# A CAR T Cell Reading List

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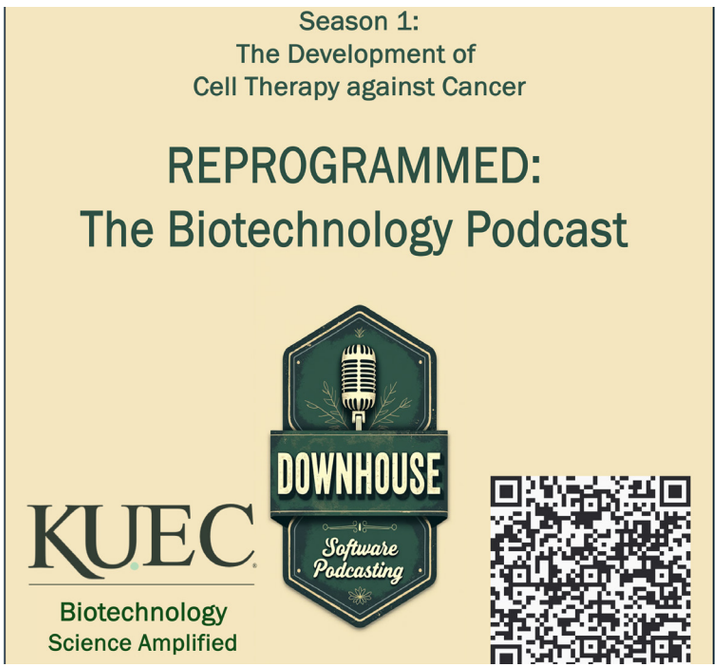
Every Spring semester, the Biotechnology program at the University of Kansas' Edwards Campus follows a series of journal articles highlighting milestones in one area of biology. This year's topic was how adoptive T Cell therapy spawned one of the most powerful techniques in modern immunotherapy, CAR T Cells. This year, the course was complemented by the podcast, 'Reprogrammed: The Biotechnology Podcast,' which featured a short discussion covering the main contribution each week's articles make to our understanding of how these CAR T Cells survive, proliferate, home to, and kill their tumor targets. Transcripts and notes for each podcast were also published on the website: https://downhousesoftware.wordpress.com/.

Admittedly, I am not much of a podcaster and it was a challenge to approximate an engaging dialog with an AI cohost, but it was nevertheless enjoyable to explore how a podcast could add to a class of this kind. Below, you will find a copy of the reading list for this course and the QR code to navigate to the podcast's home at Apple Podcasts. I encourage educators to consider this strategy to see whether it suits their courses, if for no other reason but to learn something new.

I am lucky enough to have access to a copy of Adobe Audition for recording and assembling my audio into a presentable form. Other tools I used are referenced in Table 1. I was willing to invest in some services that made my job a bit easier, which I recognize may not be readily accessible by everyone, so I encourage you to be creative in seeking out solutions that work for you.

**Format**

The main article that will be presented by students is highlighted in **bold**, while any additional recommended readings are unbolded. There is also a short introductory podcast available for each week at https://podcasts.apple.com/us/podcast/special-topics-in-biotech/id1781583786.




**Reading List:**

**Week 1 (Episode 2): The Immune System and Cancer**

In the first week of class, we will read a paper by Israel Penn from 1974 that highlights the importance of the immune system in regulating the initiation and spread of cancer. The instructor will present this paper and some figures from the Hegde et al. paper as a demonstration of the expectations for student presentations throughout the course.

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1. **Israel Penn MD. Occurrence of cancer in immune deficiencies.** First published: September 1974. https://doi.org/10.1002/1097-0142(197409)34:3+<858::AID-CNCR2820340712>3.0.CO;2-1
Immunodeficient humans and other animals increases the occurrence of tumors. This demonstrates the importance of the immune system in preventing their occurrence.
2. Hegde S, Krisnawan VE, Herzog BH, Zuo C, Breden MA, Knolhoff BL, Hogg GD, Tang JP, Baer JM, Mpoy C, Lee KB, Alexander KA, Rogers BE, Murphy KM, Hawkins WG, Fields RC, DeSelm CJ, Schwarz JK, DeNardo DG. Dendritic Cell Paucity Leads to Dysfunctional Immune Surveillance in Pancreatic Cancer. Cancer Cell. 2020 Mar 16;37(3):289-307.e9. doi: 10.1016/j.ccell.2020.02.008. PMID: 32183949; PMCID: PMC7181337.
3. Robert D. Schreiber et al., Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion. Science 331,1565-1570(2011). DOI:10.1126/science.1203486

**Week 2 (Episode 3): Adoptive T Cell Therapy, Proof of Concept**
Shu et al., present data demonstrating the capacity for isolating T Cells from lymph nodes of immunized animals for ex vivo expansion and use in Adoptive T Cell Therapy in mice. Yee et al., then show a pioneering study on the use of antigen-specific CD8+ T cell clones for treating metastatic melanoma in humans. They demonstrated that these T cells could persist and migrate effectively in vivo, providing early evidence of the potential for adoptive T-cell therapy to achieve significant antitumor effects.

