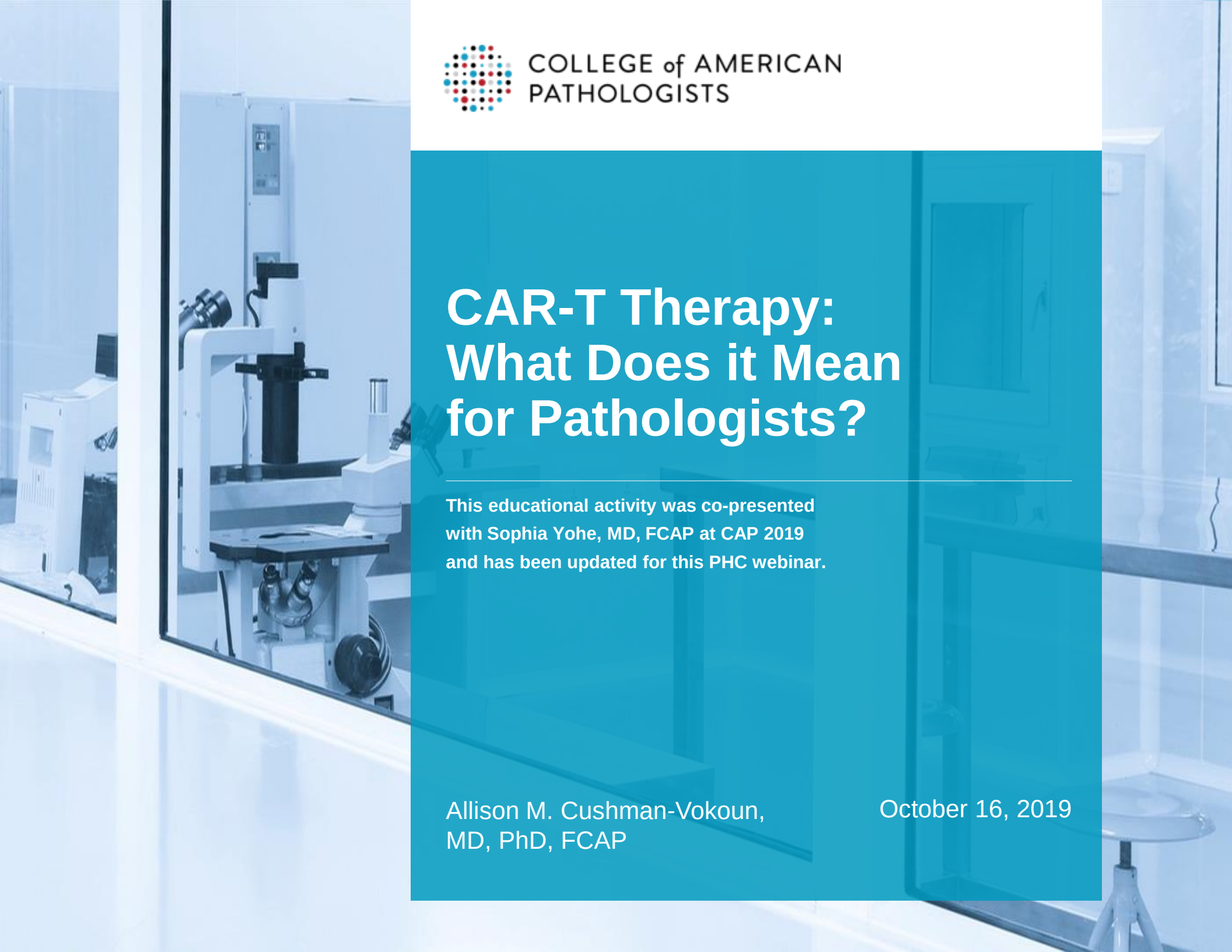

COLLEGE of AMERICAN PATHOLOGISTS

CAR-T Therapy: What Does it Mean for Pathologists?

This educational activity was co-presented with Sophia Yohe, MD, FCAP at CAP 2019 and has been updated for this PHC webinar.

Allison M. Cushman-Vokoun, MD, PhD, FCAP

October 16, 2019

Webinar Host

- **This series is sponsored by the Personalized Healthcare Committee (PHC)**
- **Today's webinar host is Amy Beckman, MD**

Housekeeping

- **This presentation will be recorded. The recording and PDF will go out to all registrants in one week**
- **All lines are muted during the presentation**
- **Please send in your questions as you think of them via the "Question Box" in your control panel**

Allison Cushman-Vokoun, MD, PhD, FCAP

- **Medical Director of Molecular Diagnostics and Associate Professor at University of Nebraska Medical Center.**
- **Organizer and Lecturer for the Molecular Didactic Course for the Pathology Residents and Cytotechnology Trainees**
- **PBL Facilitator for M1 and M2 students**

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Disclaimer, continued

- **Opinions expressed by the speaker are the speaker's own and do not necessarily reflect an endorsement by the CAP of any organizations, equipment, reagents, materials, or services used by participating laboratories.**

Disclosures

- **No Disclosures**

Objectives

- **Explain the science behind the development of chimeric antigen receptor T-cells (CAR-T) cells and the clinical utility of CAR-T in hematopoietic malignancies.**
- **List three possible adverse effects of CAR-T therapy administration.**
- **Discuss regulatory and reimbursement issues associated with CAR-T therapy.**
- **Recognize the future potential in CAR-T therapy in various cancers.**

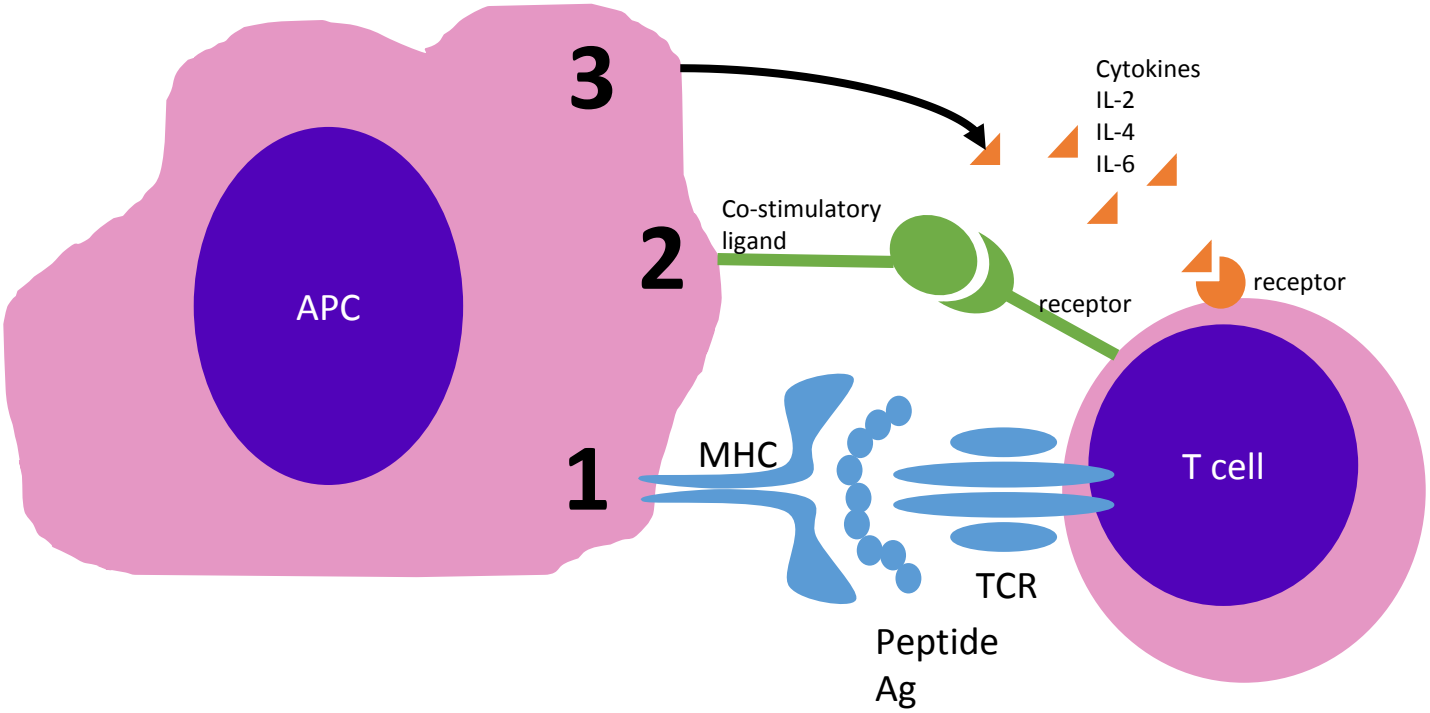
CAR-T Basic Science/Technology

Chimeric Antigen Receptor (CAR)–T Cells

- **Synthetic molecules that allow specific T cell targeting to a tumor associated Ag**
  - **Extracellular ligand recognition domain (scFv of mAb)**
  - **Intracellular signaling domain (CD3ζ chain of TCR)**
- **High affinity recognition of tumor target that triggers T cell activation similar to TCR signaling**
- **Raw material for drug development is derived from patients own T cells (autologous)**
- **Does not require antigen presenting cell/MHC**

Curr Hematol Malig Rep (2016);11:368-384.
Immunology Letters (2017);190:201-205.

