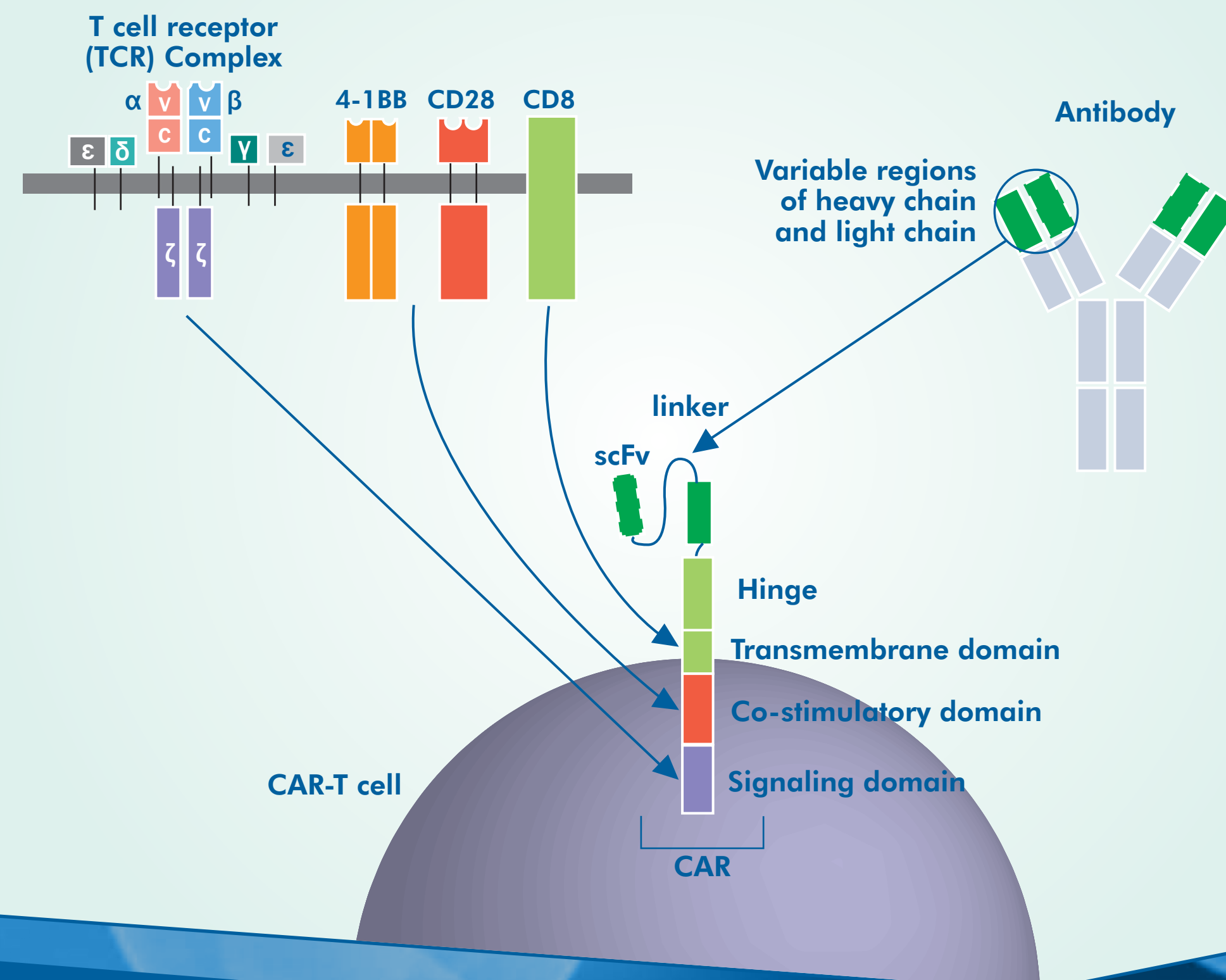


# Chimeric Antigen Receptor (CAR)-T Cell Immunotherapy

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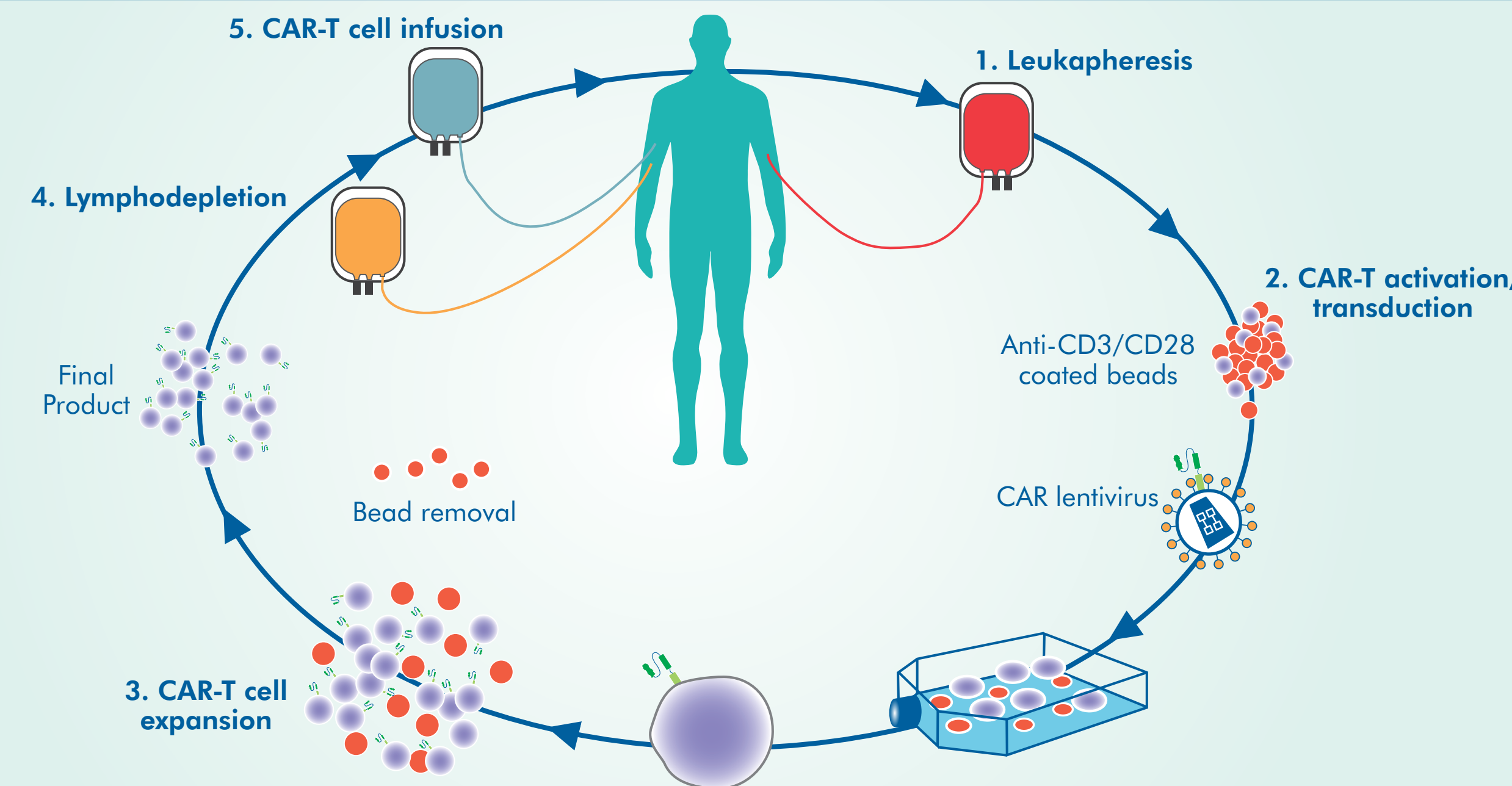
## CAR Structure:

A chimeric antigen receptor (CAR) is a synthetic fusion protein composed of a single-chain variable fragment (scFv) from a monoclonal antibody and the signaling domain of a T cell receptor. The signaling domain typically contains CD3 zeta and a co-stimulatory domain such as 4-1BB among others.



## CAR-T Manufacturing & Administration:

T cells are collected from the patient, activated, transduced, and expanded for ~10 days. Lymphodepleting chemotherapy is administered before CAR-T infusion.