1. Shu SY, Chou T, Sakai K. Lymphocytes generated by in vivo priming and in vitro sensitization demonstrate therapeutic efficacy against a murine tumor that lacks apparent immunogenicity. J Immunol. 1989;143:740–8.

2. **Yee, C., Thompson, J. A., Byrd, D. R., Riddell, S. R., Roche, P. C., Celis, E., … & Greenberg, P. D. (2002). Adoptive t cell therapy using antigen-specific cd8+ T cell clones for the treatment of patients with metastatic melanoma: in vivo persistence, migration, and antitumor effect of transferred t cells.** Proceedings of the National Academy of Sciences, 99(25), 16168-16173. https://doi.org/10.1073/pnas.242600099.

**Week 3 (Episode 4): First Generation CAR T Cells: sfv targeting + CD3 signaling domain**
3. **Gideon Gross, Tova Waks, and Zelig Eshhar. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity.** Proc. Natl. Acad. Sci. USA. Vol. 86, pp. 10024-10028, December 1989. Immunology. First attempt at making a chimeric antigen receptor on cytotoxic T Cells.

4. Dabas P, Danda A. Revolutionizing cancer treatment: a comprehensive review of CAR-T cell therapy. Med Oncol. 2023 Aug 22;40(9):275. doi: 10.1007/s12032-023-02146-y. PMID: 37608202.

Generational view of CAR T Cell Treatments, from the Dabas Review (**Figure 1**)

**Week 4 (Episode 5): Second Generation CAR T Cells** (Part 1): sfv targeting of phosphorylcholine plus alpha and beta subunits of the TCR and CD28 Costimulatory domain (or 4-1BB or OX-40)

5. **Krause A, Guo HF, Latouche JB, Tan C, Cheung NK, Sadelain M. Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes.** J Exp Med. 1998 Aug 17;188(4):619-26. doi: 10.1084/jem.188.4.619. PMID: 9705944; PMCID: PMC2213361.

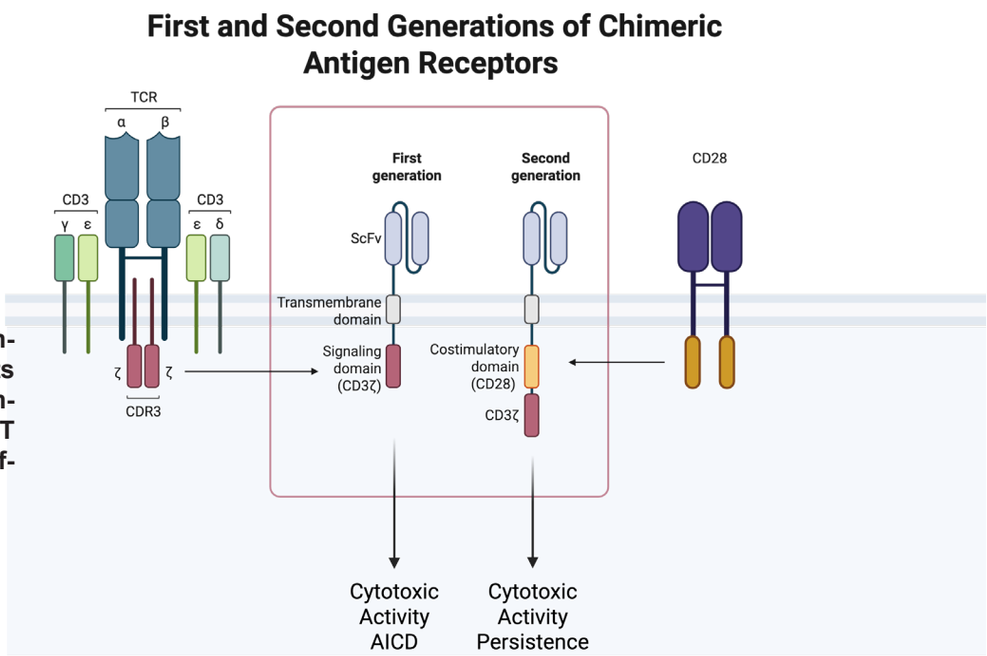


**Figure 1 | First and Second-Generation CAR T Cell Constructs show the importance of co-stimulatory signals in activating T Cells for prolonged lives as effectors.**

6. Rosenberg SA, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, Simon P, Lotze MT, Yang JC, Seipp CA, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med. 1988 Dec 22;319(25):1676-80. doi: 10.1056/NEJM198812223192527. PMID: 3264384.

