotechnology patents claiming proteins, like CARs, vulnerable to invalidity under § 112. A valid patent must claim an eligible, new, and non-obvious invention and must

> contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.[371]

For claims like those at issue in the '190 patent, directed to a broad range of proteins with common functional characteristics (i.e., a functionally-defined genus), the patent must disclose either a "representative number of species falling within the scope of the genus" or "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."[372] Although the primary innovation was the CD28 co-stimulatory intracellular signaling domain, the Federal Circuit held the '190 patent claims invalid for claiming "a binding element that specifically interacts with a selected target" (i.e., the antibody-derived, extracellular scFv region) without also disclosing "all scFvs, **known and unknown**, as part of the claimed CAR that bind to a selected target" (emphasis added).[373] Such an expansive written description requirement, especially imposed on an arguably well-known element of the claim, threatens to undermine existing biotechnology composition patent claims and future investment in biotechnology innovation.[374]

2. Trade Secret

Biotech companies may mitigate uncertainty around patent composition claims and maintain exclusivity using another area of intellectual property

368. *Juno v. Kite II* at 1334; *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

369. Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 4.

370. *Juno v. Kite III*.

371. 35 U.S.C. §§ 101, 102, 103, 112.

372. *Juno v. Kite II* at 1335 (summarizing precedent interpreting § 112).

373. *See id.* at 1333–34, 37–38.

374. Brachmann, *supra* note 175.

protection: trade secret law.[375] Trade secret protection is ideal when detection of patent infringement would be difficult and where sale of a product does not disclose the secret.[376] CAR-T cells' complex manufacturing processes, including extracting autologous T cells from patients, purifying them, engineering them to express the CAR, multiplying them, and administering them back to patients, provide several viable areas for trade secret protection.[377] Both Juno and Kite rely on trade secret protection (in addition to patents) to maintain their exclusivity and a competitive edge.[378] For example, Yescarta's FDA filings include multiple trade secret redactions related to Kite's manufacturing processes, especially Kite's method to induce cells to express the CAR protein.[379] Similarly, Juno redacted its Breyanzi FDA filings to protect trade secrets related to its manufacturing processes, methods to induce cells to express its CAR protein, and process validation and impurity testing methods.[380]

375. *See* Chorong Song, *How Non-Product-Specific Manufacturing Patents Block Biosimilars*, 71 DUKE L.J. 1923, 1934 (2022); Lisa Diependaele et al., *Similar or the Same: Why Biosimilars are Not the Solution*, 46 J.L. MED. & ETHICS 776, 777, 783 (2018).

376. *See* Daniel C. Munson, *The Patent-Trade Secret Decision: An Industrial Perspective*, 78 J. PAT. & TRADEMARK OFF. SOC'Y 689, 692, 708 (1996); *see also* Andrew Beckerman-Rodau, *The Choice Between Patent Protection and Trade Secret Protection: A Legal and Business Decision*, 84 J. PAT. & TRADEMARK OFF. SOC'Y 371, 396–97 (2002); W. Nicholson Price II & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars? Regulations for Approving Biologic Drugs Thwart the Market for Would-Be Competitors*, 348 SCI. 188, 188–89 (2015); Yaniv Heled, *The Case for Disclosure of Biologics Manufacturing Information*, 47 J.L. MED. & ETHICS 54 (2019).

377. *See* June, *supra* note 164 at 614; Hollyman, *supra* note 97, at 173; Beckerman-Rodau, *supra* note 376, at 396–97; *see also* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1046–47 (2016); Halabi, *supra* note 189, at 23–24.

378. *See* Juno Therapeutics, Inc., Registration Statement (Form S-1) at 108 (Nov. 17, 2014); Kite Pharma, Inc., Registration Statement (Form S-1) at 30–31 (May 19, 2014).

379. *Clinical Pharmacology BLA Review (BLA 125643)*, U.S. FOOD & DRUG ADMIN. 11 (Mar. 31, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (showing "(b)(4)" redactions); *see also* Michael Havert, *Summary Basis for Regulatory Action (BLA 125643)*, U.S. FOOD & DRUG ADMIN. 4–5 (Oct. 18, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (same). These redactions related to diagnostics and manufacturing processes indicate trade secrets because Kite used the "(b)(4)" label. *FOI Information*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), https://www.fda.gov/regulatory-information/freedom-information/foi-information ("Exemption 4: Protects trade secrets and confidential commercial or financial information.") (emphasis removed).