The T-cell Immune Response



3 **Differentiation**

2 **Survival**
Proliferation

1 **Activation**

Image courtesy of Sophia Yohe, MD;
University of Minnesota Medical Center

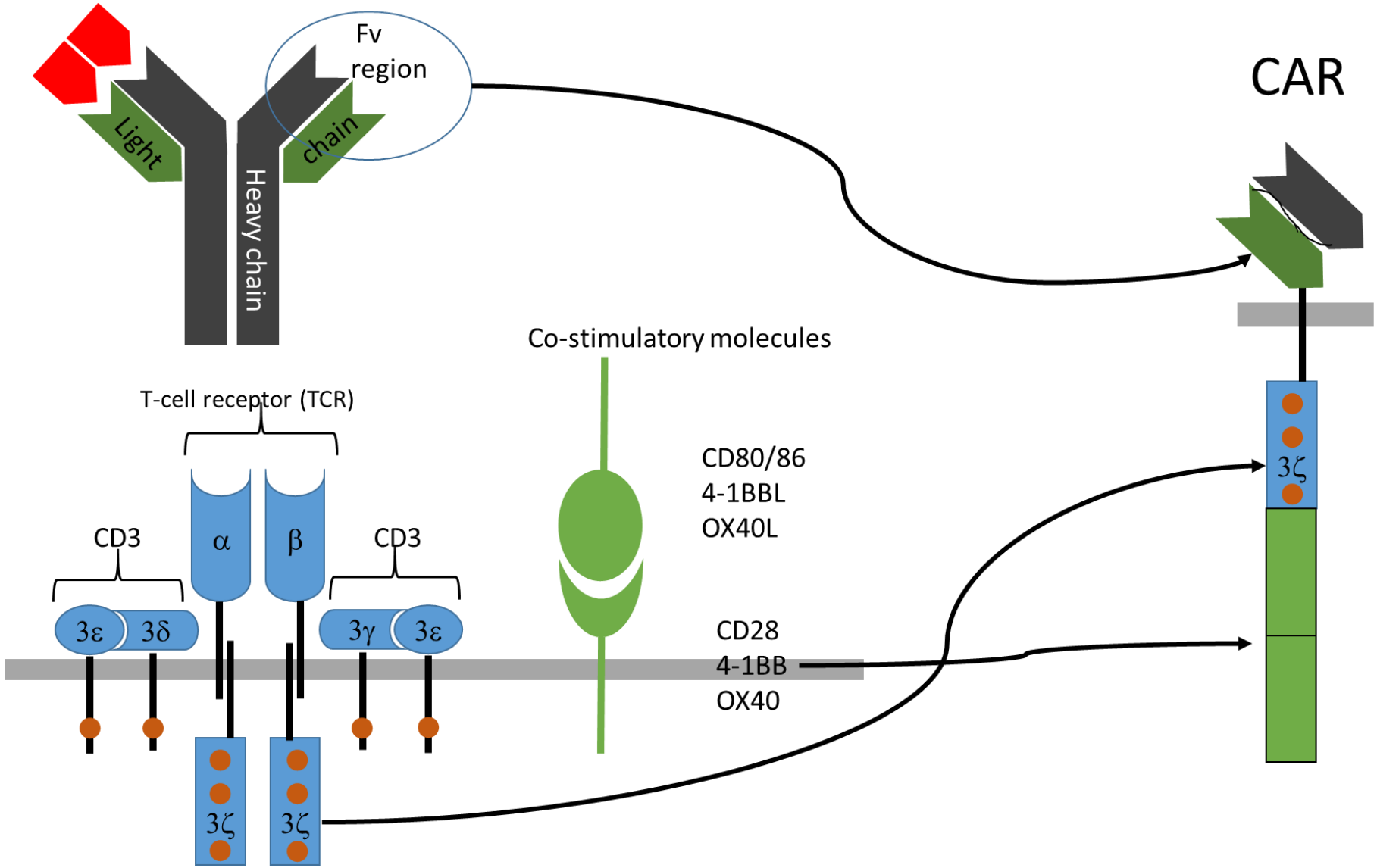
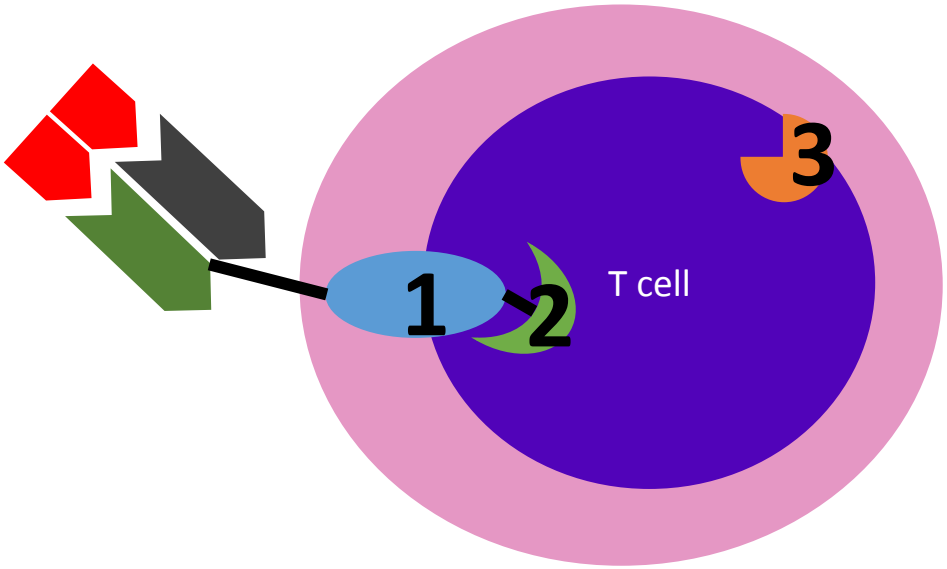


Image courtesy of Sophia Yohe, MD;
University of Minnesota Medical Center

The CAR-T response

Co-stimulatory domains mimic the co-stimulation provided by APCs to allow full physiological activation of the T cell



