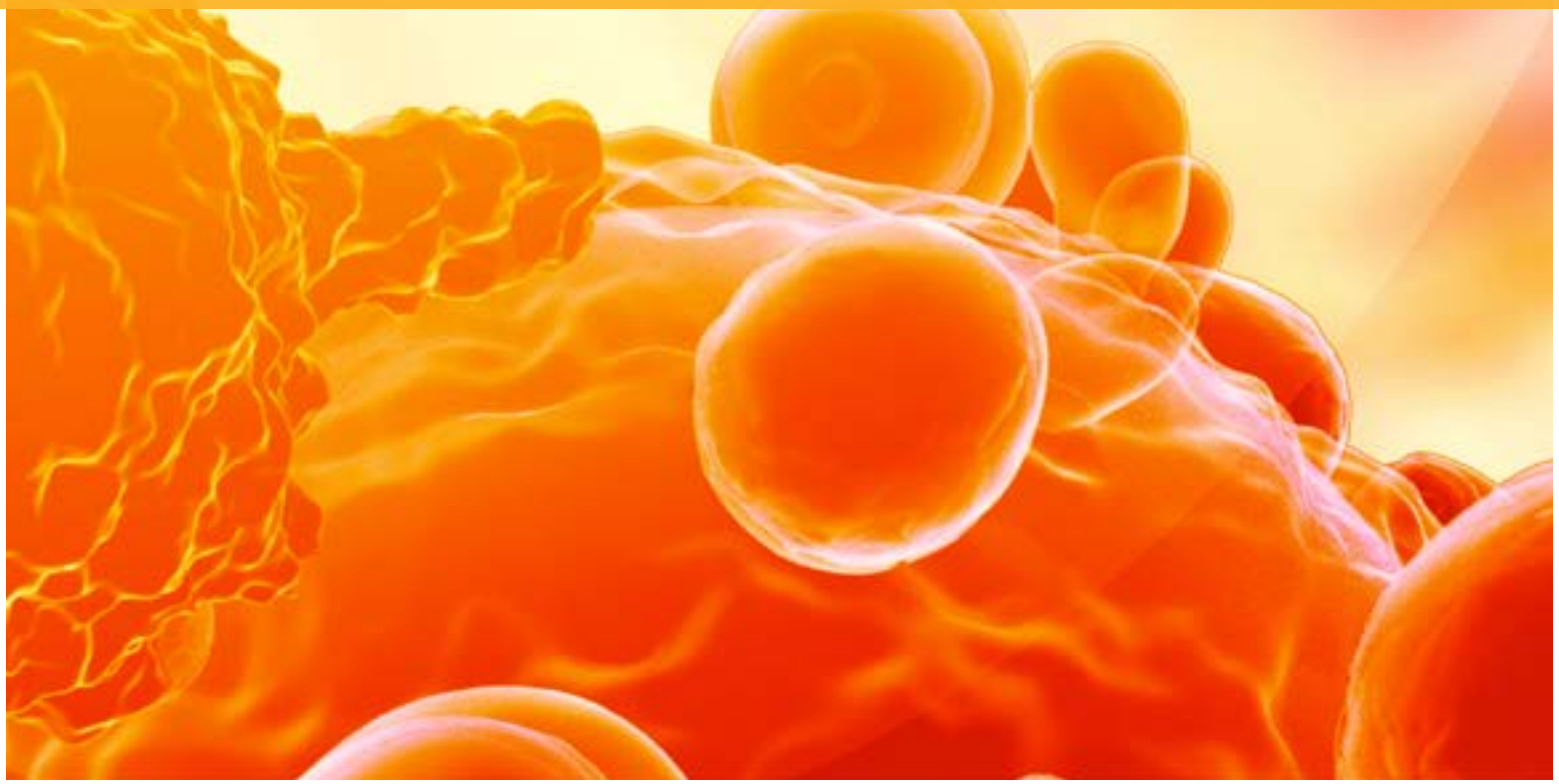
PRACTICE POINTS

Current and Emerging CAR T-Cell and Other Cellular Therapies for THE TREATMENT OF PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Strategies to Integrate Cellular Therapy into the Treatment of Hematologic Malignancies