380. Kimberly L.W. Schultz, *Summary Basis for Regulatory Action (BLA 125714)*, U.S. FOOD & DRUG ADMIN. 5–8 (Feb. 5, 2021) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel; *see also CBER CMC BLA Review Memorandum (BLA 125714)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel.

C. REGULATORY REGIMES

The U.S. Food and Drug Administration (FDA) offers accelerated review and regulatory exclusivity to mitigate the high risk of failure, high clinical study costs, and substantial upfront investment.[381] As one example, drugs "intended to treat a serious condition" and with "preliminary clinical evidence [to] indicate[] . . . the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)" may receive accelerated review under the "Breakthrough Therapy" designation.[382] After approval, the FDA cannot approve a generic, biosimilar, or interchangeable version of the drug during its regulatory exclusivity.[383] Regulatory exclusivity runs concurrently with patent exclusivity.[384] For example, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) established twelve years regulatory exclusivity for new biological products (i.e., a "reference product").[385] In addition to reference product exclusivity, biologic drugs may receive orphan drug exclusivity, new indication exclusivity, and pediatric exclusivity.[386] The most common regulatory incentives CAR-T cell

381. *See* Renu Lal, *Patents and Exclusivity*, FDA/CDER SBIA CHRONICLES (May 19, 2015), https://www.fda.gov/media/92548/download#:~:text=Exclusivity%20is%20exclusive%20marketing%20rights,with%20a%20patent%20or%20not; *Orphan Drug Act – Relevant Excerpts*, U.S. FOOD & DRUG ADMIN. (Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts ("[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss."); Barfield, *supra* note 328, at 18–21; Tam, *supra* note 321, at 552–58; Halabi, *supra* note 189, at 26–29; Stakleff, *supra* note 322, at 28–29, 45–50; *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

382. *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

383. *See* Lal, *supra* note 381; *Guidance for Industry Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*, U.S. FOOD & DRUG ADMIN. 1 (Apr. 15, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reference-product-exclusivity-biological-products-filed-under-section-351a-phs-act [hereinafter *Exclusivity for Biological Products*].

384. *See* Lal, *supra* note 381; *see also Exclusivity for Biological Products*, *supra* note 383, at 2–3.

385. *Exclusivity for Biological Products*, *supra* note 383, at 1.

386. *See* Lal, *supra* note 381.

manufacturers receive are the Breakthrough Therapy designation and orphan drug exclusivity.[387]

1. Breakthrough Therapy Designation

Progressing through clinical studies more quickly enables pharmaceutical companies to begin to profit from their investments sooner. The FDA offers the Breakthrough Therapy designation pathway to expedite review when the drug "treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies."[388] Novartis' tisagenlecleucel (later Kymriah) was the first personalized cell therapy for the treatment of cancer to receive Breakthrough Therapy designation status.[389] About one year later, in July 2015, Kite's axicabtagene ciloleucel (later Yescarta) also received Breakthrough Therapy designation.[390] All approved CAR-T cell therapies received Breakthrough Therapy designation for at least one indication (Table 5). Kymriah, Tecartus, and Carvykti received Breakthrough Therapy designation for two indications.

387. *See* Caitlin Owens, *Blockbuster Drugs are Stacking Up Orphan Approvals*, AXIOS (Feb. 19, 2019), https://www.axios.com/2019/02/19/blockbuster-drugs-are-stacking-up-1550264427; Braendstrup, *supra* note 103, at 61; *see also* Ralf Otto, *Rapid Growth in Biopharma: Challenges and Opportunities*, MCKINSEY & CO. (Dec. 1, 2014), https://www.mckinsey.com/industries/life-sciences/our-insights/rapid-growth-in-biopharma (noting Rate of advance from Phase I to Phase II is higher for biologics than for small-molecule therapeutics); Brower, *supra* note 84; *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Jan, 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy [hereinafter *FDA Breakthrough Therapy*].

388. *Frequently Asked Questions: Breakthrough Therapies*, U.S. FOOD & DRUG ADMIN. (Feb. 3, 2022), https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies#:~:text=A%20breakthrough%20therapy%20designation%20is,(s)%20over%20available%20therapies.

389. *See* Braendstrup, *supra* note 103, at 61; *see also* Brower, *supra* note 84; *FDA Breakthrough Therapy*, *supra* note 387.

390. *See* Braendstrup, *supra* note 103, at 61.

