Adoptive Cell Therapies in Solid Tumors

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Disclosures

- No personal disclosures
- CME Consideration: There are (currently) no FDA-approved cellular therapies for solid tumors. Presented early-phase and ongoing clinical trials will be clearly referenced as such.

Introduction: A Promising Paradigm

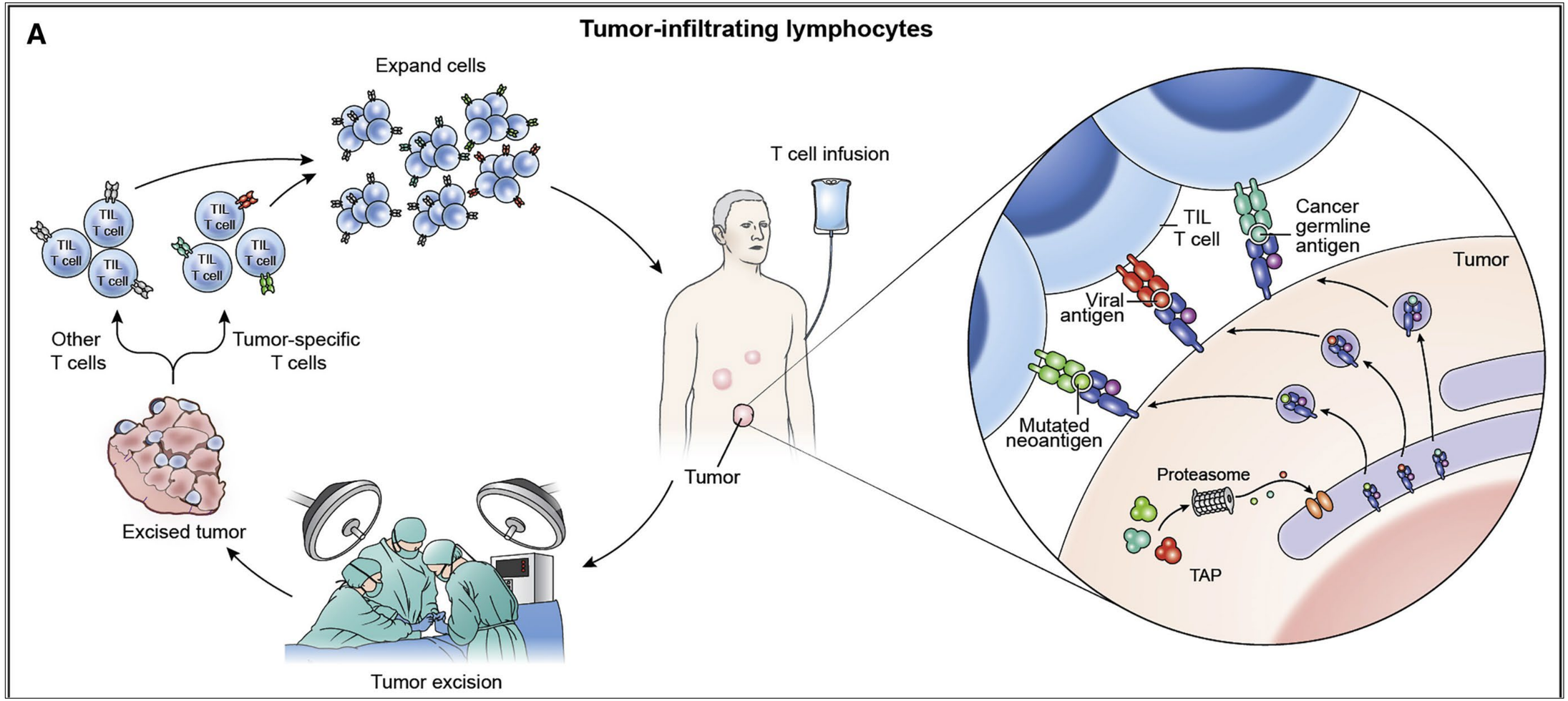
- Decades of experience using transfer of immune cells to treat cancer and infections.
- The field of oncology was revolutionized by the emergence of Chimeric Antigen Receptor (CAR)-T cell therapies for hematologic malignancies.
- Since 2017, the U.S. Food and Drug Administration (FDA) has approved four chimeric antigen receptor (CAR)-T products targeting CD19 in B cell malignancies and two CAR-T products targeting B cell maturation antigen (BCMA) in multiple myeloma.
- In comparison, there are no FDA approvals for a cellular therapy in any solid tumor.