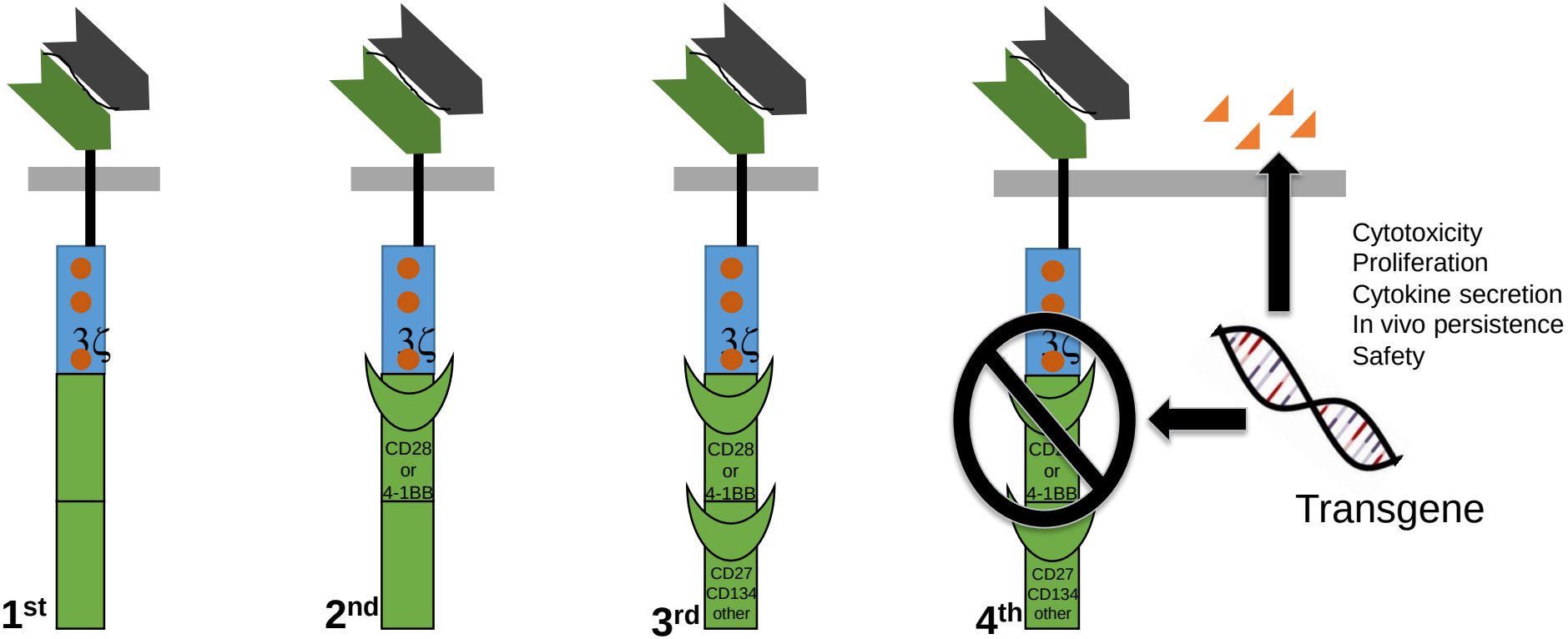
3 **Differentiation**

2 **Survival**
Proliferation

1 **Activation**

Image courtesy of Sophia Yohe, MD;
University of Minnesota Medical Center

CAR-T Family tree



1st Generation

Poor survival
And proliferation

2nd Generation

Full T cell activation
Deep antitumor response

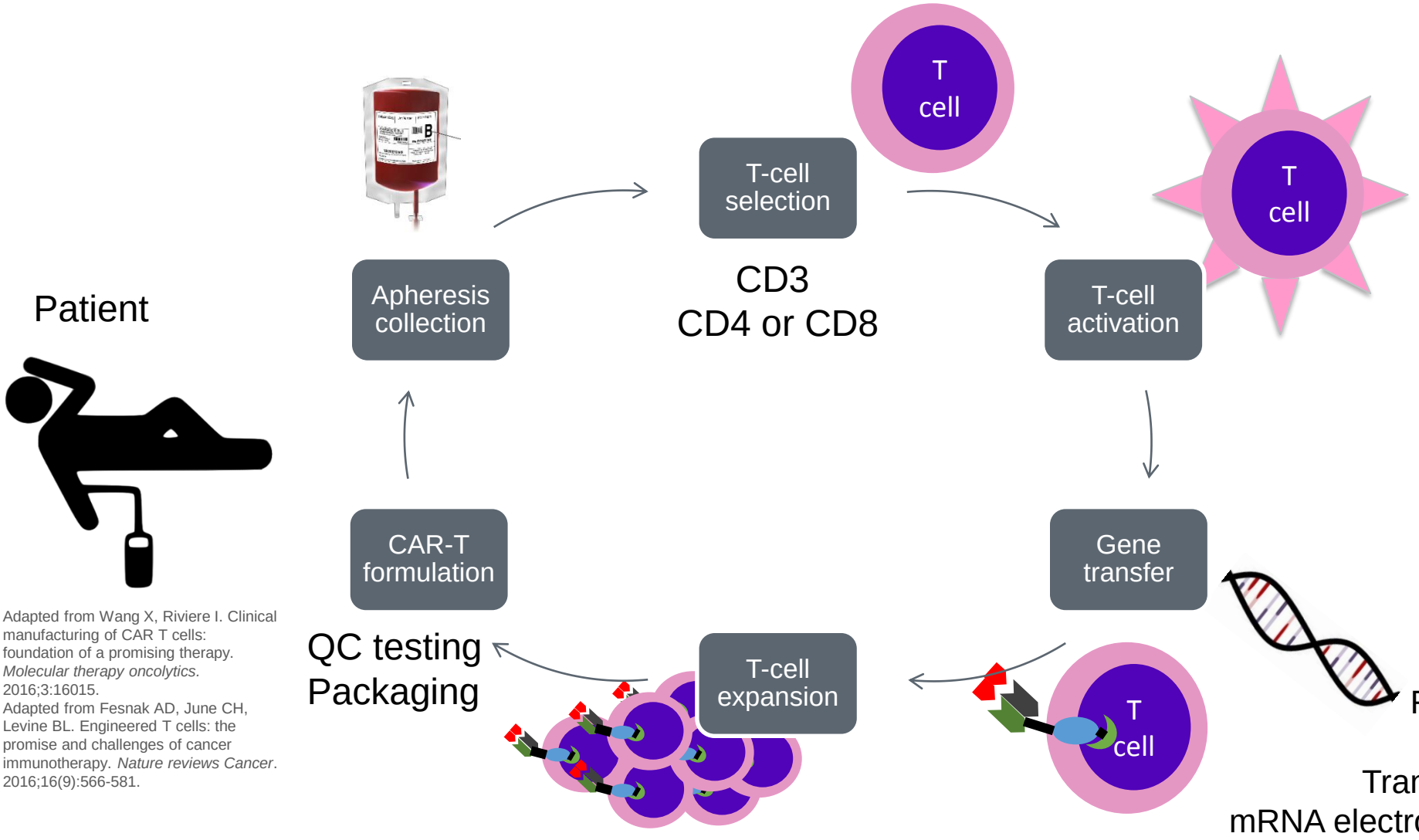
3rd Generation

4th Generation

Constitutive cytokine production
Safety switch/suicide construct

Adapted from Han X, Wang Y, Han WD. Chimeric antigen receptor modified T-cells for cancer treatment. *Chronic diseases and translational medicine.* 2018;4(4):225-243.

Manufacture of CAR-T cells



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Adapted from Fesnak AD, June CH, Levine BL. Engineered T cells: the promise and challenges of cancer immunotherapy. *Nature reviews Cancer*. 2016;16(9):566-581.

Manufacture of CAR-T cells

Effective and routine clinical use requires:

1. **Collection of an adequate number of T cells**
2. **CAR DNA construct must be introduced efficiently and safely (insertional mutagenesis, viral reactivation)**
3. **Genetically modified T cells must expand in vitro to clinically relevant doses**
4. **Upon infusion, CAR-T cells must be able to traffic to the tumor site**
5. **CAR-T cells must expand in vivo and persist at least long enough to induce a meaningful anti-tumor response (immunosurveillance)**

Blood Rev (2016);30(3):157-167.

CAR-T Therapy in the Pre-Clinical and Clinical Setting

FDA approved CAR-T Cells (2nd gen)

Tisagenlecleucel (Kymriah™) – Penn/Novartis, Aug 2017

- Murine anti-CD19; CD8 hinge and TM domain; 4-1BB co-stim domain; and CD3ζ [lentivirus]
- BALL and large B-cell lymphomas
- $475,000/one-time dose

Axicabtagene ciloleucel (Yescarta™) – NCI/Kite Pharma, Oct 2017

- Murine anti-CD19; CD28 hinge, TM, and co-stim domain; and CD3ζ [retrovirus]
- Large B-cell lymphomas
- $373,000

https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states
https://www.cancer.gov/news-events/cancer-currents-blog/2017/yescarta-fda-lymphoma

Kymriah (tisagenlecleucel)

- **Patients up to 25 years old B-cell acute lymphoblastic leukemia (B-ALL)**
  - **Relapsed two or more times or has been refractory**
- **Relapsed or refractory large B-cell lymphoma**
  - **Diffuse large B-cell lymphoma (DLBCL),**
  - **High grade B-cell lymphoma/DLBCL arising from follicular lymphoma**
  - **After two or more lines of systemic therapy.**

Research C for BE and. KYMRIAH (tisagenlecleucel). FDA. April 2019. http://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel. Accessed July 3, 2019.