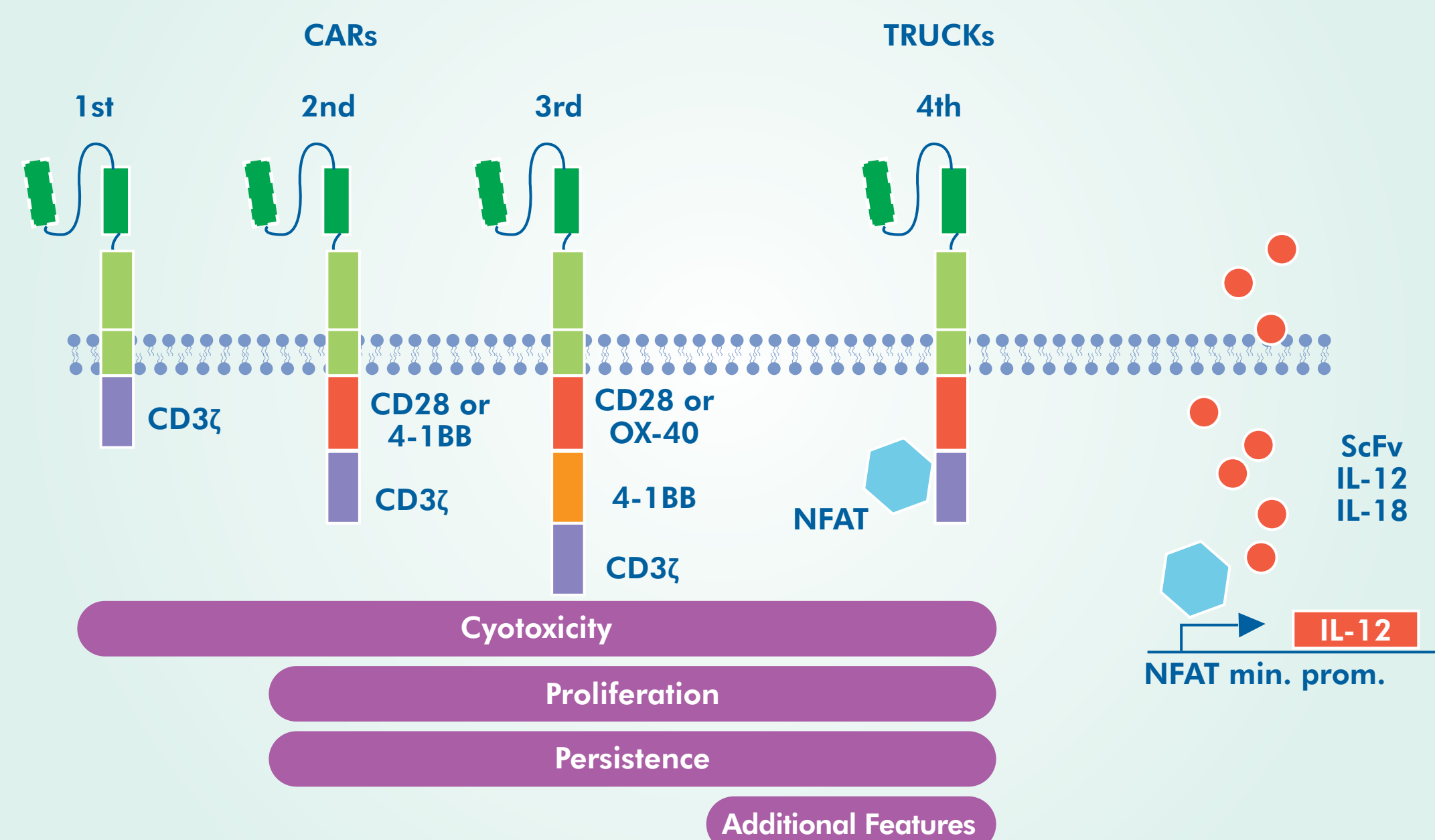
## Key targets for CAR-T cell therapy and established clinical results

Disease	Target	Effector	Efficacy	Toxicity	Citation
B-cell Acute Leukemia (pediatric-young adult)	CD19	CTL019 (4-1BB)	CR 81% [61/75] RFS (12 months) 59%	CRS 77% Gr. 4 CRS 25% Neurotoxicity 40%	Maude et al., 2018 [NEJM; PMID: 29385370]
B-cell Acute Leukemia (adult)	CD19	JCAR017 (CD4/CD8; 4-1BB)	CR 93% [27/29] RFS: n/a	CRS 83% Severe CRS (Doesn't Specify) 23% Neurotoxicity 50%	Turtle et al., 2017 [JCI; PMID: 27111235]
B-cell Lymphoma (DLBCL, FL)	CD19	CTL019 (4-1BB)	CR 57% [16/28] PFS (28.6 months) 57%	CRS 57% Severe CRS (Grade 3 or higher): 18% Neurotoxicity 39%	Schuster et al., 2017 [NEJM; PMID: 9226764]
B-cell Chronic Leukemia	CD19	CTL019 (4-1BB)	CR 29% [4/14] PFS (18 months) 29%	CRS 64% Severe CRS 29% (43%) Neurotoxicity 37% [6/16]	Porter et al., 2015 [STM; PMID: 26333935]
B-cell Acute Leukemia (pediatric-young adult)	CD22	CAR-T-22 (4-1BB)	CR 57% [12/21] PFS (6 months) 50%	CRS 76% Severe CRS 0% Neurotoxicity 37% [6/16]	Fry et al., 2017, [Nat Med; PMID: 29155426]
Multiple Myeloma	BCMA	BCMA-CAR-T (4-1BB)	ORR 100% [15/15] sCR+VGPR 73% [11/15]	CRS 78% [14/18] Severe CRS 11% [2/18]	Bergdeja et al., 2017 [ASH; Paper 107984, Session: 653]

CR = complete remission; PFS = progression-free survival; DFS = disease-free survival; CRS = cytokine release syndrome; n/a = not applicable sCR = stringent CR; VGPR = very good partial remission; ORR = overall response rate