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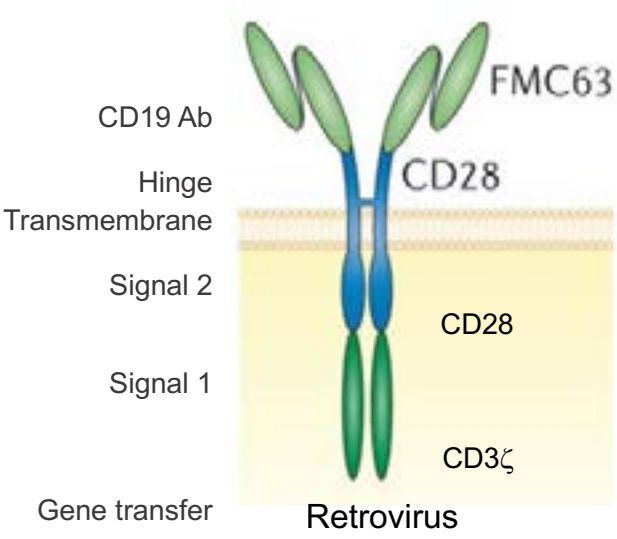
Axicabtagene ciloleucel



FDA approval:

- R/R large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- R/R follicular lymphoma after 2 or more lines of systemic therapy
- Not indicated for the treatment of patients with primary central nervous system lymphoma

Study	ZUMA1
CAR T dose	2 x 10^6/kg
Conditioning therapy	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL
Treated/Enrolled	101/111 (91%)
Relapsed/Refractory	Refractory
Relapse post-ASCT	21%
Bridging therapy	None
Manufacturing success	99%
ORR / CR (%)	82 / 54

Safety

CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
93%	13%	64%	28%

Yescarta. Prescribing information. Kite Pharma, Inc.; 2021. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544. doi:10.1056/NEJMOA170744 van der Stegen S, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Discov.* 2015;14(7):499-509. doi:10.1038/nrd4597

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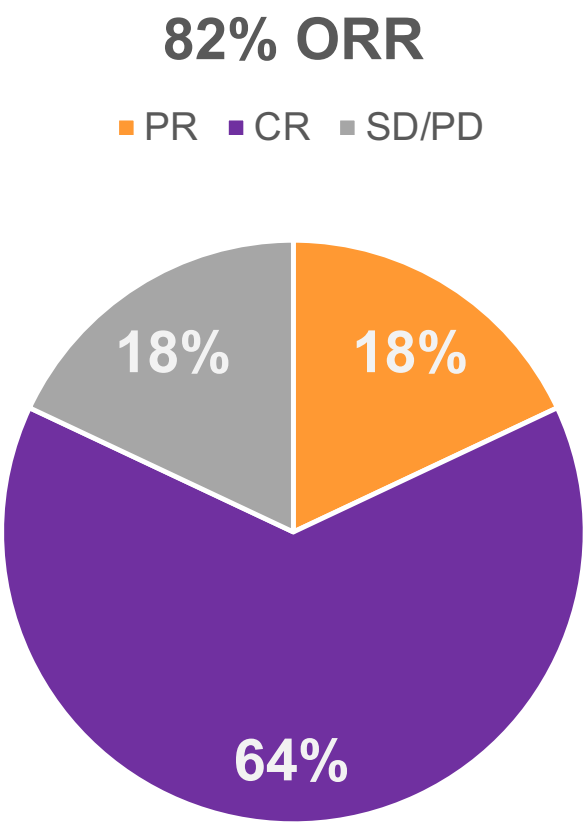
Axi-Cel in Clinical Practice