Yescarta (axicabtagene ciloleucel)

- **Diffuse large B cell lymphoma (DLBCL)**
- **Primary mediastinal large B-cell lymphoma**
- **High grade B-cell lymphoma and**
- **DLBCL arising from a follicular lymphoma**
- **Must have failed at least two other treatment forms.**
  - **Not approved for primary central nervous system lymphoma.**

Research C for BE and. YESCARTA (axicabtagene ciloleucel). FDA. http://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel. Published April 24, 2019. Accessed July 3, 2019.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

- **ELIANA trial: phase II international trial (25 sites)**
  - **92 kids/young adults (11 years, range 3-23)**
  - **Treatment delay and issues making biologics**
    - **75 infused (7 product related issues, 10 deaths)**
    - **Time from enrollment to infusion 45 days (30-105)**
  - **Relapsed/refractory**
    - **Median # of previous tx: 3 (1-8)**
    - **61% prior allo-HCT**

N Engl J Med (2018);378(5):439-448.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

- **Single infusion provided durable remission with transient high-grade toxic effects**
  - **60% CR & 21% CRi within 3 months**
  - **Among responding patients: no MRD & median duration of remission not reached**
  - **OS: 90% (6 months), 76% (12 months)**
  - **Grade 3-4 adverse events: 73%; CRS in 77% (46% grade 3-4), neurotoxicity 40% (13% grade 3)**
  - **Persistence of CAR-T cells in PB: up to 20 months (4 years in prior single center study)**

Other FDA approved agents for r/r pediatric B-cell ALL
Clofarabine: CR 20% , median OS 13 weeks
Blinatumomab (CD19-CD3 bispecific Ab): CR 39%, median OS 7.5 months

N Engl J Med (2018);378(5):439-448.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

- **JULIET trial: phase II international trial**
  - **93 adults infused**
    - **≥2 failed therapies, ineligible for or disease progression after auto-HCT**
  - **ORR 52% (CR 40%)**
    - **Many have durable response**
  - **Median OS 12 months (if received infusion)**
  - **Persistence of CAR-T cells in PB for up to 2 years in responding patients**
    - **Six patients with ongoing CR had B-cell counts return to normal range**
  - **CRS 58% (22% grade 3-4); neurotoxicity 21% (12% grade 3-4)**

Conventional therapy (Scholar-1 study)
ORR 26%
CR 7%
median OS 6.3 months

N Engl J Med (2019);380(1):45-56.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

- **Zuma-1 trial: phase II multicenter trial (22 sites in USA, Israel)**
  - **Enrolled 111 adults, 101 infused (1 product failure), median time from apheresis to infusion 17 days**
    - **85% stage III-IV disease**
    - **Nearly all failed second-line or subsequent therapy or autologous transplant**

N Engl J Med (2017);377(26):2531-2544.

Zuma-1 trial

- **Analysis at median f/u 27.1 months**
  - **ORR 83%,**
  - **CR 58%; median time to response 1 month (but up to 6 months)**
  - **OS 50.5% at 24 months (median not reached)**
  - **Toxicity: grade 3-4 CRS 11% (2 deaths); grade 3-4 neurotoxicity 32%**

Conventional therapy (Scholar-1 study)
ORR 26%
CR 7%
median OS 6.3 months

N Engl J Med (2017);377(26):2531-2544
Lancet Oncol (2019);20(1):31-42.

Product	ScFv	Hinge	TM	Co-stim	Signal	Other	Gene transfer	CR Rates
Tisagenlecleucel (CTL019) Penn/Novartis	Murine anti-CD19	CD8	CD8	4-1BB	CD3ζ		Lentivirus	81% r/r B-ALL (Eliana) 40% r/r LBCL (Juliet)
Axicabtagene (KTE-C19) NCI/Kite Pharma	Murine anti-CD19	CD28	CD28	CD28	CD3ζ		Retrovirus	58% r/r LBCL (Zuma-1) Zuma-2 MCL, Zuma3,4 ALL
JCAR014 Juno Therapeutics	Murine anti-CD19	IgG4	CD28	4-1BB	CD3ζ	CD4:CD8 CM 1:1	Lentivirus	93% r/r pB-ALL (n=29) Phase I: r/r B-NHL, +Durvalumab (anti-PD-L1)
Lisocabtagene (JCAR017) Juno Therapeutics	Murine anti-CD19	IgG4	IgG4	4-1BB	CD3ζ	CD4:CD8 1:1	Lentivirus	91% r/r pB-ALL (n=37) Transcend trial (r/r NHL)
CART19 Baylor/Cellgene/Bluebird Bio	Murine anti-CD19	IgG1	CD4	CD28	CD3ζ	Dual tropic CAR Virus specific (CMV, EBV, adeno)	Rertrovirus	Phase I Multiprat trial +/- checkpoint blockade (ipilimumab)
CART19 City of Hope	Murine anti-CD19	IgG4	CD28	CD28	CD3ζ	Memory enriched ECFRt	Lentivirus	
SB CART19 MD Anderson /Ziopharm	Murine anti-CD19	IgG4	CD28	CD28	CD3ζ		Sleeping Beauty	
Juno Therapeutics – Fred Hutchinson Cancer Research Center, Memorial Sloan Kettering Cancer Center, Seattle Children's Research Institute								

Adapted from Ruella M, June CH. Chimeric Antigen Receptor T cells for B Cell Neoplasms: Choose the Right CAR for You. *Current hematologic malignancy reports.* 2016;11(5):368-384.

Side Effects of CAR-T Therapy

Cytokine Release Syndrome (CRS)

- Rapid, large release of cytokines a day to days after CAR-T infusion
- Fever, hypotension, coagulopathy and capillary leak syndrome
- Grading criteria include (Porter et al):
  - Creatinine measurement
  - Liver function testing
  - Fever
  - Blood pressure
  - Evaluation of fluid/vasopressor support and oxygen requirements

J Hematol Oncol 2018;11(1):81.

Cytokine Release Syndrome

- **Earlier the fever (less than 24 hours), the higher the grade of CRS**
- **70% of CAR-T recipients developed CRS (Hay et al)**
- **CRS demonstrates that the CAR-T cells are working**
- **Requires immediate diagnosis to prevent mortality**
  - **Tocilizumab (anti-IL-6 receptor monoclonal antibody)**
  - **Anti-inflammatories, ventilatory support and pressor support**
  - **Steroids will affect T cell function**

Blood. 2017;130(21):2295-2306.

Neurotoxicity

- **Often occurs with CRS/similar risks**
- **Not understood, likely blood brain barriers compromise**
  - **Associated with high cytokine levels**
  - **Endothelial activation**
- **Visual Hallucinations**
- **Aphasia**
- **Disorientation**
- **Unresponsiveness**
- **Encephalopathy**

Blood. 2019;133:2114-2116.

Risk Factors for CRS and Neurotoxicity

- **Higher disease burden**
- **Higher infused CAR-T dose**
- **High intensity lymphodepletion**
- **Thrombocytopenia and/or preexisting endothelial cell activation**

B- Cell Aplasia

- **CAR-T anti-CD19 targets malignant and normal B cells**
- **Occurs up to 9 weeks after CAR-T infusion; can persist for years**
- **Results in persistent hypogammaglobulinemia**
  - **Risk of infection**
- **Treatment with Intravenous Immunoglobulin (IVIG)**
  - **Pooled plasma from thousands of healthy individuals**
  - **Potential requirement for long-standing IVIG therapy**
- **Even if B-cells rise, they may not produce IgG–test IgG regularly**
- **Highlights potential problem with CAR-T targeting therapy in general**
  - **Target antigens on normal cells also**

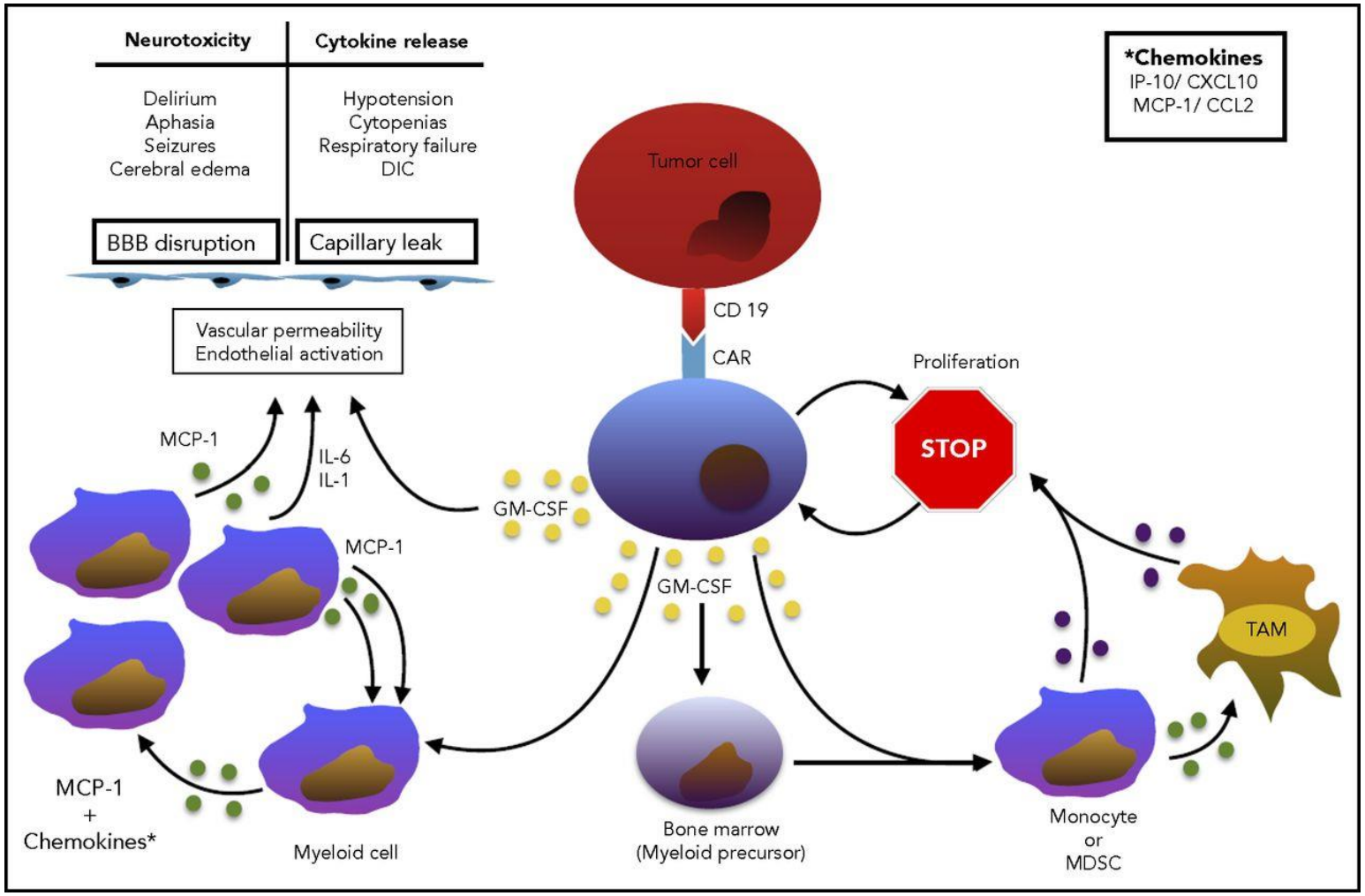
Pediatr Blood Cancer. 2018;65(4).