Objectives

- This talk will give a broad overview of the current field of research using adoptive T-cell therapies in solid tumors, with a focus on basic principles and trials that have reported clinical outcomes.
- At the end of this session, attendees will be able to:
  1. Describe the main three categories of Adoptive T-cell Therapy
  2. Classify different types of targeted antigens
  3. Recognize the inherent pros and cons of chosen targets and approaches

Adoptive Cellular Therapy (ACT) for Cancer

- Administration of tumor-targeting cells for the treatment of cancer
- Most commonly mature T lymphocytes, though other cells (e.g. Natural Killer (NK), specifically selected subsets, etc.) are also being investigated.
- Three main categories of T lymphocyte therapies:
  - Tumor Infiltrating Lymphocytes (TIL)
  - Chimeric Antigen Receptor (CAR)-T cells
  - T cell Receptor (TCR)-T cells



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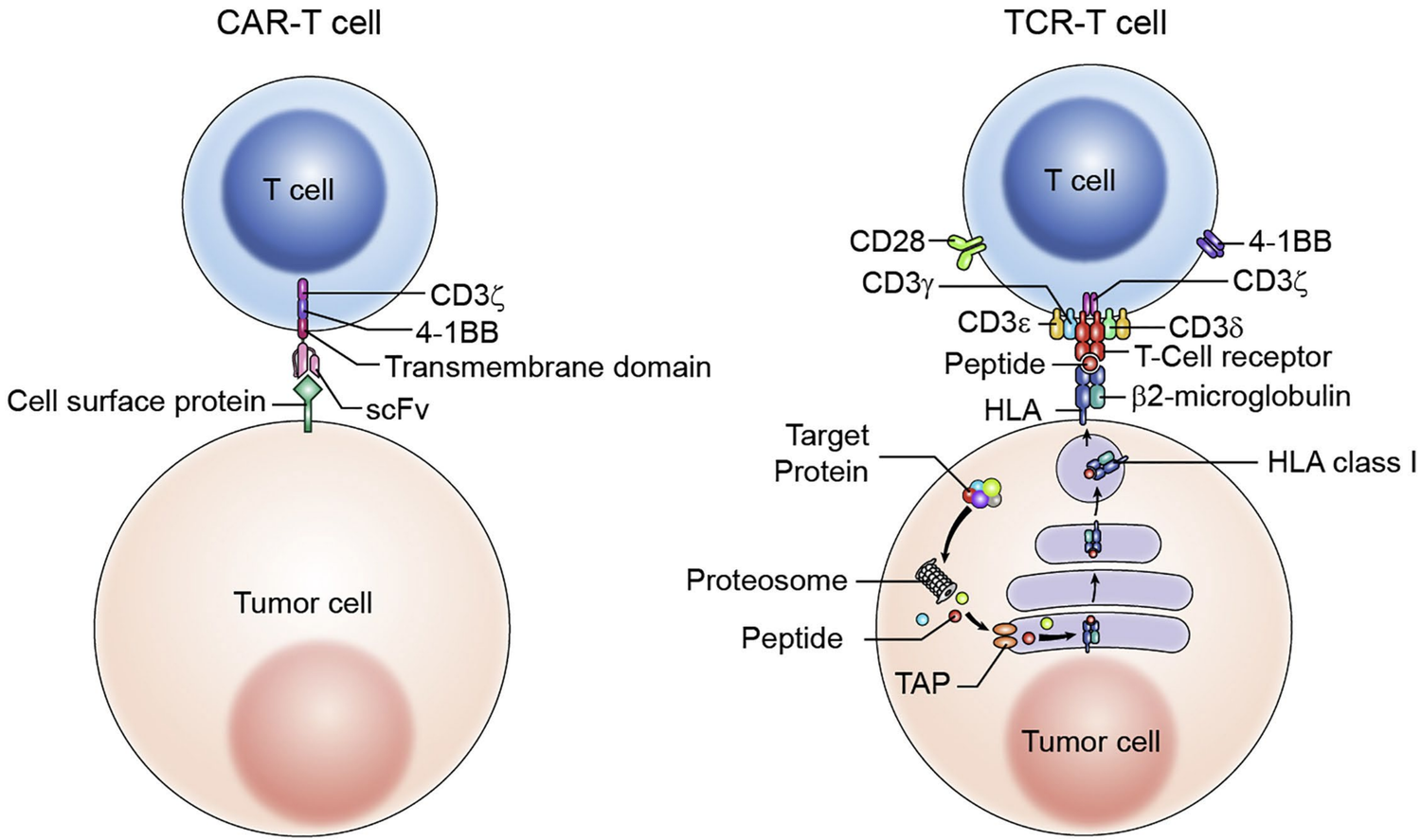
Differences in antigen recognition and intracellular signaling between CAR-T and TIL/TCR-T cells