Response to SOC Axi-Cel Treatment



- Median time to response was 30 days, and no patients achieved a first response beyond day 90
- Most patients who achieved a CR (n = 121) at day 30 remained in CR at day 90 (78%)
- Among the 93 patients with a PR at day 30, 32% improved to a CR at day 90, and even 1 (7%) of 14 patients with stable disease at day 30 improved to a CR at day 90

Safety

	SOC axi-cel N=255	ZUMA 1 N=108
All grade CRS	251 (91%)	100 (93%)
Grade ≥ 3	19 (7%)	14 (13%)
Median time to onset	3 days	2 days
All grade neurotoxicity	189 (69%)	70 (65%)
Grade ≥ 3	85 (31%)	33 (31%)
Median time to onset	6 days	5 days
Median hospital stay	14	NA
ICU stay	91 (33%)	NA
Tocilizumab use	170 (62%)	45%
Corticosteroid use	149 (54%)	29%

Nastoupil L, Jain MD, Feng L, et al. Axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol.* 2020;38(27):3119-3128. doi: 10.1200/JCO.19.02104

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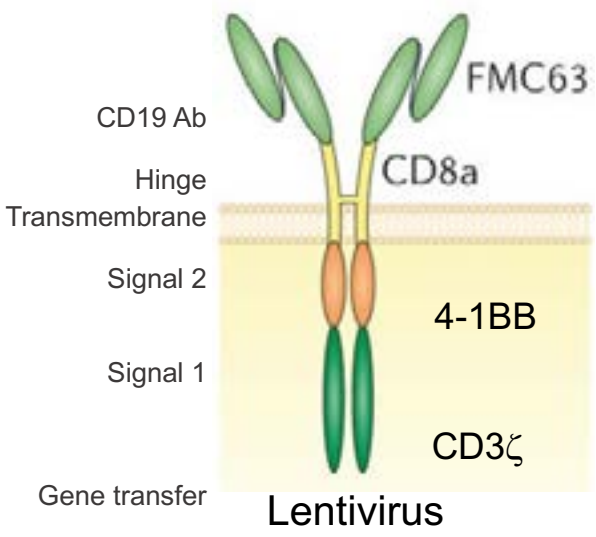
Tisagenlecleucel



FDA approval:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- R/R large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- Not indicated for treatment of patients with primary central nervous system lymphoma

Study	JULIET
CAR T dose	0.6-6 x 10^8
Conditioning therapy	Cy/Flu or Bendamustine
Lymphoma subtypes	DLBCL / TFL
Treated/Enrolled	111/165 (67%)
Relapsed/Refractory	Relapsed or refractory
Relapse post-ASCT	49%
Bridging therapy	Allowed
Manufacturing success	93%
ORR / CR (%)	52 / 40

Safety

N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
111	58%	22%	21%	12%

Kymriah. Prescribing information. Novartis Pharmaceuticals Corporation; 2021. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med.* 2018;380(1):45-56. doi:10.1056/NEJMoa1804980. van der Stegen S, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Discov.* 2015;14(7):499-509. doi:10.1038/nrd4597

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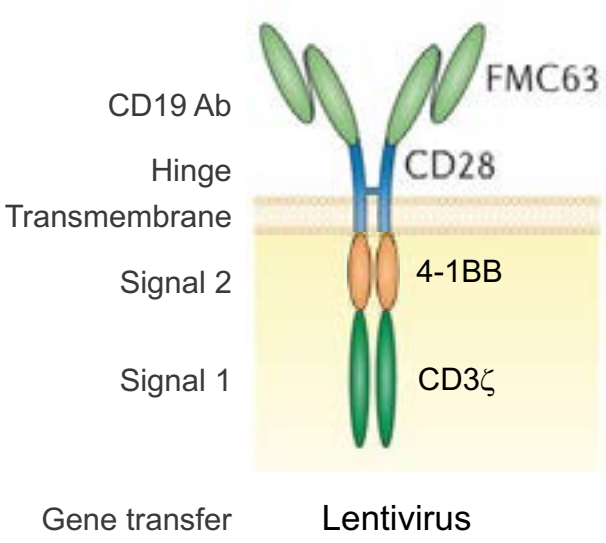
Lisocabtagene maraleucel