TABLE 1 Hypogammaglobulinemia and IVIG in CAR T-cell therapy

Characteristics	Duration	Infection	Patients who received IVIG treatment (n)	Comments	Reference
Immunoglobulin below detectable limit	Weeks 9–39 after infusion	Pneumonia	1	No subsequent infections after starting IVIG	Kochenderfer et al.[5]
CD5 and CD19 cells were nearly absent 13 weeks after treatment	6 months after infusion	Not mentioned	4	None	Kochenderfer et al.[8]
B-cell aplasia in all patients with response	B-cell aplasia lasted ≤2 years after infusion	Bronchitis (n = 1), acute otitis media (n = 2), *Salmonella* infection (n = 1), recurrent urinary tract infections (n = 1)	27	All patients required IVIG replacement, and no serious infectious complications were observed as a result of B-cell aplasia	Maude et al.[9]
B-cell aplasia and hypogammaglobulinemia in all patients with CR	B-cell aplasia lasted ≤4 years after infusion	Not mentioned	6	None	Porter et al.[4]

CAR, chimeric antigen receptor; CR, complete response; IVIG, intravenous immunoglobulin.

Doan A, Pulsipher MA. Hypogammaglobulinemia due to CAR T-cell therapy. *Pediatric blood & cancer*. 2018;65(4):e26914.



Republished with permission of American Society of Hematology, from CAR-T-cell neurotoxicity: hope is on the horizon, Ahmed O.,133(20), 2018; permission conveyed through Copyright Clearance Center, Inc.

CAR-T Monitoring

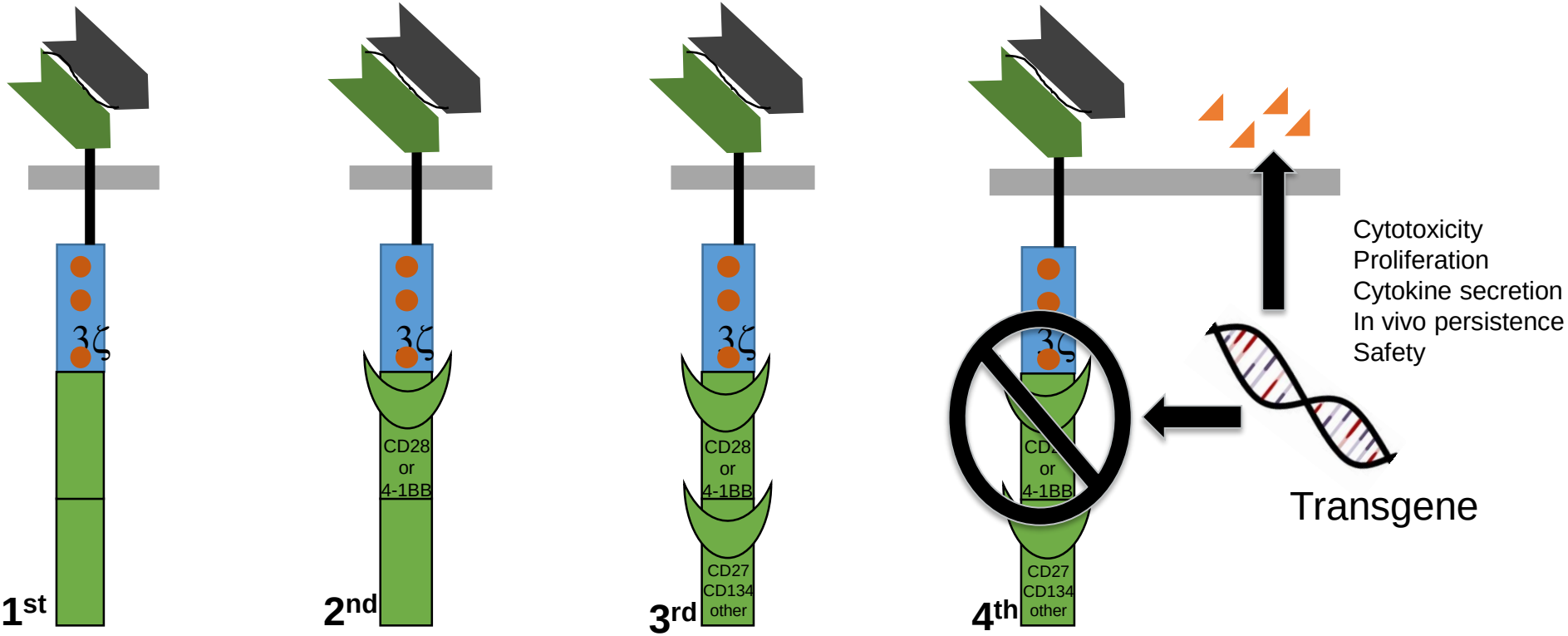
How do we monitor for CAR-T Cells?

- **Specific testing is not required for use of CAR-T therapy**
  - **No established criteria that would change patient eligibility**
- **Testing for CD19 performed routinely by flow cytometry**
- **Required effort required to interpret the CD19+ % percentage before or after therapy**
  - **CD19 immunohistochemistry - may not be routine**
  - **Currently lack of standard criteria (unlike Her2-neu or PD-L1)**
  - **Different methodology/antibodies may give variable results**
- **Difficult follow-up with flow for recurrent CD19+ malignant populations**
- **Monitoring issues will extend to other tumors that have other targeted antigens**

How do we monitor for CAR-T Cells

- **Will pathology laboratories be required to monitor CAR-T persistence?**
- **Theoretically could monitor for the CAR gene "cassette" molecularly**
- **Information from companies developing therapies is proprietary**
  - **No standard cassette or target that all companies are required to use**
  - **Different viruses and gene constructs used**
  - **FDA has not mandated this**
- **Uncertain how CAR-T affect the T cell/immunologic repertoire**
- **Pathology labs are not being asked to do monitoring of CAR-T cell therapy persistence at this time**

CAR-T Family tree



1st Generation

Poor survival
And proliferation

2nd Generation

Full T cell activation
Deep antitumor response

3rd Generation

4th Generation

Constitutive cytokine production
Safety switch/suicide construct

Adapted from Han X, Wang Y, Han WD. Chimeric antigen receptor modified T-cells for cancer treatment. *Chronic diseases and translational medicine.* 2018;4(4):225-243.