**Week 4 (Supplemental Episode 5a):** T Cell Signaling and Activation
(This Episode does not have a corresponding Special Topics in Biotechnology course)

7. Smith-Garvin JE, Koretzky GA, Jordan MS. T cell activation. Annu Rev Immunol. 2009;27:591-619. doi: 10.1146/annurev.immunol.021908.132706. PMID: 19132916; PMCID: PMC2740335.

8. Lotze, M.T., Olejniczak, S.H. & Skokos, D. CD28 co-stimulation: novel insights and applications in cancer immunotherapy. Nat Rev Immunol 24, 878–895 (2024). https://doi.org/10.1038/s41577-024-01061-1

9. Shah, K., Al-Haidari, A., Sun, J. et al. T cell receptor (TCR) signaling in health and disease. Sig Transduct Target Ther 6, 412 (2021). https://doi.org/10.1038/s41392-021-00823-w

**Week 5 (Episode 6): Second Generation CAR T Cells** (Part 2)
Second-generation CARs T cells are able to survive, proliferate, and kill prostate cancer cells in the lab, establishing the feasibility of CAR T cell therapy.

10. **Maher, J., Brentjens, R., Gunset, G. et al. Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ / CD28 receptor.** Nat Biotechnol 20, 70–75 (2002). https://doi.org/10.1038/nbt0102-70

11. Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Geiger TL, Campana D. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia. 2004 Apr;18(4):676-84. doi: 10.1038/sj.leu.2403302. PMID: 14961035.

**Week 6 (Episode 7): Anti-CD19 CAR T Cells proof of concept**
These target uniquely susceptible 'liquid' tumor cells in the mouse.

12. **Brentjens, R., Latouche, JB., Santos, E. et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15.** Nat Med 9, 279–286 (2003). https://doi.org/10.1038/nm827

13. Claudia M. Kowolik, Max S. Topp, Sergio Gonzalez, Timothy Pfeiffer, Simon Olivares, Nancy Gonzalez, David D. Smith, Stephen J. Forman, Michael C. Jensen, Laurence J.N. Cooper; CD28 Costimulation Provided through a CD19-Specific Chimeric Antigen Receptor Enhances In vivo Persistence and Antitumor Efficacy of Adoptively Transferred T Cells. Cancer Res 15 November 2006; 66 (22): 10995–11004. https://doi.org/10.1158/0008-5472.CAN-06-0160

**Week 7 (Episode 8): Anti-CD19 CAR T Cell clinical response**
This paper examines the clinical response in patients given CAR T Cells.

14. **Renier J. Brentjens et al., CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia.**Sci. Transl. Med.5,177ra38-177ra38(2013). DOI:10.1126/scitranslmed.3005930

15. Hollyman D, Stefanski J, Przybylowski M, Bartido S, Borquez-Ojeda O, Taylor C, Yeh R, Capacio V, Olszewska M, Hosey J, Sadelain M, Brentjens RJ, Rivière I. Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. J Immunother. 2009 Feb-Mar;32(2):169-80. doi: 10.1097/CJI.0b013e318194a6e8. PMID: 19238016; PMCID: PMC2683970.

**Week 8 (Episode 9): CRISPR-targeted CARs**
Eyquem et al., examine how intentionally integrating the CAR construct into the T Cell Receptor locus improves the regulation and efficacy of these cells.

16. **Eyquem, J., Mansilla-Soto, J., Giavridis, T. et al. Targeting a CAR to the TRAC locus with CRISPR/Cas9 enhances tumour rejection.** Nature 543, 113–117 (2017). https://doi.org/10.1038/nature21405

**Week 9 (Episode 10): Mutation-specific T cells**
Shifting focus from engineered CAR T cells to the body's natural immune capabilities, Tran *et al.*, highlight how mutation-specific CD4+ T cells derived from a patient with metastatic cholangiocarcinoma were isolated, expanded, and infused back to achieve significant tumor regression.

17. **Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, Wunderlich JR, Somerville RP, Hogan K, Hinrichs CS, Parkhurst MR, Yang JC, Rosenberg SA. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.** Science. 2014 May 9;344(6184):641-5. doi: 10.1126/science.1251102. PMID: 24812403; PMCID: PMC6686185.