FDA approval:

- Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
- Not indicated for the treatment of patients with primary central nervous system lymphoma

Study	TRANSCEND
CAR T dose	0.5-1.5 x 10^6
Conditioning therapy	Cy/Flu
Lymphoma subtypes	DLBCL/PMBCL/TFL/FL Gr 3B
Treated/Enrolled	269/344 (78%)
Relapsed/Refractory	Relapsed or refractory
Relapse post-ASCT	33%
Bridging therapy	Allowed
Manufacturing success	99%
ORR / CR (%)	73 / 53

N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
268	42%	2%	30%	10%

Breyanzi. Prescribing information. Juno Therapeutics Inc.; 2021. 2. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet.* 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0 3. van der Stegen S, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Discov.* 2015;14(7):499-509. doi:10.1038/nrd4597

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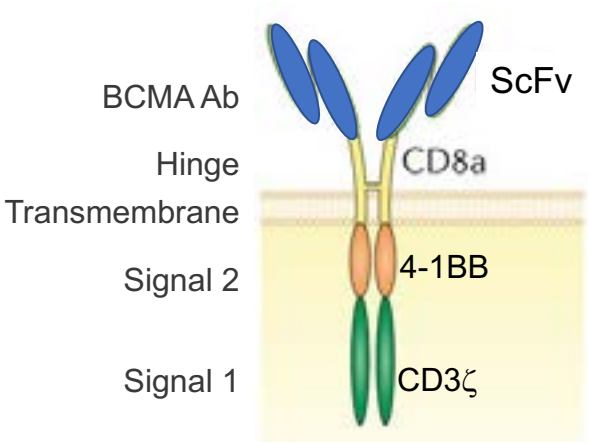
Idecabtagene vicleucel



Gene transfer Lentivirus

FDA approval:

- Adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Study	KarMMA
CAR T dose	150-450 x 10^6
Treated / Enrolled	128
Relapsed / Refractory	Relapsed or refractory
Manufacturing success	99%
ORR / CR (%)	73 / 33

N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
128	84%	5%	18%	3%

Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med.* 2021;384(8):705-716. doi:10.1056/NEJMOA2024850 2. Abecma. Prescribing information. Celgene Corporation; 2021.

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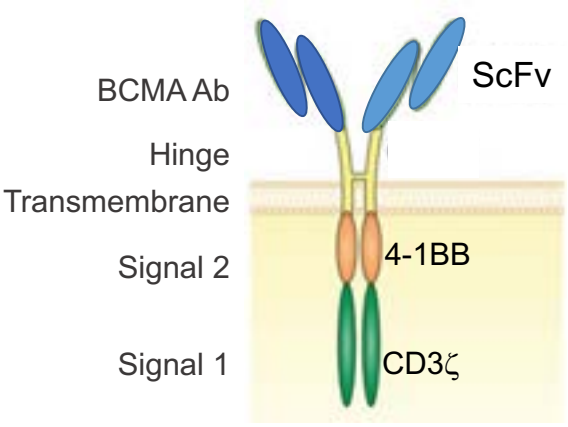
Ciltacabtagene autoleucel

2 BCMA-targeting epitopes:
VHH1 and VHH2



Gene transfer — Lentivirus

NOT FDA APPROVED YET

Study	CARTITUDE
CAR T dose	0.75×10^6
Treated / Enrolled	96
Relapsed / Refractory	Relapsed or refractory
ORR / CR (%)	95 / 67

N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
97	95%	4%	21%	10%

Usmani S. Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1. Abstract #8005 [Oral]. Presented at: the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021; Chicago, IL.