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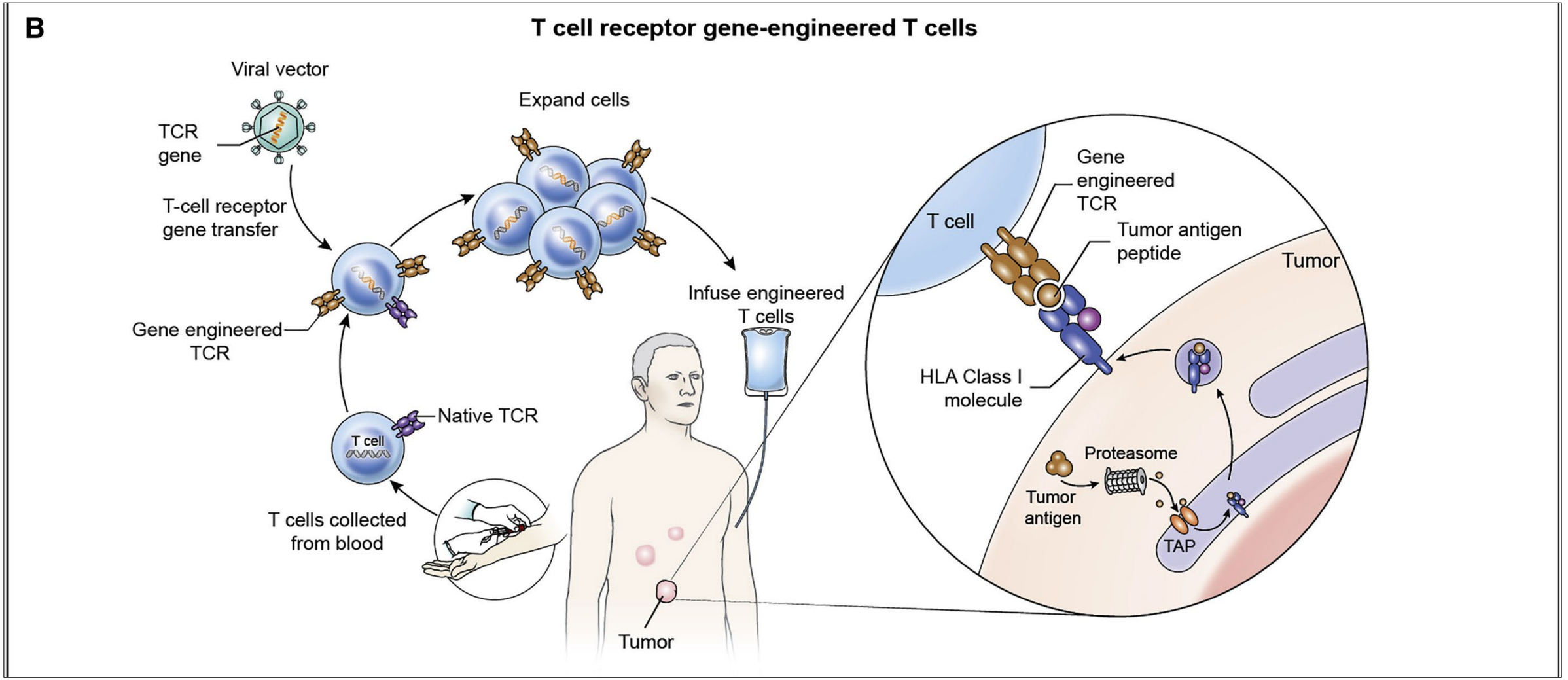

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Shared Features of Different ACTs

- All approaches (TIL, CAR, TCR) typically require an extended inpatient stay and **nonmyeloablative lymphodepleting chemotherapy** (e.g. cyclophosphamide/fludarabine)
- Majority are administered intravenously
- TIL and TCR therapy frequently use **intravenous interleukin-2**
- All share **hematologic toxicities and infection risks** from chemotherapy. Ratews of cytokine release syndrome, neurotoxicity, off-target toxicity, etc. depend on the product.

