Update on CAR-T Therapy

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UNC LINEBERGER UNC CANCER CARE

Overview

- CAR-T Cell Therapy Overview
- Clinical Trial Results and FDA Approvals
- Toxicities and Management
  - Cytokine Release Syndrome
  - Neurotoxicity
- Future Directions

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CAR-T Cell Therapy Overview

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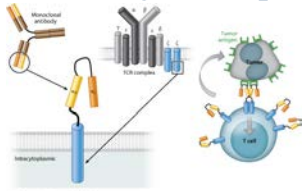
Cancer and the Immune System

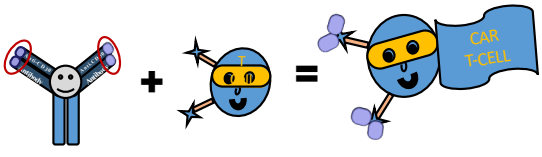
- Cancer often develops when tumor cells evade immune surveillance or suppress immune response, leading to cell proliferation
- Therapeutic approaches:
  - overcome immune tolerance helping immune system be more targeted and effective at eliminating tumor cells

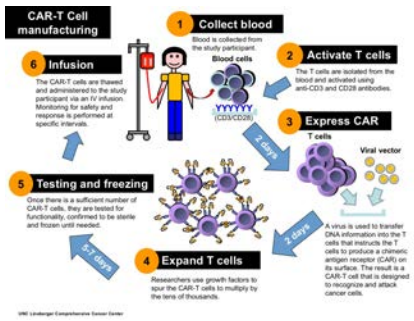
Chimeric antigen receptor T-



Ramos CA, et al. 2016. Annu. Rev. Med. 67:165-83

- Hybrid molecule composed of an extracellular antigen-recognition site from an antibody and intracellular signaling domain of T-cell receptor
- CAR binds antigen on surface of tumor cells -> T cell activation and killing of tumor cells
- Second generation CARs have costimulatory region which can enhance activation





Lymphodepletion

- Usually prior to CAR-T cell infusion, patients receive lymphodepletoin
- Reduces endogenous lymphocytes
- Increases availability of homeostatic cytokines that promote survival of transferred T cells
- Cyclophosphamide/fludarabine most common regimen used

Clinical Activity of CAR-T Cells

Case Example

- 18 yo F initially diagnosed with ALL in 2010 at age 11
- Treated with aggressive pediatric regimen and achieved remission
- However, relapsed 1 year post therapy – underwent transplant
- 5 years later, found to have relapsed on routine blood work

Anti-CD19 CAR-T Cells

- CD19 – cell surface marker present on B cells -> potential target in B-cell malignancies such as B-ALL and B-cell lymphoma

CD19 Directed CAR-T Cells in ALL

- CAR-T cell trials in ALL show high complete response (CR) rates of 70-90% with durable remissions
- Is this treatment feasible in our patients?

Phase II ELIANA trial

- Global CAR-T cell therapy registration trial with study enrollment across 25 centers in US, Canada, European Union, Australia, and Japan
- Product name: Tisagenlecleucel
- Enrolled patients aged 3 to 23 years with relapsed or refractory B-cell ALL
  - Primary refractory, refractory to chemotherapy after first relapse, relapsed after second line therapy, ineligible for allogeneic stem cell transplant
- Patients received median of 3 prior lines of therapy and 61% had prior transplant

Maude et al., NEJM 2018

Phase II ELIANA Trial: Patients

- 92 patients enrolled -> 75 underwent infusion of CAR-T cells
- What happened to other 17 patients?
  - 7 had CAR-T product related issues
  - 7 died
  - 3 had adverse events prior to CAR-T infusion
- Median time of 45 days from enrollment to infusion