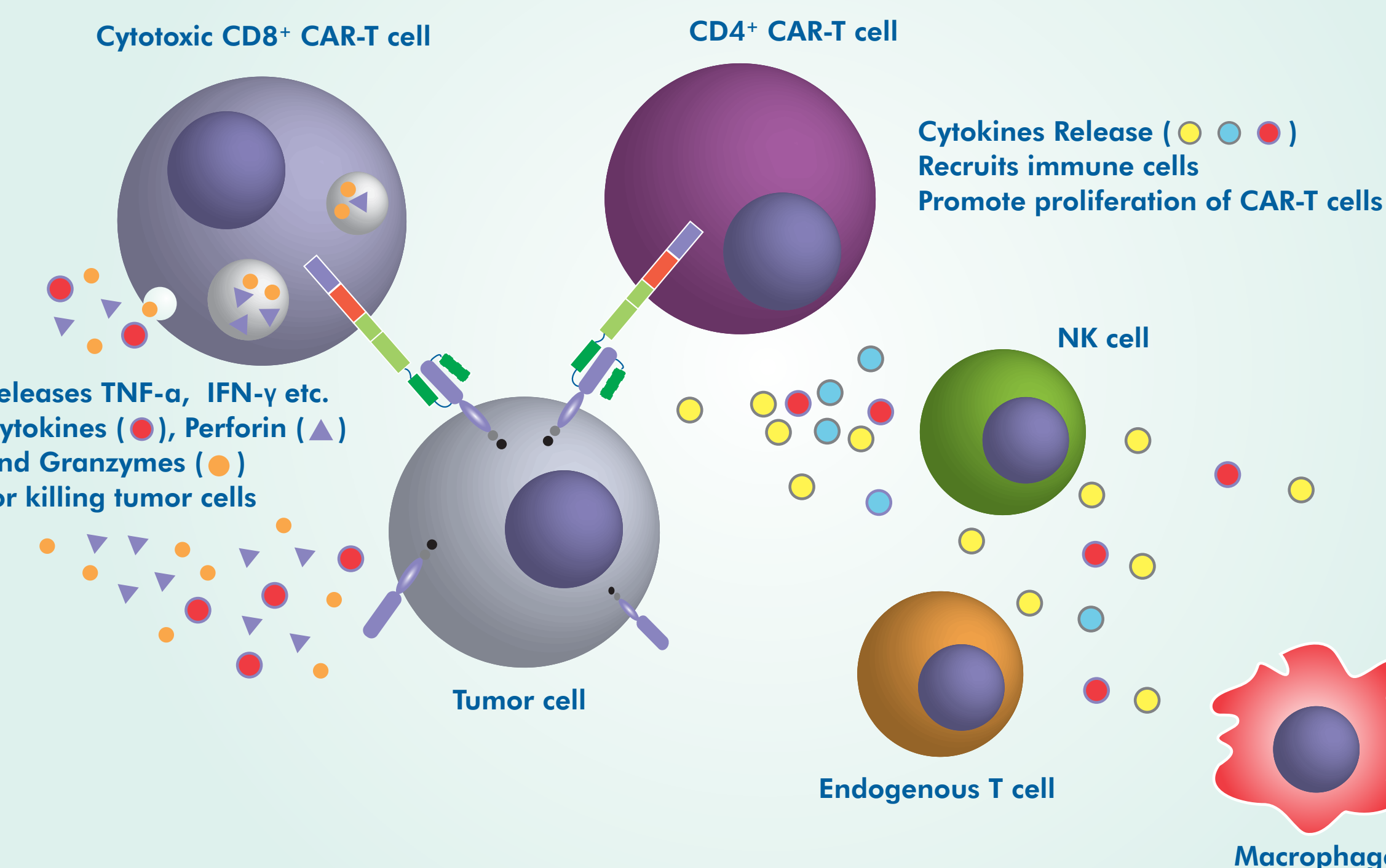
## CAR Generations:

1st generation CARs only contain a CD3 zeta domain while 2nd and 3rd generation CARs have one or two co-stimulatory moieties respectively. TRUCKs or Armored CARs are 4th generation constructs that include additional features such as increased release of scFv, cytokine production (e.g. IL-12, IL18) or co-expression of a functional receptor (e.g. PD-1 switch, 4-1BB, CCR4)



## CAR-T Cell Killing:

The presence of a CAR on CD8<sup>+</sup> and CD4<sup>+</sup> T cells triggers the antigen-specific release of perforin, granzymes, and cytokines, which leads to tumor killing and activation of the immune system.



## Next-generation CAR-T:

Several new CAR designs are under development, including dual-specific CAR-T, exhaustion-resistant CAR-T, and universal "off-the-shelf" CAR-T.