Table 5: All CAR-T therapeutics received accelerated FDA review under the Breakthrough Therapy designation.[391]

Breakthrough Therapy	Sponsor	Approval Date	Indication
Kymriah	Novartis Pharmaceuticals, Inc.	Aug. 30, 2017	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
		May 1, 2018	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) who are ineligible for autologous transplant
Yescarta	Kite Pharma, Inc.	Oct. 18, 2017	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Tecartus	Kite Pharma, Inc.	July 24, 2020	Adult patients with relapsed/refractory mantle cell lymphoma
		Oct. 1, 2021	Adult patients with relapsed/refractory mantle cell lymphoma
Breyanzi	Juno Therapeutics, a Bristol-Myers Squibb Company	Feb. 5, 2021	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Abecma	Celgene Corporation, a Bristol-Myers Squibb Company	Mar. 26, 2021	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
Carvykti	Janssen Biotech, Inc.	Feb. 28, 2022	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody

391. *Previous (Cumulative) CY CBER BT Totals*, U.S. FOOD & DRUG ADMIN. 1–2 (Dec. 31, 2023), https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/cber-approvals-breakthrough-therapy-designated-drugs.

		Dec. 21, 2023	Adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody

2. Orphan Drug Designation Exclusivity

Congress enacted orphan drug exclusivity in the Hatch-Waxman Act (1984) to incentivize therapeutic development for diseases affecting too few people for pharmaceutical companies to "reasonably expect" to recoup their investment.[392] Drugs treating qualifying indications receive seven years of regulatory exclusivity for each indication approved by the FDA.[393] The FDA may not approve a subsequent application for the "same" drug for the "same" orphan indication for seven years.[394] The FDA determines a subsequent drug is the "same" if it "contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use or indication as a previously approved drug," unless the subsequent drug is "clinically superior."[395] The same drug may receive multiple orphan drug exclusivity periods for each additional FDA approval for a qualifying indication.[396]

Cell therapies, and personalized therapeutics more broadly, approach regulatory regimes with different challenges and opportunities than the traditional small molecules available when Congress initially created orphan drug exclusivity. For example, personalized medicines appear to have a lower risk of failure because they often cause fewer off-target effects than small-

392. *Orphan Drug Act – Relevant Excerpts*, U.S. FOOD & DRUG ADMIN. (Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts ("[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss.").

393. *See id.*

394. *See Guidance for Industry - Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, U.S. FOOD & DRUG ADMIN. 2–3 (Sept. 2021), https://www.fda.gov/media/134731/download#:~:text=The%20orphan%20drug%20regulations%20define,a%20previously%20approved%20drug%2C%20except.

395. *See id.* at 3–4.

396. *See id.*; *see also* Owens, *supra* note 387; Otto *supra* note 387.

molecule therapeutics.[397] But, CAR-T cell therapies require substantially greater manufacturing and supply chain investment: companies must develop entirely new processes *and* create an individual treatment for every patient.[398] These differences from small-molecule therapeutics may require Congress to tailor orphan drug and other exclusivity regimes to more personalized therapeutics.

But, while CAR-T manufacturers routinely seek and receive orphan drug designation, the status does not prevent other CAR-T cell therapies from approval for the same indication. All FDA-approved CAR-T cell therapies currently have at least one orphan drug designation (Table 6).[399] Because the sameness requirement narrows this exclusivity regime, multiple CAR-T cell therapies received orphan drug designation for the same disease. For example, Kymriah and Yescarta both received orphan drug designation for "diffuse large B-cell lymphoma." Kymriah and Yescarta are likely not the "same," at least in part, because their CAR constructs (i.e., their "principal molecular structural features") differ (4-1BB-CD3ζ vs. CD28-CD3ζ).[400] Interestingly, even Abecma and Carvykti (both 4-1BB-CD3ζ CARs with receptors targeting BCMA) received orphan drug designation for the same disease (multiple myeloma). Either Abecma and Carvykti rely on different "principal molecular structural features" (e.g., the BCMA binding elements rely on different amino acid sequences) or one demonstrated clinical superiority to the other.[401] In either case, the Abecma and Carvykti examples demonstrate the narrowness of orphan drug exclusivity.

397. *See* Denise Myshko, *The Business of Biologics*, PHARMAVOICE (Sept. 1, 2018), https://www.pharmavoice.com/news/2018-09-biologics/612566/; *see also* Tam, *supra* note 321 at 557–58.