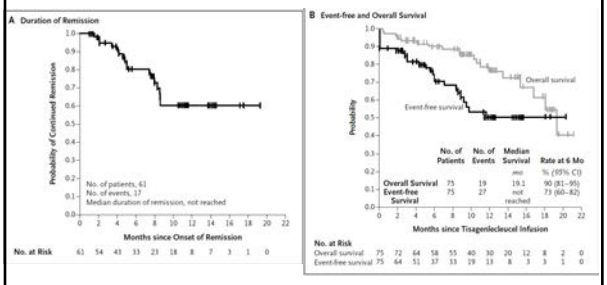
Phase II ELIANA Trial: Patient Characteristics

- Medan age: 11 years
- Median of 3 prior therapies
- 61% had undergone prior allogeneic stem cell transplant

Phase II ELIANA Results

- 81% of patients achieved complete remission or complete remission with incomplete blood count recovery
- Event free survival: 73% at 6 months, 50% at 12 months
- Overall survival: 90% at 6 months, 76% at 12 months

Phase II ELIANA Results



Maude et al., NEJM 2018

FDA Approval

- August 30, 2017 – FDA approved first anti-CD19 CAR-T cell product, tisagenlecleucel (Kymriah), for the treatment of pediatric and young adult patients (under 25) with relapsed/refractory B-cell precursor acute lymphoblastic leukemia

CD19-Directed CAR-T Cells in B-cell Lymphoma

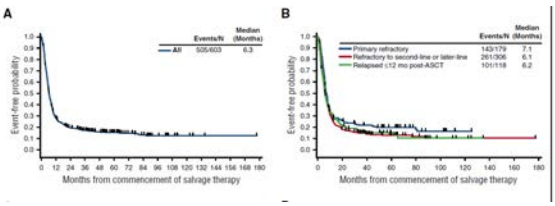
- Responses have also been seen in patients with heavily pre-treated Diffuse Large B-cell lymphoma and Follicular Lymphoma

Refractory DLBCL Prognosis

- Prognosis terrible for patients with DLBCL resistant to chemotherapy or who relapse within 12 months of autologous stem cell transplantation
- Objective response rate – 26%
- Complete response rate – 7%
- Median overall survival – 6.3 months

Crump et al., Blood 2017

Refractory DLBCL Prognosis



Crump et al., Blood 2017

Zuma Trial

- Multicenter phase 2 study in patient with refractory DLBCL
- Product: Axicabtagene ciloleucel (axi-cel)- Yescarta

Neelapu et al., NEJM 2017

Phase II Zuma Trial: CAR-T Manufacturing

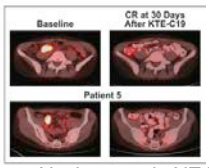
- 111 patients enrolled, 101 treated
- What happened to other 10 patients?
  - 1 unsuccessful manufacture
  - 4 adverse events
  - 1 died from disease progression
  - 2 did not meet criteria (no longer measurable disease)
- Median time from cell procurement to delivery of axi-cel – 17 days

Phase II Zuma Trial: Patients

- Median age: 58 years (range 23-76)
- 24% were 65 years or older
- 69% had 3 or more prior lines of therapy

Phase II Zuma Trial: Results

- Objective response rate -82%
- Complete response rate – 54%
- Overall survival at 18 months – 52%

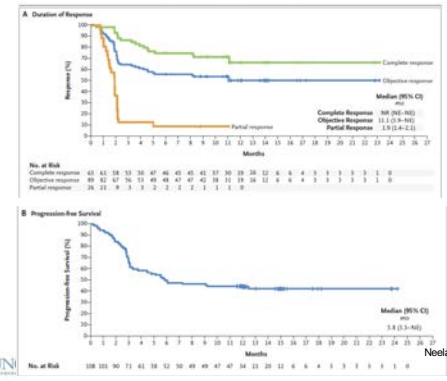


Neelapu et al., NEJM 2017

Phase II Zuma Trial: Sustained Remissions

- At median follow up of 15.4 months, 42% of patients continued to have response with 40% continuing to have complete response