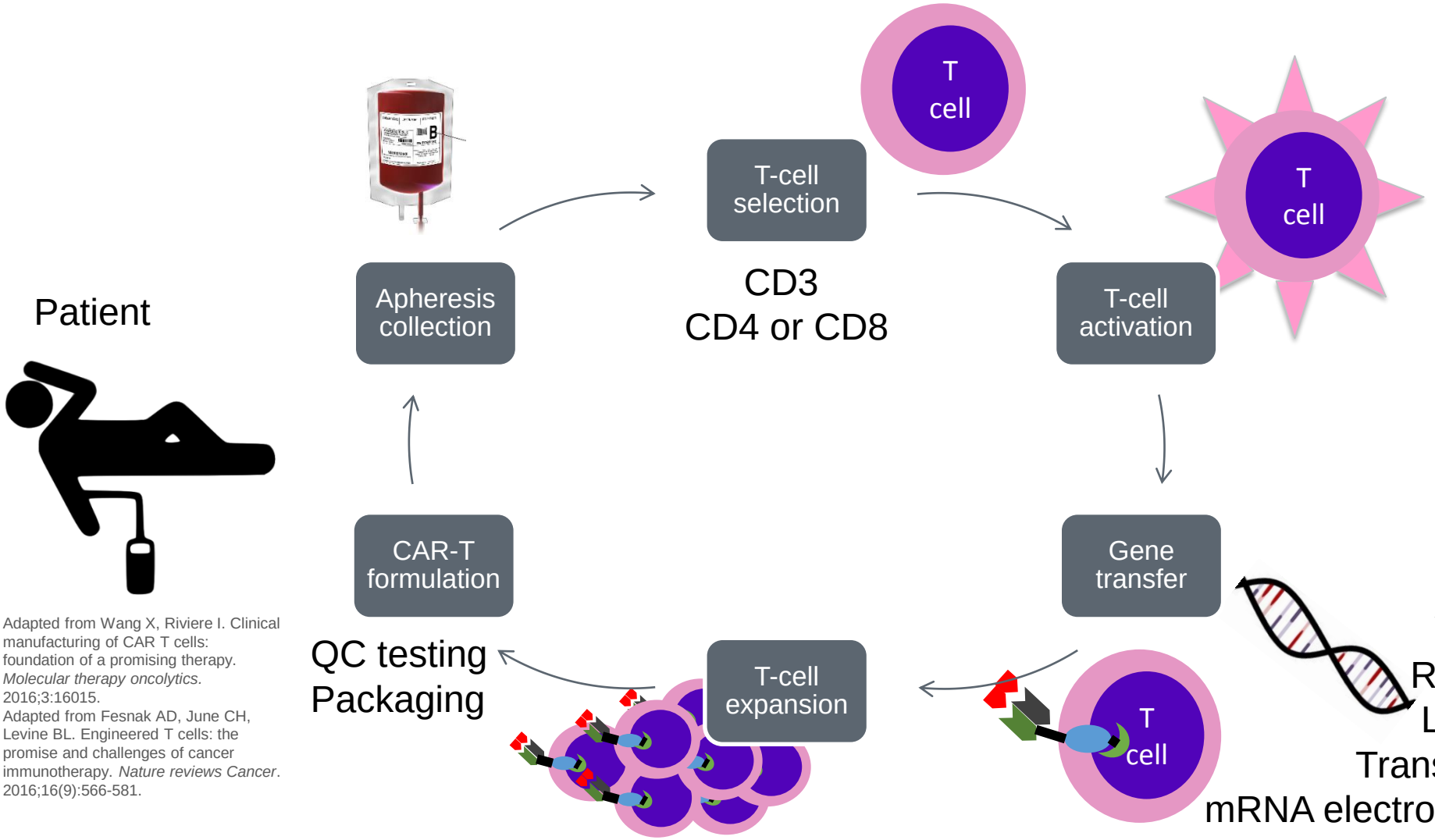
Monitoring for adverse effects

- **Monitoring for cytokines (IL-6) to detect CRS**
  - **Currently not mainstream**
  - **Would need to be a rapid test (same day)**
  - **Monitoring for organ dysfunction is currently used**
- **Neurotoxicity**
  - **Monitoring for signs and symptoms**
  - **Occurs similarly to CRS**
- **B-cell aplasia**
  - **B-cell counts by flow cytometry (not necessarily indicative of IgH levels)**
  - **Monitoring of immunoglobulin levels**

Regulatory Handling of CAR-T

Acknowledgement to CAP Advocacy for information and discussion related to regulation and reimbursement

Manufacture of CAR-T cells



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Adapted from Fesnak AD, June CH, Levine BL. Engineered T cells: the promise and challenges of cancer immunotherapy. *Nature reviews Cancer*. 2016;16(9):566-581.

Administration of CAR-T Cells

- **CAR-T therapy administration is complex**
- **To become a center for CAR-T**
  - **Manufacturer performs an on-site evaluation and inspection**
  - **Documented protocols for:**
    - **Mononuclear-cell collection**
    - **Cell counting**
    - **Sterility and viability assessment (flow)**
    - **Identity verification (by blood typing) and storage**
    - **Cell processing**
    - **Cryopreservation**
    - **Preparation for shipping to manufacturer and back to administering institution**
- **Institutions are expected to adhere to Good Manufacturing Practices (GMP).**
- **Chain of custody maintenance**

Administration of CAR-T Cells

- **Approximately 2-3 weeks for the company to manufacture the CAR-T cells by:**
  - **Introduction of the vector carrying the anti-CD19 CAR molecule and expansion of the CAR-T cells**
    - **Anti-CD19 CAR is transduced into the cells using a lentiviral vector for Kymriah and a ɣ-retroviral construct for Yescarta**
  - **Manufacturer quality checks that include:**
    - **Visual inspection**
    - **Testing to ensure the CAR is present and/or functional**
    - **Viability cell count**
    - **Dosing information**
    - **Purity including measures of contaminating cells and sterility**
- **Final cryopreserved product is shipped back to the site that will administer the therapy in an infusion setting within the hospital**

Jurisdiction over CAR-T in Hospital

- **Can vary in hospital settings**
- **Directors may include:**
  - **Pathology**
  - **Transfusion medicine**
  - **Oncology - may oversee the laboratory processes involved in CAR-T**
  - **May be disease-specific separation of sub-specialty oversight**
    - **Lymphoma may be lymphoma oncologist**
    - **Leukemia may be the bone marrow transplant team**
  - **Important to have specifics outlined in protocols**

Federal Regulatory Oversight

- **FDA-approved therapies; FDA oversees the manufacturing**
- **Administered under the FDA's Risk Evaluation and Mitigation Strategies (REMS) program**
  - **Specific to the safety of the licensed product itself; not to the individual institutions or programs that partake in the administration**
  - **Serious Adverse Events must be reported to the company and relayed to the FDA**
- **Much of the regulation relevant to production of CAR-T products fall under the FDA's Center for Biologics and Evaluation Research (CBER)**
- **Laboratory testing in support of CAR-T therapy is performed in CLIA-certified labs**
  - **Falls under CMS regulations**
  - **FDA may consider certain test systems to fall under the medical device regulations**
  - **CAP is closely monitoring of activities and decisions surrounding genetically modified biologic products**

Institutional Oversight

- **Institutional oversight uses standards from the Foundation for the Accreditation of Cellular Therapy (FACT)**
  - **Non-profit accreditation body for the American Society for Blood and Marrow Transplantation (ASBMT)**
- **FACT Standards for Immune Effector Cellular Therapy**
  - **Defines an immune effector cell as "a cell that has differentiated into a form capable of modulating or effecting a specific immune response"**
- **FACT does not oversee the development of the CAR-T therapy (efficacy, clinical utility or clinical validity)**
  - **Instead the safe administration of the products with stringent quality control**