18. Lang F, Schrörs B, Löwer M, Türeci Ö, Sahin U. Identification of neoantigens for individualized therapeutic cancer vaccines. Nat Rev Drug Discov. 2022 Apr;21(4):261-282. doi: 10.1038/s41573-021-00387-y. Epub 2022 Feb 1. Erratum in: Nat Rev Drug Discov. 2024 Feb;23(2):156. doi: 10.1038/s41573-023-00873-5. PMID: 35105974; PMCID: PMC7612664.

**Week 10 (Episode 11): Third Generation CAR T Cells: 4-1BB and CD28** (CD3ζ-CD28-OX40, CD3ζ-CD28-41BB, CD3ζ-ICOS-4-1BB, and CD3ζ-TLR2-CD28)
Roselli et al.1, explore a critical frontier in CAR T cell engineering: how to build T cells that don't just kill tumors effectively, but also survive, persist, and adapt in the complex and hostile environments characteristic of solid tumors and relapsing hematologic malignancies.

19. **Roselli E, Boucher JC, Li G, Kotani H, Spitler K, Reid K, Cervantes EV, Bulliard Y, Tu N, Lee SB, et al. 4-1BB and optimized CD28 co-stimulation enhances function of human mono-specific and bi-specific third-generation CAR T cells.** J Immunother Cancer. 2021;9:e003354. doi: 10.1136/jitc-2021-SITC2021.105.
20. Sadelain M, Brentjens R, Rivière I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013 Apr;3(4):388-98. doi: 10.1158/2159-8290.CD-12-0548. Epub 2013 Apr 2. PMID: 23550147; PMCID: PMC3667586.

**Week 11 (Episode omitted): Fourth Generation CAR T Cells,** also known as T-cell redirected for universal cytokine-mediated killing (TRUCK), universal CAR (UniCAR-T), or armored CAR-T-cells

21. **Avanzi MP, Yeku O, Li X, Wijewarnasuriya DP, van Leeuwen DG, Cheung K, Park H, Purdon TJ, Daniyan AF, Spitzer MH, Brentjens RJ. Engineered Tumor-Targeted T Cells Mediate Enhanced Anti-Tumor Efficacy Both Directly and through Activation of the Endogenous Immune System.** Cell Rep. 2018 May 15;23(7):2130-2141. doi: 10.1016/j.celrep.2018.04.051. PMID: 29768210; PMCID: PMC5986286.

22. Chang, P. S., Lee, J. C., Koneru, M. & Brentjens, R. J. 408. CD19-Targeted CAR T Cells "Armored" To Secrete IL-12 Demonstrate Superior Efficacy Against B Cell Acute Lymphoblastic Leukemia and Resist Treg Immunosuppression. Molecular Therapy 23, S161 (2015).

23. Pegram HJ, Lee JC, Hayman EG, Imperato GH, Tedder TF, Sadelain M, Brentjens RJ. Tumor-targeted T cells modified to secrete IL-12 eradicate systemic tumors without need for prior conditioning. Blood. 2012 May 3;119(18):4133-41. doi: 10.1182/blood-2011-12-400044. Epub 2012 Feb 21. PMID: 22354001; PMCID: PMC3359735.

24. Chmielewski M, Abken H. TRUCKs: the fourth generation of CARs. Expert Opin Biol Ther. 2015;15(8):1145-54. doi: 10.1517/14712598.2015.1046430. Epub 2015 May 18. PMID: 25985798.

**Week 12 (Episode 12): Traffic Signals**

Craddock et al., explore how engineering T cells to express the chemokine receptor CCR2b—matching the tumor's secretion of CCL2—can dramatically improve tumor infiltration without sacrificing cytotoxic function.

25. **Craddock JA, Lu A, Bear A, et al. Enhanced tumor trafficking of GD2 chimeric antigen receptor T cells by expression of the chemokine receptor CCR2b.** J Immunother. 2010;33(8):780-788. doi:10.1097/CJI.0b013e3181ee6675.

26. Tokarew N, Ogonek J, Endres S, von Bergwelt-Baildon M, Kobold S. Teaching an old dog new tricks: next-generation CAR T cells. Br J Cancer. 2019 Jan;120(1):26-37. doi: 10.1038/s41416-018-0325-1. Epub 2018 Nov 9. PMID: 30413825; PMCID: PMC6325111.