Phase II Zuma Trial: Results



Neelapu et al., NEJM 2017

JULIET Trial

- Multicenter phase 2 study in patient with relapsed/refractory DLBCL
- Received >/= 2 lines of therapy (including rituximab and anthracycline) or relapsed following transplant
- Product: CTL019 - Tisegenlecleucel - Kymriah

Schuster et al., NEJM 2017

Phase II Juliet Trial: CAR-T Manufacturing

- 160 patients enrolled, 106 treated
- What happened to other patients?
  - 11 unsuccessful manufacture
  - 16 deaths
  - 16 physician discretion
  - 3 adverse events
- Only 68 evaluable for efficacy
- Median time from leukapheresis to infusion: 113 days

Phase II Juliet Trial: Patients

- Median age: 56 years (range 22-74)
- Median number of prior therapies: 3 (range: 1-6)

Phase II Juliet Trial: Results

- Objective response rate -53% (50%)
- Complete response rate – 40% (32%)
- Median duration of response and S not reached but probability relapse free at 6 months – 74%

FDA Approved

- October 18, 2017: FDA approved Axi-cel (Yescarta) for treatement of adults with relapsed or refractory large B-cell lymphoma following 2 prior therapies
- May 1, 2018: FDA expanded Kymriah (tisagenlecleucel) to include treatment of adult patients with relapsed or refractory DLBCL after 2 or more lines of systemic therapy

TABLE 1. Composition, efficacy and safety comparisons

	Axicaptagene ciloleucel[1]	Tisagenlecleucel[2]	Lisocaptagene maraleucel[3]
Study populations	DLBCL, TFL, PMBCL	R/R DLBCL	[3]CORE DL 2
Target Antigen	CD19	CD19	CD19
Lymphodepletion	Flu/Cy	Flu/Cy	Flu/Cy
Costimulatory Domain	CD28	4-1BB	4-1BB
T-cell Composition	Unspecified	Unspecified	1:1 CD4:CD8
Cell Dose	2×10^6 cells/kg	5×10^8	1×10^8
OR (Best)	82% (N=108)	53% (N=81)	81% (N=27)
OR (6 Month)	41% (N=101)	37% (N=46)	50% (N=14)
CR (Best)	58% (N=108)	40% (N=81)	63% (N=27)
CR (6 Month)	36% (N=101)	30% (N=46)	50% (N=14)
Any Grade[††] CRS / NT	94% / 87% (N=108)	58% / 21% (N=99)	24% / 17% (N=29)
≥ Grade 3 CRS[††]	12% (N=108)	23% (N=99)	0% (N=29)
≥ Grade 3 NT[††]	31% (N=108)	12% (N=99)	7% (N=29)
Grade 5 AEs	4% (N=108)[^]	none	-

[1]Neelapu, NEJM 2017, ZUMA-1
[2]Schuster, ASH 2017, JULIET
[3]Abramson, ASH 2017, TRANSCEND
[^]2 patients Grade 5 CRS
[3]CORE Group (proposed pivotal pop'n) including DLBCL, NOS tFL, FL3B, ECOG 0-1, and R/R patients
[††]CAR T toxicity grading scales differ across studies

Courtesy of and adapted from C. Turtle MBBS, PhD

Chow et al., Blood 2018

Questions for DLBCL

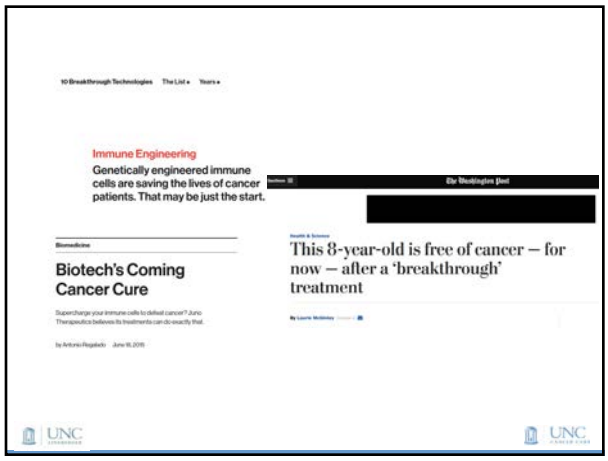
- When to use CAR-T?
- Current clinical trial comparing autoSCT to CAR-T