Comparing different types of T cell therapy

Chimeric antigen receptor	T cell receptor	Tumor-infiltrating lymphocyte
Advantages • Treatment not limited by HLA type • Antigen presentation machinery not required • Shorter manufacturing time than TILs • Does not require surgery	**Advantages** • Targeting not restricted by antigen localization • Shorter manufacturing time than TILs • Does not require surgery	**Advantages** • Potential for targeting of multiple antigens • Antigen targeting does not need to be defined • Targeting not restricted by antigen localization
Disadvantages • Targeting limited to the extracellular domain of a membrane-anchored protein (some exceptions) • Defined target antigen required • Evasion by loss of target antigen surface expression • Targets a single antigen (some exceptions)	**Disadvantages** • Treatment limited by HLA type • Evasion by loss of antigen presentation machinery • Defined target antigen required • Targets a single antigen	**Disadvantages** • Antigen targeting is highly variable between cell products • Requires surgery • Longer manufacturing time than engineered cells

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TIL Therapy in Solid Tumors- Melanoma

- Foundation of ACT is TIL therapy in metastatic melanoma (1988)[1]
- Randomized, phase 2 study had ORR of 54% (54/101) with 24% CR[2]
- Multicenter, phase 3 study of TIL vs ipilimumab in 168 patients showed median OS was higher in TIL compared to ipilimumab (25.8 vs 18.9 months) and 20% of patients experienced complete response[3]
- A biologics license application (BLA) was filed in May 2023 for the TIL product Lifileucel for treatment of advanced melanoma. FDA update expected February 24, 2024[4]

[1]Rosenberg et al. NEJM 1988
[2]Goff et al. JCO 2016
[3]Rohaan et al. NEJM 2022
[4]Mullard Nat Rev Drug Disc 2024

TIL Therapy in Solid Tumors- GYN and GI Cancers

- Single, phase 2 study of TIL for metastatic **HPV-associated cancer** demonstrated ORR 24% (7/29) including 2 prolonged CRs in patients with metastatic cervical cancer (>10 years)[1]
- Industry-sponsored, phase 2 study of TIL (LN-145) in patients with metastatic **cervical cancer**, ORR was 44% (12/27)[2]
- LN-145 was granted Breakthrough Therapy designation by the US FDA for advanced cervical cancer
- Case reports of impressive PRs to TIL in **cholangiocarcinoma** and **colon cancer**[3,4]

[1]Stevanovic et al. CCR 2019
[2]Jazaeri et al. ASCO 2019
[3]Tran et al. Science 2014
[4]Tran et al. NEJM 2016

TIL Therapy in Solid Tumors- Combination Therapy

- A single-arm, phase 1 study of TIL + nivolumab in patients with **PD-1 refractory, advanced NSCLC** demonstrated responses in 3 of 13 patients including 2 CRs (duration >1.5 years)[1]
- A case series of TIL + pembrolizumab in patients with **metastatic breast cancer** demonstrated responses in 3 of 6 patients including 1 CR (duration >5.5 years)[2]
- Pre-clinical and current clinical data suggest a potential additive effect for a combination approach but await more data[3]

[1]Creelan et al. Nat Med 2021
[2]Zacharakis et al. JCO 2022
[3]Davies et al. JITC 2022

Summary of TIL Therapy

- There are no current approvals, but if the pending BLA is approved, Lifileucel in metastatic melanoma would become the first FDA-approved adoptive cellular therapy for a solid cancer.
- Small studies in a variety of malignancies support continued development of TIL, but in the near term expect this option to only remain available on a clinical trial
- Research to improve TIL, such as by using novel combination therapies or strategies to select TIL with superior activity, is ongoing and exciting

CAR-T and TCR-T Therapies

- Unlike in TIL, use of CAR-T and TCR-T requires defining an appropriate target antigen in advance
- In general, CAR-T target surface antigens on the outside of the cell and TCR-T target intracellular antigens that are expressed on MHC molecules.
- Ideally, a target would be absent from vital healthy tissues, or else "**on-target, off-tumor toxicity**" will be encountered and the therapeutic window will be limited.