398. *See* June, *supra* note 164, at 614 (distinguishing CAR-T cell manufacturing from the traditional pharmaceutical company model: spending "half a billion dollars to make the first vial of a new drug, so long as the second vial can be produced for a few dollars"); *see also* Otto, *supra* note 387; Barfield & Calfee, *supra* note 328, at 15–18; Fraiser Kansteiner, *Bristol Myers, Hot Off Breyanzi Nod, Plots New Cell Therapy Factory in Massachusetts*, FIERCE PHARMA (Feb. 23, 2021), https://www.fiercepharma.com/manufacturing/bristol-myers-hot-off-breyanzi-nod-plots-new-cell-therapy-factory-massachusetts.

399. *Orphan Drug Designations and Approvals: Yescarta*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=515615 (last visited Nov. 11, 2022).

400. *See Guidance for Industry - Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, U.S. FOOD & DRUG ADMIN. 3–4 (Sept. 2021), https://www.fda.gov/media/134731/download#:~:text=The%20orphan%20drug%20regulations%20define,a%20previously%20approved%20drug%2C%20except.

401. *See id.*

Table 6: All FDA-approved CAR-T cell therapies have at least one orphan drug designation, where * indicates the drug candidate received orphan drug status pending approval for the listed indication.[402]

Approved CAR-T Cell Therapy	Composition Claim Expiration[403]	Orphan Drug Exclusivity Ends	Orphan Designation
Kymriah	12/9/2031[404]	Aug. 30, 2024	Acute lymphoblastic leukemia
		May 27, 2029	Follicular lymphoma
		May 1, 2025	Diffuse large B-cell lymphoma
Yescarta	5/28/2023; 5/31/2031[405]	Oct. 18, 2024	Diffuse large B-cell lymphoma
		Oct. 18, 2024	Follicular lymphoma
		-	Extranodal marginal zone lymphoma*
		-	Nodal marginal zone lymphoma*
		Oct. 18, 2024	Primary mediastinal B-cell lymphoma
Tecartus	5/28/2023; 5/31/2031[406]	July 24, 2027	Mantle cell lymphoma
		Oct. 1, 2028	Acute lymphoblastic leukemia
Breyanzi	5/28/2023[407]	Feb. 5, 2028	Primary mediastinal large B-cell lymphoma
		Feb. 5, 2028	Follicular lymphoma
		Feb. 5, 2028	Diffuse large B-cell lymphoma
		-	Chronic lymphocytic leukemia*
		-	Mantle cell lymphoma*
Abecma	7/23/2035[408]	Mar. 26, 2028	Multiple myeloma
Carvykti	8/10/2036[409]	Feb. 28, 2029	Multiple myeloma

402. *See Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.

403. The estimated expiration dates are 20 years after the earliest utility application filing date and reflect any patent term extension.

404. *See* U.S. Provisional Patent Application No. 61/421,470 (filed on Dec. 9, 2010) (converted to many applications, including U.S. Patent No. 9,499,629 (filed on Dec. 9, 2011)).

405. *See* '190 patent, *supra* note 77; '465 patent, *supra* note 319. The '465 patent approximate expiration date reflects patent term extension. *See Applications for patent term extension and patent terms extended under 35 U.S.C. § 156*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/patents/laws/patent-term-extension/patent-terms-extended-under-35-usc-156 (last visited Oct. 6, 2023).

406. *See* sources cited, *supra* note 405; Alissa Poh, *Treating MCL with CAR T Cells*, 10 CANCER DISCOVERY 9 (2020).

407. *See* Brachmann, *supra* note 175.

408. *See* PCT/US2015/041722.

409. *See* PCT/CN2016/094408; U.S. Patent No. 10,934,363 (filed Feb. 9, 2018).

V. CONCLUSION

Because cancer is a pervasive and diverse disease, cancer therapeutic development requires basic research, discovery, and innovation across multiple fields. CAR-T cell therapy required foundational research in immune system processes as well as practical advances in gene sequencing, genetic engineering, cell culture methods, and antibody production methods. Government and charitable foundation grants largely funded the riskiest early-stage innovation. Patents, trade secret protections, and regulatory exclusivity incentivized companies and private investors to fund research when small-scale CAR-T clinical studies showed promising results. Relative to other pharmaceutical products, patents provide less incentive for CAR-T cell manufacturers due to early composition claim expiration dates, disclosure requirement uncertainty, and fragmented patent ownership. As a result, trade secret and regulatory exclusivity appear to be more important incentives for pharmaceutical companies.

CAR-T cell therapies are already transforming cancer treatment. U.S. policy makers should learn from the CAR-T cell therapy innovation drivers to ensure the next-generation of life-changing treatments reach patients.