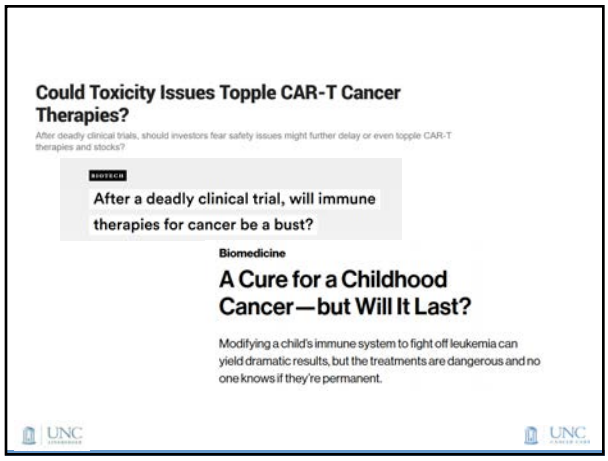
Poll 1

Which of the following is NOT currently approved for indications for CAR-T cells?

- Tisagenlecleucel
- Axicabtagene ciloleucel (axi-cel)- Yescarta
- Cabazitaxel
- Rituximab
- Anthracycline

Toxicities and Management





Case Example

- 18 yo F with ALL treated with CD19 directed CAR-T cells
- Developed high grade fever to 40C within 24 hours of CAR-T cell infusion with tachycardia, fatigue, decreased appetite
- Managed with Tylenol, cooling blanket
- Received empiric broad spectrum antibiotics
- Work up negative for infection

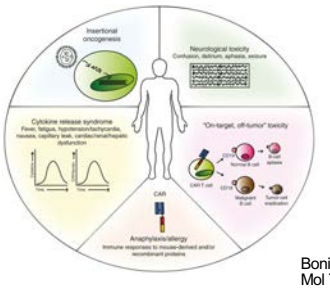
Case Example

- On day 1 after CAR-T cell infusion, developed hypotension with systolic blood pressure of 80 mmHg with hypoxia
- Treated with IV fluid bolus and supplemental O2
- Hypotension not responsive to fluid boluses and required vasopressor support
- Received dose of tocilizumab with response to hypotension and hypoxia

Case Example

- On day 6, she developed handwriting impairment and the following day she became confused and disoriented
- She subsequently developed expressive aphasia and slurred speech
- These symptoms lasted for 3 days and then resolved and she was discharged

Toxicities of CAR-T Therapy



Bonifant et al.,
Mol Ther Oncolytics, 2016

Cytokine Release Syndrome

- Systemic inflammatory event triggered resulting from release of cytokines (including IL-6 and interferon-gamma) associated with proliferation and activation of T cells
- Typically presents with constitutional symptoms, such as fever, malaise anorexia, and myalgias, but can affect any organ system
- Usually occurs within first week after CAR-T cell therapy and peaks within 1-2 weeks of cell administration (differs according to product)
  - Median time of onset – Kite product – 2 days; Novartis product – 3 das

CRS Symptoms

TABLE 1. Signs and Symptoms of CRS

Organ system	Signs/Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, myalgias/arthralgias, nausea/vomiting
Dermatologic	Rash
Gastrointestinal	Nausea/vomiting/diarrhea
Respiratory	Tachypnea, hypoxemia (potentially requiring supplemental oxygen/ventilation)
Cardiovascular	Tachycardia, hypotension
Coagulation	Disseminated intravascular coagulation (DIC) characterized by elevated D-dimer, hypofibrinogenemia, bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Altered mental status, confusion, delirium, aphasia, hallucinations, tremor, seizures, ataxia