Targetable Classes of Antigens

Class	Present in Tumors	Present in Healthy Tissue	Example(s)
Shared tumor/self	+++	+	CD19 (lymphoma, lymphocytes) MART1 (melanoma/healthy melanocytes) CEA (colon cancer/healthy colonocytes)
Neoantigens (patient tumor specific)	+/-	-	Mutant KRAS (pancreas, colon, lung, many cancers)
Cancer Germline Antigens	+/-	Germ Cells	NY-ESO-1 (synovial cell sarcoma)
Viral Antigens (in Virus-Associated Cancers)	+	-	HPV antigens (cervical cancer, HNSCC)

CAR-T Therapy in Solid Tumors

- Unlike the explosive growth of CAR-T cell therapy in hematologic malignancies, extension to solid tumors has been slower
- Cell surface targets largely limited to the shared tumor/self category of antigens, which has a shown a narrow therapeutic window (tumor expression > healthy cell expression)
- Early CAR-T cell trials had significant toxicity, including a death due to a CAR-T based on Trastuzumab that targeted ERBB2(HER2) and dose-limiting liver toxicity in CAR-T targeting carbonic anhydrase 9[1,2]

[1]Morgan et al. Mol. Ther. 2010
[2]Lamers et al. Mol. Ther. 2013

CAR-T Therapy: More Recent Outcomes

- In a phase 2 study of CAR-T cells targeting claudin 18.2 (CLDN18.2) in patients with **gastric/GEJ malignancies**, GI-related toxicity was dose limiting (GI hemorrhage), but a favorable ORR of 49% (18/37) was seen[1] Larger confirmatory studies are pending.
- In a phase 1/2 study of CAR-T cells targeting mesothelin in expressing cancers (**mesothelioma, ovarian carcinoma, cholangiocarcinoma**), the ORR was 20% (6/30) though pulmonary toxicity (including a death) was dose limiting[2]. A larger phase 2 study is underway.

[1]Qi et al. Nat. Med. 2022
[2]Hassan et al. Nat Med 2023

TCR-T Therapy in Solid Tumors

- Advantage of ability to target intracellular antigens (far more targets)
- Reports of TCR-T cell activity in a broad range of solid tumors, including **melanoma, synovial cell sarcoma, ovarian, esophageal, urothelial, osteosarcoma, colorectal, pancreas** and **HPV-associated cancers**[1]
- As with CAR-T, early trials targeting shared self/tumor antigens showed toxicity, including GI toxicity with CEA TCR-T cells in **colon cancer**[2]
- Major disadvantage is HLA restriction. The most common haplotype (HLA-A*02:01) is present in <50% of the overall US population

[1]Parkhurst Mol Therapeutics 2011
[2]Norberg et al. Cancer Cell 2023

TCR-T Therapy in Solid Tumors: Outcomes

- Pilot trial testing NY-ESO-1 TCR-T cells in advanced NY-ESO-1+ tumors (**synovial cell sarcoma, melanoma**) demonstrated an ORR of 58% (22/38)[1] .
- Multi-center, phase 1 study of TCR-T cell therapy targeting MAGEA4 in patients with relevant tumors (**synovial cell sarcoma, ovarian, head and neck**) demonstrated an ORR of 24% (9/38)[2].
- Phase 1 study of TCR-T cell therapy targeting HPV16 E7 in **HPV+ cancer** demonstrated PRs in 6 of 12 patients[3]. A multicenter phase II is ongoing.
- Phase 1 of hepatitis B virus (HBV) TCR-T cells in **hepatocellular carcinoma** showed ORR in 1/8 patients, with PR lasting >2 years[4]

[1]Robbins et al. CCR. 2015
[2]Hong et al. Nat Med. 2023
[3]Nagarsheth et al. Nat Med. 2021
[4]Meng et al. Hepatol Int. 2021