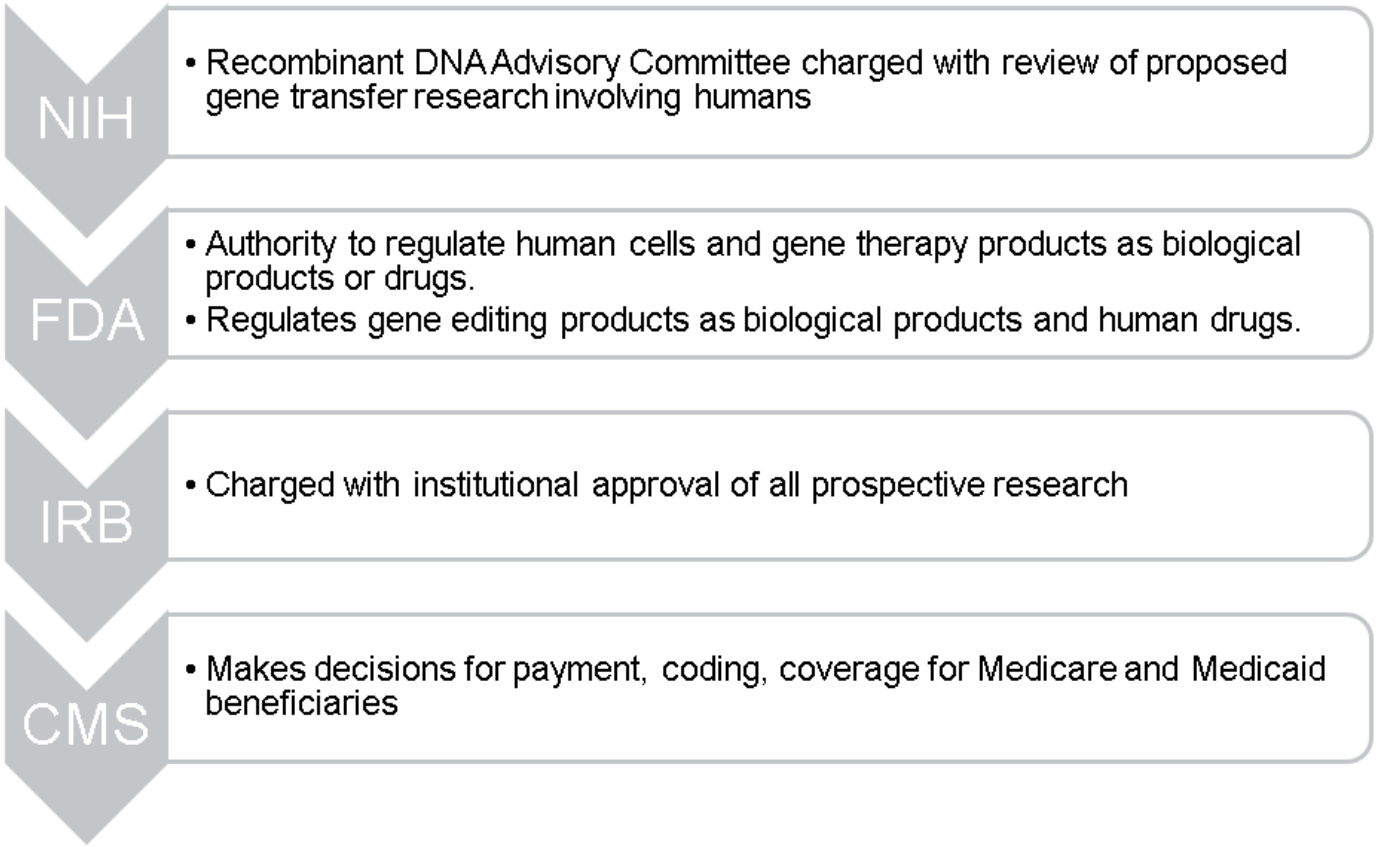
Product: First Edition, Version 1.1 FACT Standards for Immune Effector Cells [Free Download]: FACT. Foundation for the Accreditation of Cellular Therapy. https://www.factweb.org/forms/store/ProductFormPublic/first-edition-v1-1-fact-standards-for-immune-effector-cells-free-download. Published March 18, 2019. Accessed March 18, 2019.

Clinical Trials Oversight

- **Non-FDA approved CAR-T therapies (CAR-T production occurs within a local GMP facility)**
  - **Regulated under an FDA Investigational New Drug Application (IND) and FACT standards**
- **FDA has released a *Draft Guidance for Industry* (July 2018) for "Long Term Follow-Up After Administration of Human Gene Therapy Products".**
  - **defined "as all products that mediate their effect by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences"**
  - **Includes *ex vivo* genetically modified human cells**
  - **Final draft to address:**
    - **potential delayed risks of gene therapy**
    - **biodistribution and persistence of gene therapy products**
    - **vector persistence**
    - **integration activation and genome modifications**
    - **preclinical evaluation of products**
    - **how long term follow-up is to be performed by industry.**
- **Under IND designation SAEs must be reported to both the FDA as well as IRB**

https://www.federalregister.gov/documents/2018/07/12/2018-14867/long-term-follow-up-after-administration-of-human-gene-therapy-products-draft-guidance-for-industry. Published July 12, 2018.

Federal Regulatory Structure



FACT

Oversees safe administration of the products with stringent quality control

Proficiency Testing, Inspection and CAR-T

- **CAP has been approved by FACT as an accrediting organization providing histocompatibility services appropriate for hematopoietic cellular therapy transplant**
- **CAP Laboratory Accreditation Program will likely play a role in accrediting laboratories involved in processing specimens for CAR-T therapy**
- **Diagnostic Immunology and Flow Cytometry Committee (DIFC) has PT for CD19 assessment**
- **Supplemental questions regarding CAR-T developed by DIFC to accompany PT in a 2019 survey to assist in information gathering regarding CAR-T monitoring**
- **CAP members and committees should consider CAR-T therapy when considering or modifying checklist questions for each specialty within the clinical laboratory**

Coverage and Reimbursement

- **CAR-T Therapy is expensive (up to $500,000)**
- **May 2018 - CMS initiated a National Coverage Determination Analysis (NCD) for CAR-T cell therapies**
  - **CAP submitted comments to CMS**
  - **“pathologists play a critical role as integral members of the cancer patient management team during this therapy.”**
- **CAP urged CMS to pursue established mechanisms for recognizing physician services and facility reimbursement through the development of AMA CPT codes and/or HCPCS Level II “G” codes and subsequent valuation.**
- **June 2018 - AMA CPT Editorial Panel accepted a multispecialty society proposal (including the CAP) to establish four new category III CPT codes related to CAR-T cell therapy.**
  - **Capture physician services/CAR-T related services effective January 1, 2019**
  - **CPT category III codes may be considered for conversion to new category I CPT codes by the AMA CPT editorial panel**
    - **advanced for appropriate Relative Value Scale Update Committee (RUC) and CMS review and valuation of services provided by pathologists or other physicians**

New CAR-T Coding

New CPT Code	Effective Date	Descriptor
●0537T	January 1, 2019	**Chimeric antigen receptor T-cell (CAR-T) therapy;** harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day
●0538T	January 1, 2019	**Chimeric antigen receptor T-cell (CAR-T) therapy;** preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)
●0539T	January 1, 2019	**Chimeric antigen receptor T-cell (CAR-T) therapy;** receipt and preparation of CAR-T cells for administration
●0540T	January 1, 2019	**Chimeric antigen receptor T-cell (CAR-T) therapy;** CAR-T cell administration, autologous

Coverage and Reimbursement

- **August 22, 2018 - CMS convened a meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), which advises CMS on national coverage issues**
  - **MEDCAC does not make coverage determinations, but reviews the state of evidence and makes recommendations to CMS**
  - **Assesses whether scientific evidence supports outcome assessments, study design characteristics, study duration, and suitable controls for applying Patient Reported Outcomes (PROs)**
  - **Presentations before the panel included a review of trial data on existing CAR-T treatments and the PROs under consideration (manufacturers, health researchers, and policy makers)**
  - **CAP comment letter to CMS in March, 2019 requesting:**
    - **1) a flexible process for routinely extending coverage as newer CAR therapies become available**
    - **2) recognition for all provider services as separate and distinct processes from the manufacturing step**
    - **3) allowance of MACs to determine coverage for new therapies/technologies at the local level**

CMS-1694-F and CMS-1694-CN2. Centers for Medicare & Medicaid Services. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2019-IPPS-Final-Rule-Home-Page-Items/FY2019-IPPS-Final-Rule-Regulations.html. Accessed March 21, 2019.

August 7th, 2019

CMS.gov | Centers for Medicare & Medicaid Services

Newsroom Press Kit Data Contact Blog Podcast

Press release

Trump Administration Makes CAR T-Cell Cancer Therapy Available to Medicare Beneficiaries Nationwide

Aug 07, 2019 | Coverage

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Trump Administration Makes CAR T-Cell Cancer Therapy Available to Medicare Beneficiaries Nationwide

Decision ensures consistency in access to the innovative new cancer therapy, and CMS is working closely with sister agencies to monitor outcomes for patients receiving the therapy

Today the Centers for Medicare & Medicaid Services (CMS), under the leadership of President Trump and Secretary Azar, finalized the decision to cover FDA-approved Chimeric Antigen Receptor T-cell, or "CAR T-cell" therapy, which is a form of cancer treatment that uses a patient's own genetically-modified immune cells to fight disease. FDA-approved CAR T-cell therapies are approved to treat some people with specific types of cancer – certain types of non-Hodgkin lymphoma and B-cell precursor acute lymphoblastic leukemia.

https://www.cms.gov/newsroom/press-releases/trump-administration-makes-car-t-cell-cancer-therapy-available-medicare-beneficiaries-nationwide
Accessed October 9th, 2019