Risk Factors for Severe CRS

- Bulky disease
- Comorbidities
- Early onset CRS (within 3 days of cell infusion)

CRS Management - Symptoms

- Fever- usually first presenting symptom and occur in most patients with CRS
  - Use acetaminophen for comfort but often doesn't relieve fever
  - Often experience fever-associated tachycardia and chills
  - Work up and treat for infection
- May develop anorexia, nausea, vomiting -> require anti-emetics
  - Nausea and anorexia can last for weeks after other symptoms have resolved
- Myalgias and headaches – require pain meds

CRS Management - Labs

- Check IL6 (takes longer to return), CRP, and ferritin
- IL6 induces CRP production by hepatocytes so CRP good marker for CRS
  - Fast and easily available
  - Declining CRP levels, although potentially lagging behind declines in cytokine levels by 1-2 days, may be useful to identify peak of syndrome in individual patient

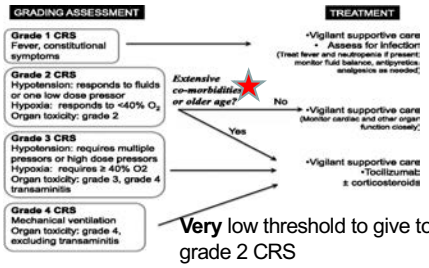
CRS Grading

Table 2 | **Grading of cytokine-release syndrome (CRS)**

Symptom or sign of CRS	CRS grade 1*	CRS grade 2‡	CRS grade 3§	CRS grade 4¶
Vital signs				
Temperature ≥38 °C (fever)	Yes	Any	Any	Any
Systolic blood pressure <90 mmHg (hypotension)	No	Responds to IV fluids or low-dose vasopressors	Needs high-dose or multiple vasopressors§	Life-threatening
Needing oxygen for SaO_2 >90% (hypoxia)	No	FiO_2 <40%	FiO_2 ≥40%	Needing ventilator support
Organ toxicities‖				
• Cardiac: tachycardia, arrhythmias, heart block, low ejection fraction • Respiratory: tachypnoea, pleural effusion, pulmonary oedema • GI: nausea, vomiting, diarrhoea • Hepatic: increased serum ALT, AST, or bilirubin levels • Renal: acute kidney injury (increased serum creatinine levels), decreased urine output • Dermatological: rash (less common) • Coagulopathy: disseminated intravascular coagulation (less common)	Grade 1	Grade 2	Grade 3 or grade 4 transaminitis	Grade 4 except grade 4 transaminitis

Neelapu et al., Nature Reviews Clinical Oncology 2017

CRS Management Algorithm



Very low threshold to give tocilizumab for grade 2 CRS

Lee, D.W., et al., *Current concepts in the diagnosis and management of cytokine release syndrome.* Blood, 2014. **124**(2): p. 188-95.

Tocilizumab

- Anti-IL-6 receptor antibody
- FDA approved for the treatment of CRS occurring after CAR-T cell therapy
- Use does not seem to affect efficacy of CAR-T cell therapy
- Fever often resolves within a few hours and pressors and other supportive care measures can be weaned quickly
- Give second dose after 6 hours if condition does not improve or stabilize
- If hypotentsion persists after 1-2 doses of toclizumab, can give steroids

FDA Approval

- August 30, 2017: At the same time FDA approved Kymriah, FDA also approved tocilizumab for treatment of cytokine release syndrome

Corticosteroids

- Suppress inflammatory response
- Since suppress T cell function and can induce T cell apoptosis, concern that could interfere with efficacy
- Use in CRS refractory to tocilizumab or neurotoxicity