Target antigens for engineered T cell therapy in solid cancers

			Clinical trial outcomes[a]			
Class	Examples	Normal tissue expression	Antigen-targeting receptor	Cancer type	Tumor responses (responses/N)	On-target toxicity
Shared tumor/self	MART1, gp100, CEA, CA9, ERBB2, ROR1, GD2, GPC3, CLDN18.2	variable	MART1 TCR[51]	Melanoma	6/20	skin, eye, and ear
			gp100 TCR[51]	melanoma	3/16	skin, eye, and ear
			CEA TCR[52]	colorectal carcinoma	1/3	colon
			CA9 CAR[53]	renal cell carcinoma	0/12	liver
			ERBB2 CAR[54]	colorectal carcinoma	0/1	heart and lung
			CLDN18.2 CAR[10]	gastrointestinal cancers	18/37	GI mucosa
Cancer germline	NY-ESO-1, select MAGE antigens, KK-LC-1	germ cells	NY-ESO-1 TCR[49]	synovial cell sarcoma, melanoma	22/38	none
			NY-ESO-1 TCR[56]	synovial cell sarcoma	6/12	none
			NY-ESO-1 TCR[57]	synovial cell sarcoma	9/30	none
			MAGE-A3 TCR[42]	solid tumors	4/17	none
			MAGE-A3/A9/A12[63]	solid tumors	5/9	brain[b]
Neoantigen (mutation, frameshift, splice variant, etc.)	mutant RAS, mutant BRAF, EGFRvIII	none	N/A[c]	N/A[c]	N/A[c]	N/A[c]
Viral	HPV, HBV, EBV	none	E6 TCR[9]	HPV-associated cancers	2/12	none
			E7 TCR[8]	HPV-associated cancers	6/12	none

Norberg et al. Cancer Cell 2023
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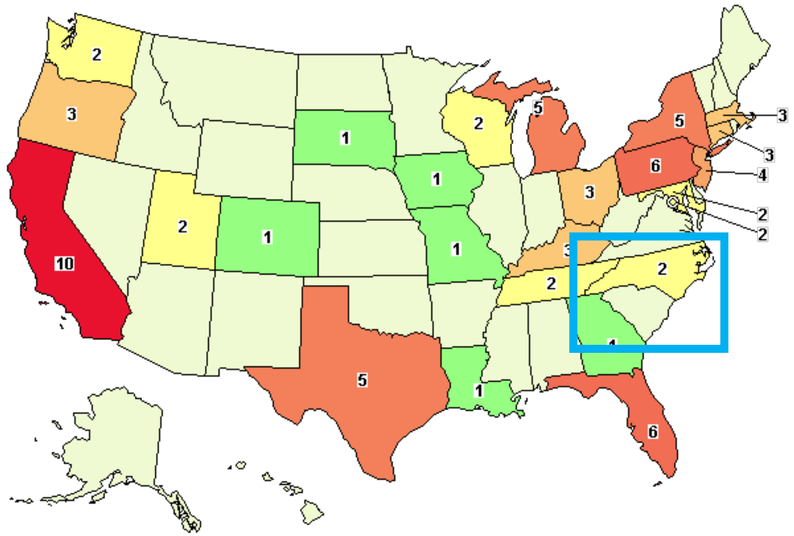
Summary of CAR-T and TCR-T Therapies

- Limited reports of activity in a broad range of solid tumors using both CAR-T and TCR-T approaches
- FDA has granted Breakthrough Therapy Designation to NY-ESO-1-TCR T cells for **synovial sarcoma** and Fast-Track Designation to HBV TCR-T cells for **hepatocellular carcinoma,** however no full FDA approvals are expected in the near term
- Ongoing clinical trials are investigating expanded target antigens, personalized TCRs, mechanisms to overcome tumor resistance, and ways to mediate toxicity