27. Majumder, A. (2024). Evolving CAR-T-Cell Therapy for Cancer Treatment: From Scientific Discovery to Cures. Cancers, 16(1), 39. https://doi.org/10.3390/cancers16010039

**Week 13 (Episode 13): AND Logic Gate CARs**

Lanitis et al., developed a trans-signaling CAR strategy, consisting of two independent CAR constructs where activation signal 1 (CD3zeta) is physically dissociated from costimulatory signal 2 (CD28) using two CARs of differing antigen specificity: mesothelin and a-folate receptor (FRa).

28. **Lanitis E, Poussin M, Klattenhoff AW, Song D, Sandaltzopoulos R, June CH, Powell DJ Jr. Chimeric antigen receptor T Cells with dissociated signaling domains exhibit focused antitumor activity with reduced potential for toxicity in vivo.** Cancer Immunol Res. 2013 Jul;1(1):43-53. doi: 10.1158/2326-6066.CIR-13-0008. PMID: 24409448; PMCID: PMC3881605.

**Week 14 (Episode 14): OR Logic Gate CARs, bivalent cells targeting two antigens**
Qin et al., explore how simultaneous targeting of two independent targets (CD19 and CD22, both expressed on B-ALL cells) may reduce the likelihood of antigen loss and improve sustained remission rates.

29. **Qin H, Ramakrishna S, Nguyen S, Fountaine TJ, Ponduri A, Stetler-Stevenson M, Yuan CM, Haso W, Shern JF, Shah NN, Fry TJ. Preclinical Development of Bivalent Chimeric Antigen Receptors Targeting Both CD19 and CD22.** Mol Ther Oncolytics. 2018 Nov 6;11:127-137. doi: 10.1016/j.omto.2018.10.006. PMID: 30581986; PMCID: PMC6300726 (**Figure 1**).

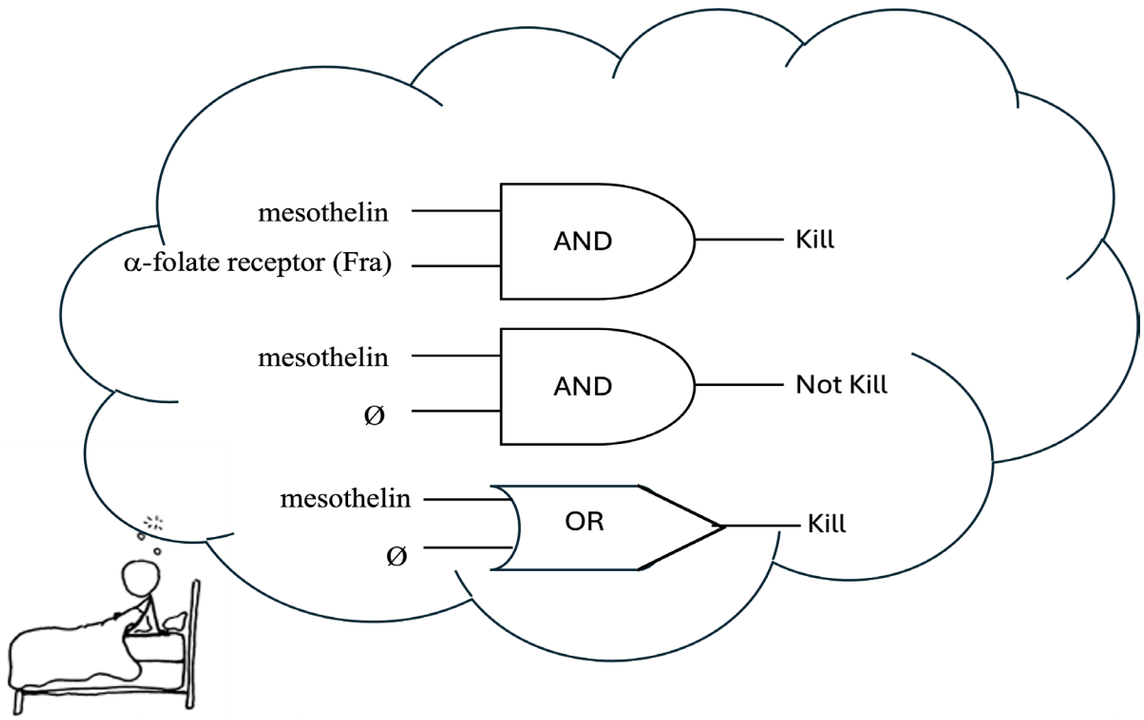


**Figure 1 | AND / OR gating of CAR T Cell Immune Responses regulates the cytotoxicity of cells to function under only strictly defined conditions.**