CRS in Clinical Trials

- ALL trial
  - CRS occurred in 77% of patients
  - Median time to onset: 3 days
  - Median duration: 8 days
  - 37% received tocilizumab
  - 47% admitted to ICU with median stay of 7 days
  - 25% treated with high dose pressors
  - 13% intubated
  - 9% received dialysis

CRS in Lymphoma Clinical Trials

- Kite
  - CRS occurred in 93% of patients
  - 37% grade 1, 44% grade 2, 9% grade 3, 3% grade 4, 1% grade 5
  - 17% patients received vasopressors
  - Median time after infusion to onset: 2 days, median time to resolution – 8 days
- Novartis
  - CRS occurred in 74% of patients (23% grade 3 or higher)
  - 21% received tocilizumab

Neurotoxicity/CAR-T cell related encephalopathy syndrome (CRES)

- Typically present with toxic encephalopathy -> diminished attention, language disturbance, impaired handwriting
- Confusion, disorientation, agitation, aphasia, somnolence, tremors
- Severe symptoms: seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, cerebral edema

Example of Dysgraphia

Neelapu et al., Nature Reviews Clinical Oncology 2017

Neurotoxicity

- Risk factors: high tumor burden, cell dose, CRS, pre-existing neurological abnormalities
- Can have neurologic symptoms during CRS associated with high fevers
- Can occur later after CRS has subsided, often after day 5
- Delayed neurotoxicity with seizures and confusion has occurred during 3rd to 4th week after CAR-T cell therapy in 10% of patients
- Mechanism of action unknown -> IL-6 directed neurotoxicity? Infiltration of CAR-T cells into CSF?

Grading of Neurotoxicity/CRES (CAR-T Related Encephalopathy Syndrome)

Table 4 | Grading of CAR-T-cell-related encephalopathy syndrome (CRES)

Symptom or sign	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment score (by CARTOX-10*)	7–9 (mild impairment)	3–6 (moderate impairment)	0–2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
Raised intracranial pressure	NA	NA	Stage 1–2 papilloedema‡, or CSF opening pressure <20 mmHg	Stage 3–5 papilloedema‡, or CSF opening pressure ≥20 mmHg, or cerebral oedema
Seizures or motor weakness	NA	NA	Partial seizure, or non-convulsive seizures on EEG with response to benzodiazepine	Generalized seizures, or convulsive or non-convulsive status epilepticus, or new motor weakness

CAR, chimeric antigen receptor; CARTOX-10, CAR-T-cell-therapy-associated toxicity 10-point neurological assessment; CSF, cerebrospinal fluid; EEG, electroencephalogram; NA, not applicable.
*In the CARTOX-10, one point is assigned for each of the following tasks that is performed correctly (normal cognitive function is defined by an overall score of 10): orientation to year, month, city, hospital, and President/Prime Minister of country of residence (total of 5 points); name three objects — for example, point to clock, pen, button (maximum of 3 points); write a standard sentence, for example, 'our national bird is the bald eagle' (1 point); count backwards from 100 in tens (1 point). ‡Papilloedema grading is performed according to the modified Frisén scale[48].

Neelapu et al., Nature Reviews Clinical Oncology 2017

Management of Neurologic Toxicity of CAR-T cells

- Work up depends on presentation: MRI, lumbar puncture, EEG
- Tocilizumab does not cross BBB and therefore hasn't been shown to be effective - > use only if concurrent CRS
  - Could saturate IL-6 receptors and increase serum IL-6 levels which would increase CSF IL-6 levels which could worsen neurotoxicity
- First line agent: systemic corticosteroids
  - Dexamethasone – preferred first line treatment for patients with neurological toxicity given excellent CNS penetration
- Treat seizures with standard anti-epileptic therapy
- Consider keppra prophylaxis

Neurotoxicity in Clinical Trials

- ALL trial
  - 40% experienced neurotoxicity
  - 13% grade 3 neurologic events
  - 50% grade 3 neurologic events resolved within 10 days