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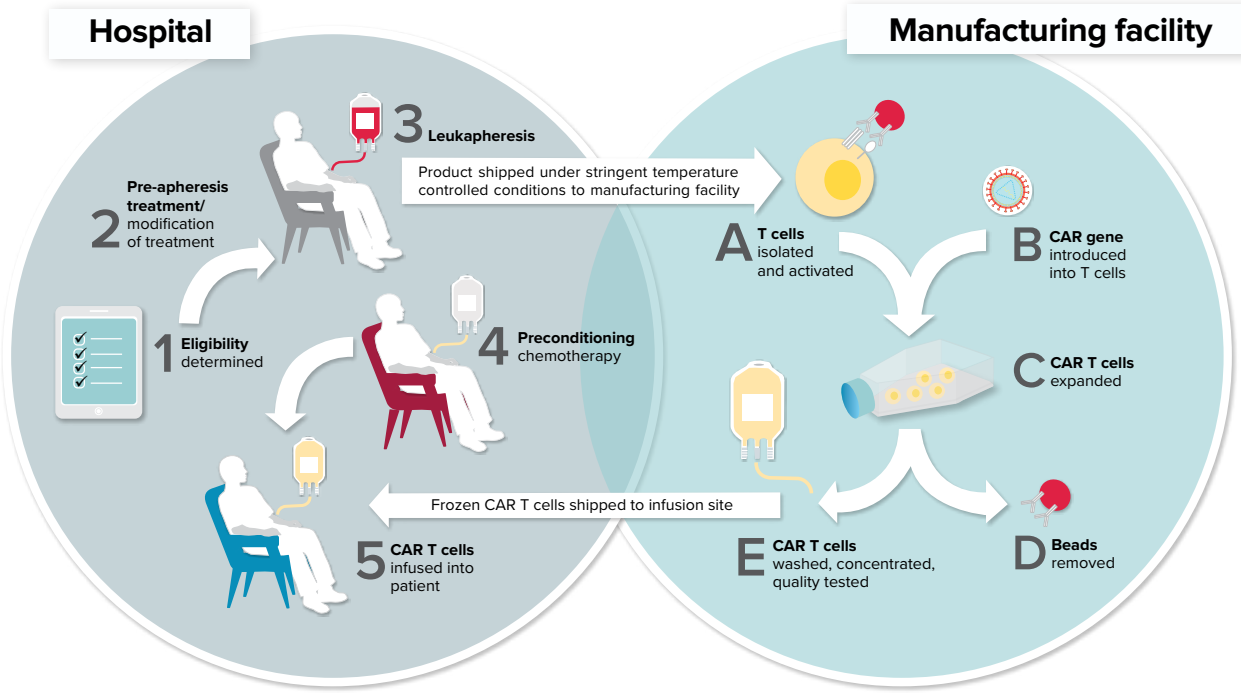
How Are CAR T Cells Manufactured/Engineered?



- On average, the production of CAR T cells takes approximately 10 to 14 days
- The time from endogenous T-cell collection to CAR T-cell infusion varies, but typically ranging from 1 to 4 weeks

Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. Revised September 2020. Accessed November 8, 2021. https://www.lls.org/sites/default/files/2021-05/FSHP1_CART_Factsheet_Sept2020_Rev.pdf

Strategies for Bridging the Gap Between Academic and Community Practices

Referral for CAR T

- Patients with relapsed or refractory large B-cell lymphoma who have failed 2 or more prior therapies and/or autologous bone marrow transplant
- Patients with RRMM who have failed 3 or more prior therapies and/or autologous bone marrow transplant
- Patients who progress on first-line therapy in a short period should be referred directly to academic centers for comanagement because high rates of relapse are observed with second-line treatments
- Multidisciplinary approach is best early on
- Refer patients early and broadly, as the time of referral to CAR T-cell infusion can take 4 to 6 weeks.
- Know which centers in your state offer CAR T-cell therapy
- Develop relationships with CAR T oncologists early on

Return to Community Oncologist

- Any patient in response/remission who does not experience a serious adverse event after a 4- to 8-week stay returns home
- Patients treated with CAR T-cell therapy are advised to carry a wallet card with them at all times that defines symptoms that could indicate a serious adverse event for which to seek medical attention
- The CAR T-cell treatment center, in coordination with the local oncologist, may have patient follow-ups every 2 weeks until month 3, then decreasing in frequency to 6 months and 12 months after CAR T-cell infusion, then yearly until 5 years after CAR T-cell infusion