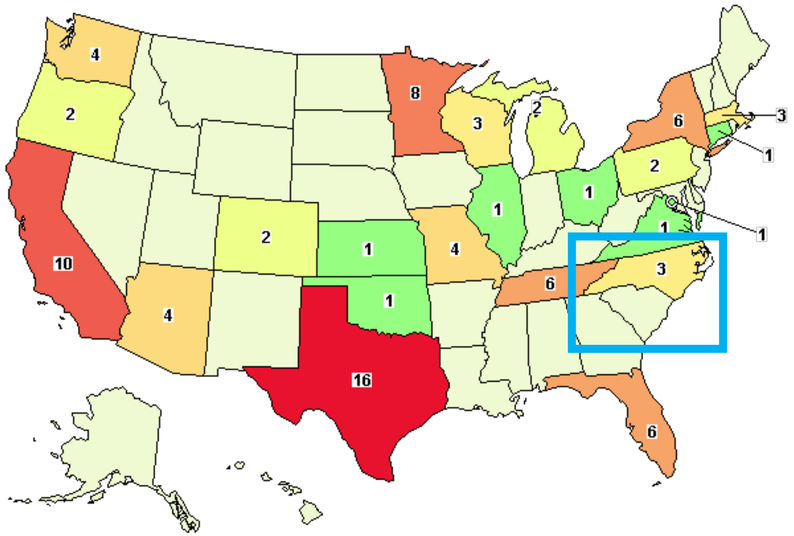
Recruiting Studies for Cellular Therapies in Solid Neoplasms per Clinicaltrials.gov

TIL



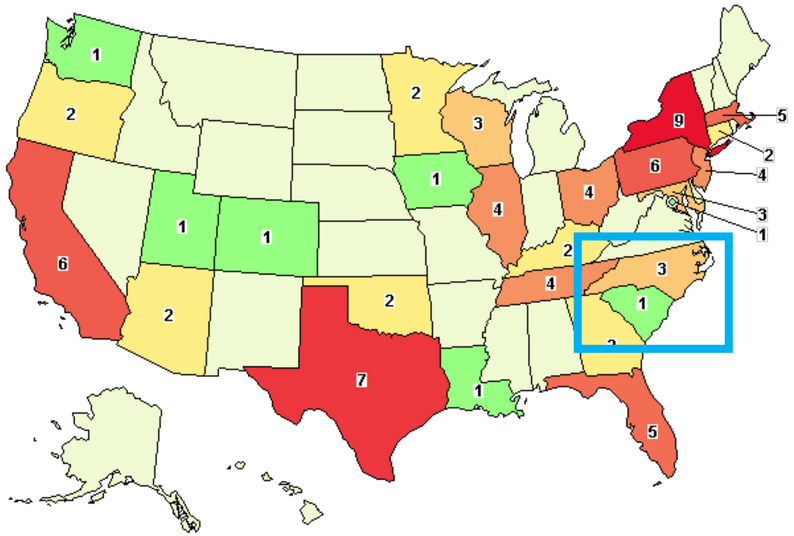
USA: 17
Worldwide: 49

CAR



USA: 24
Worldwide: 82

TCR



USA: 16
Worldwide: 31

Clinicaltrials.gov Search as of February 6th, 2024

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NIH Center for Immuno-Oncology Ongoing ACT Trials

- Actively Recruiting: Phase I KK-LC-1 TCR-T cell therapy for **Gastric, Breast, Cervical, Lung** and other KK-LC-1 positive cancers (NCT05035407)
- Actively Recruiting: Phase II trial of E7 TCR-T cell therapy for **HPV-Associated Cancers** (NCT02858310)
- Upcoming in 2024: Phase I/II expanding E7 TCR-T cells to patients with HIV and HPV-Associated **Anal, Cervical,** and **Head and Neck Cancers**
- The NIH Clinical Center in Bethesda, MD covers all treatment costs and travel reimbursements for patients/caregivers
- Remote/tele prescreening and mail blood tests for optimal convenience
- Happy to answer questions, direct contact at stacey.doran@nih.gov

Key Takeaways/Review of Objectives

- Three main categories of Adoptive Cell Therapy are TIL, CAR-T, and TCR-T, and all three are being actively used in clinical trials.
- Antigen targets include shared tumor/self antigens, cancer germline antigens, mutated neoantigens, and viral antigens.
- In more than ten years of effort, both activity and toxicity have been encountered, with most persistent toxic outcomes largely due to the presence of targeted antigen on vital healthy tissues.
- Field is pushing forward with more rational development of treatments and continued improvement in safety and clinical activity

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