Neurotoxicity in Clinical Trials

- Kite Trial
  - 64% experienced neurotoxicity (28% grade 3 or higher)
  - Median time of onset on day 5 post infusion with median time of resolution of day 17 post infusion
- Novartis Trial
  - 58% experienced neurotoxicity (18% grade 3 or higher)
  - Median time of onset on day 6 from infusion and median duration of 14 days

B Cell Aplasia (CAR-19)

- CAR-19 targets any cells expressing CD19, including normal B cells, leading to B cell aplasia
- B cell aplasia leads to hypogammaglobulinemia since B cells produce immunoglobulins
- Patients receive monthly IVIG as long as B cell aplasia occurs

Poll 2

Which of the following can be given to a patients when they present Grade 3 CRS (hypotension and/or hypoxia) or Grade 4 CRS (mechanical ventilation)?

- Tocilizumab
- Corticosteroids
- Dexamethasone
- Keppra prophylaxis

Future Directions and UNC Trials

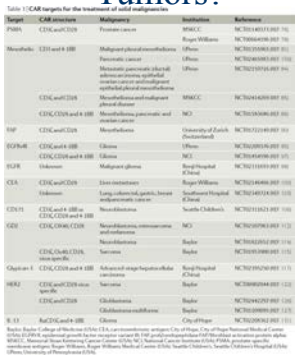
Future CAR Approvals

- BCMA CAR – myeloma – will likely be approved soon

Current and Upcoming UNC Trials

- CD30 CAR – Lymphoma (Hodgkin, ALCL, etc.)
- CD19 CAR with suicide gene (ALL, CD19+ lymphoma)
- CD138 CAR – Multiple myeloma

Future Directions – Solid Tumors?



Challenges to CAR-T in Solid Tumors

- **Problem:** Solid tumors generally more heterogeneous so they are harder to target
  - More difficult to find universal target antigen
- **Possible solution:** CARs that can target multiple antigens

Challenges to CAR-T in Solid Tumors

- **Problem:** Suppressive tumor microenvironment
- **Possible solution:** "armored" T cells that express molecules that reduce suppression by Tregs; e.g., preclinical studies of CAR-T cells that secrete checkpoint blocking antibodies

Challenges to CAR-T in Solid Tumors

- **Problem:** Often less accessible to CAR-T cells (surrounded by other tissues, organized into different compartments)
- **Possible solution:** Improve CAR-T cells' ability "breech tumor defenses"

Challenges to CAR-T in Solid Tumors

- **Problem:** Difficult to target because many target antigens also expressed by normal cells
- **Possible solution:** Identify more specific antigens; tune CARs to "react only to cells that express target antigens at high levels;" "safety valve" measures such as suicide genes

Off the Shelf CARs?

- Gene editing being used to delete T cell receptor and other endogenous genes for preparation of allogeneic "off-the-shelf" CAR-T cells

Poll 3

In your opinion, which is the most interesting challenge of developing CAR-T cells for solid tumors?

Questions about Applications of CAR-T Cells

- How best to deliver to patients?
- Cost?
- Insurance coverage?
- Management of toxicities?
- What line of care to use?

Summary

- CD19 directed CAR-T cells have shown promising efficacy in the treatment of ALL and B-cell lymphomas
- Toxicities of therapy include cytokine release syndrome and neurotoxicity
- Cytokine Release Syndrome (CRS)
  - CRS can be seen within 24 hours after CAR-T treatment until 3 weeks after treatment
  - Treatment for CRS will include standard supportive care/infectious workup
  - Additional treatment can include tocilizumab
  - Steroids should be avoided when possible
- Neurotoxicity
  - Can present with a range of neurological symptoms including stroke like symptoms
  - Standard altered mental status workup is appropriate
  - Seizures should be treated with standard anti-epileptic medications
  - Treatment of severe symptoms with dexamethasone

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