Post CAR T Management

- Coordination and communication between the local oncologist and CAR T-cell treatment oncologist are important during the months after patients return home
- These patients can experience prolonged hypogammaglobulinemia and B-cell aplasia. Patients may require supportive care with IVIG
- Prolonged cytopenias
- Observe patients for prolonged cytopenias

Jacobson CA, Farooq U, Ghobadi A. Axicabtagene ciloleucel, an anti-CD19 chimeric antigen receptor T-cell therapy for relapsed or refractory large B-cell lymphoma: practical implications for the community oncologist. **Oncologist.** 2020;25:e(1)138-e146. doi: 10.1634/theoncologist.2019-0395.

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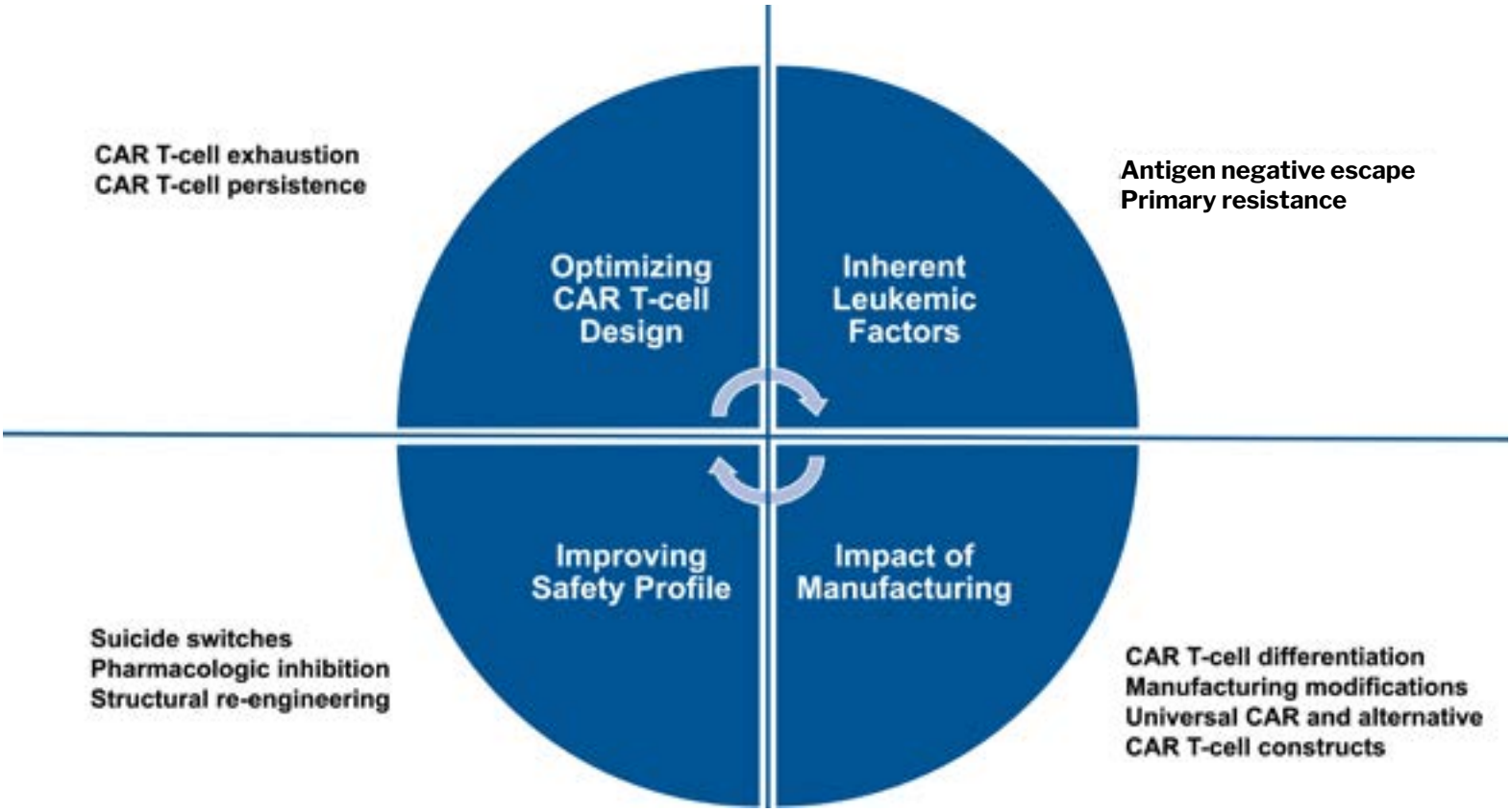
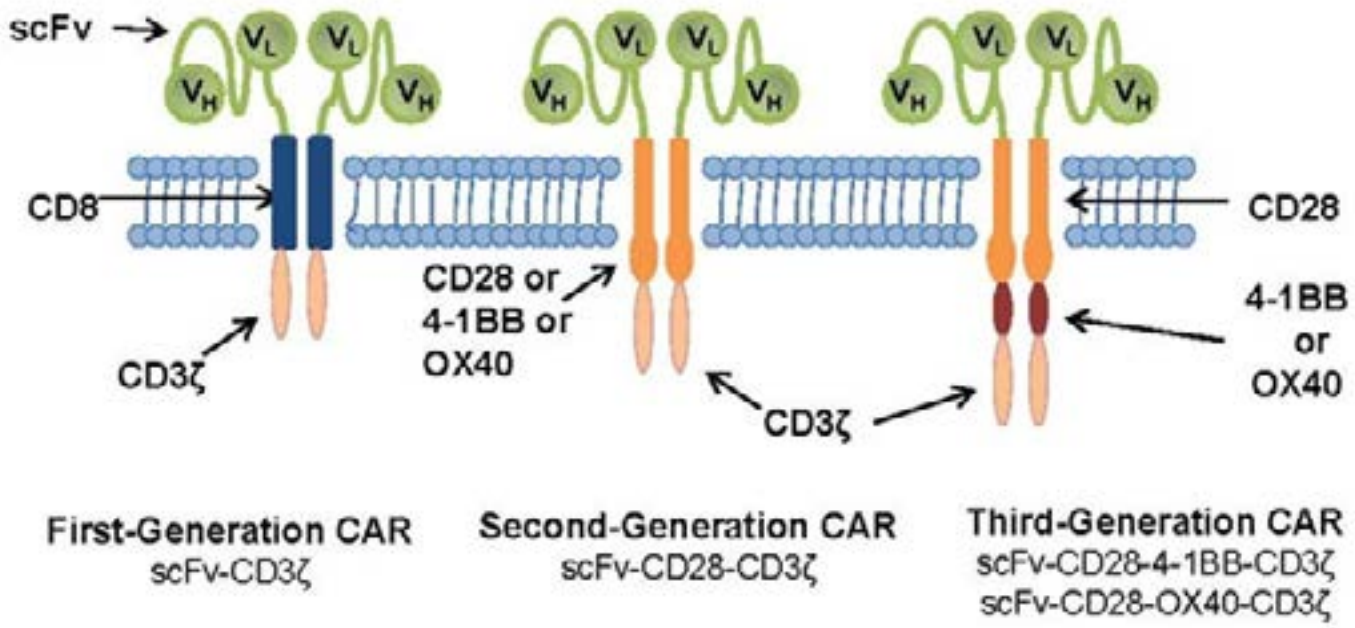
CAR T-CELL IMPROVEMENTS



Building a Better CAR T-Cell Product



Park JH, Brentjens RJ. Adoptive immunotherapy for B-cell malignancies with autologous chimeric antigen receptor modified tumor targeted T cells. *Discov Med.* 2010;9(47):277-288.