Future of CAR-T

Other Hematologic Diseases

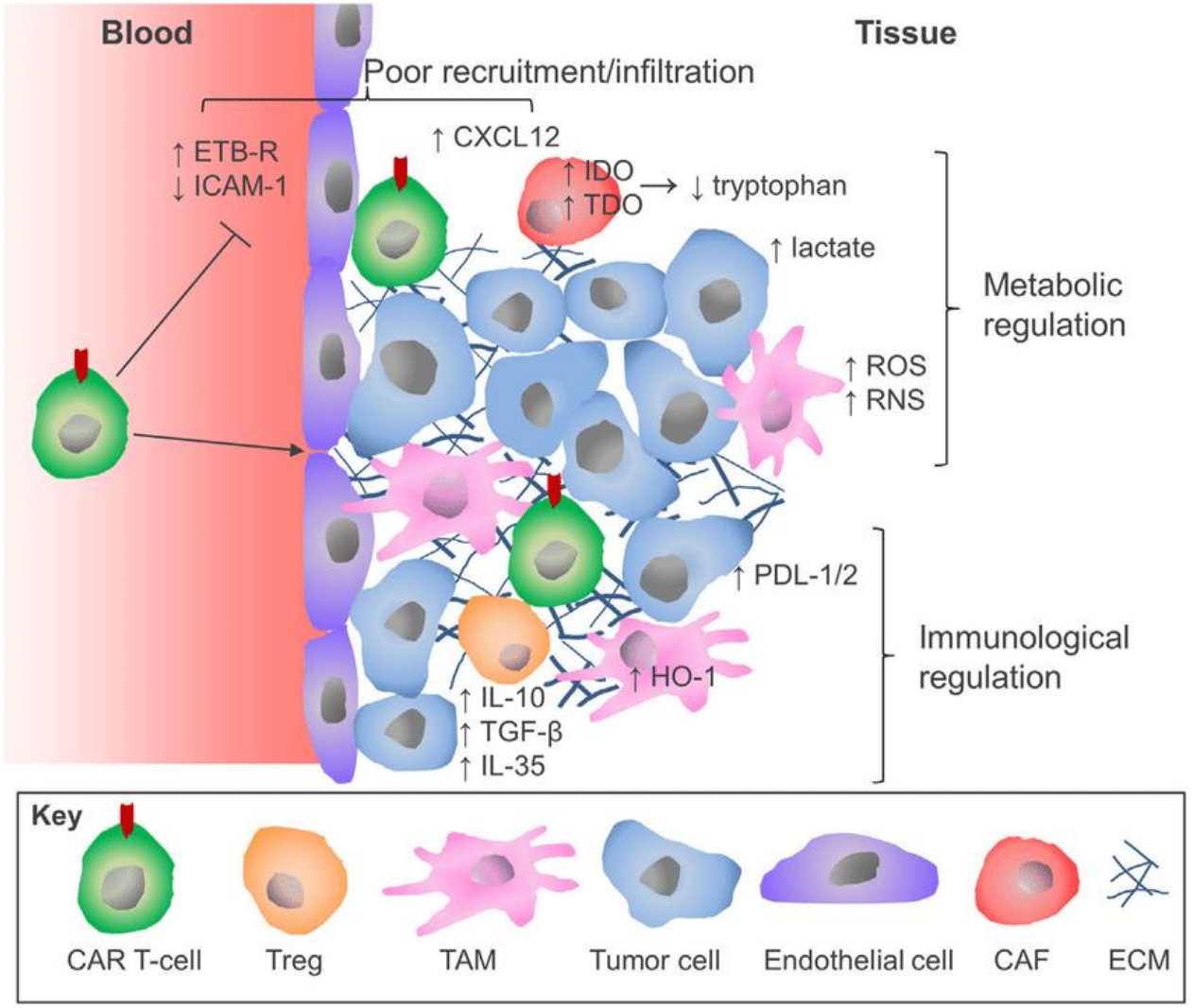
- **Refractory CLL**
  - **CAR-T CD19 targeted therapy**
  - **sustained remission with an overall response rate of 57%**
  - **no relapse in patients with a complete response**
- **Refractory multiple myeloma**
  - **CAR-T cells transduced with CAR-anti-BCMA**
  - **overall response rate of 81%**
- **Acute Myeloid Leukemia**
  - **CAR-T cells targeting FLT3 may be effective in treating AMLs**
  - **pre-clinical evidence in cell lines and mice**

Sci Transl Med. 2015;7(303):303ra139.
J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(22):2267-2280.
Leukemia. 2017;31(8):1830-1834.
Leukemia. 2018;32(5):1168-1179.

Solid Tumors and CAR-T

- **Solid tumors has been less successful**
  - **Lack of specific targetable antigens (e.g. various cytokeratins are found on multiple epithelial cell types)**
  - **Heterogeneity of antigen expression**
  - **Difficulty in overcoming "protective" barriers**
    - **Fibrosis and extracellular matrix**
    - **Immune suppression mechanisms by tumor**
    - **Cytokine/chemokine imbalance favoring the tumor**
    - **Tumor endothelial barriers preventing extravasation of T cells**
    - **Poor metabolic and hypoxic states inhibiting CAR-T cell growth**
  - **Manipulation of CAR-T therapy**
    - **e.g. "armored" CARs engineered to produce IL-12 to mitigate the tumor microenvironment**

Cell Death Dis. 2018;9(3):282.



Kosti P, Maher J, Arnold JN. Perspectives on Chimeric Antigen Receptor T-Cell Immunotherapy for Solid Tumors. *Frontiers in immunology*. 2018;9:1104. Reused under license CC BY 4.0.

Examples of Disease Antigen Targets Assessed for CAR-T Therapy		
Disease	**Target antigen**	Reference(s)
Chronic Lymphocytic Leukemia	**CD19**	Porter et al. *Sci Transl Med*. 2015;7(303):303ra139. Fraietta et al. *Nat Med*. 2018;24(5):563-571.
Refractory Multiple Myeloma	**CD19**	Garfall et al. *JCI Insight*. 2018;3(8).
Multiple Myeloma	**B-cell maturation antigen (BCMA)**	Brudno et al. *J Clin Oncol Off J Am Soc Clin Oncol*. 2018;36(22):2267-2280.
Acute Myeloid Leukemia	**FLT3**	Chen et al. *Leukemia*. 2017;31(8):1830-1834. Jetani et al. *Leukemia*. 2018;32(5):1168-1179.
Breast	**Her-2/ErbB2**	Priceman et al. *Clin Cancer Res*. 2018;24(1):95-105.
Renal Cell Carcinoma	**Carboxy-anhydrase-IX (CAIX)**	Lamers et al. *Biochem Soc Trans*. 2016;44(3):951-959.
Non-small Cell Lung Cancer	**EGFR**	Li et al. *Cell Death Dis*. 2018;9(2):177.
Glioma	**IL13Rα2**	Brown et al. *N Engl J Med*. 2016;375(26):2561-2569.
Glioma	**EGFRvIII**	O'Rourke et al. *Sci Transl Med*. 2017;9(399):eaaa0984. Sahin et al. *PLOS ONE*. 2018;13(7):e0199414. Ren et al. *Curr Pharm Des*. 2017;23(14):2113-2116.
Ovarian Carcinoma	**MUC-CD (retained, non-secreted portion of MUC16/CA-125)**	Chekmasova et al. *Clin Cancer Res*. 2010;16(14):3594-3606. Koneru et al. *OncoImmunology*. 2015;4(3):e994446.
Colorectal Cancer	**CEA**	Zhang et al. *Mol Ther*. 2017;25(5):1248-1258. Wang et al. *OncoImmunology*. 2016;5(9):e1211218.
Prostate	**Prostate Specific Membrane Antigen**	Junghans et al. *The Prostate*. 2016;76(14):1257-1270. Zuccolotto et al. *PLOS ONE*. 2014;9(10):e109427.

Table courtesy of Allison Cushman-Vokoun, MD PhD; Nebraska Medicine

“Off the shelf” Allogeneic CAR-T therapies

- **Eliminating the need for patient cell collection and the lengthy manufacturing time**
- **Barriers**
  - **Rejection of the infused product by the host immune system**
  - **Risk of graft versus host disease**
  - **Gamma-delta T cells are currently being examined as a way to prevent GVHD development**
  - **Removal of MHC class I proteins from donor T cells to decrease the chance of rejection**
  - **MHC I is the ligand for KIR (killer-immunoglobulin like receptor)**
    - **Normally inhibits NK cells, allowing for NK-mediated cell killing of infused cells**

Cancer Discov. 2018;8(7):787-788.

Alloreactive Natural Killer Cells

- **“off the shelf” NK cells**
- **Mediate anti-cancer effects without GVHD or autoimmune toxicity**
- **Rapidly available**
- **Short term life-span, reduced potential for long-term adverse events (cytopenias, aplasia)**
- **Difficult to harvest and transduce**
- **Require cytokine support for persistence (IL-2 or IL-15), unwanted side-effects**
- **Cord blood has been shown to be a good source of allo-NK cells**
  - **Tolerance to HLA mismatches**
  - **Better transduction efficiency**
  - **Incorporation of cytokine genes (*IL2* or *IL15*) to assist in NK cytokine support**
  - **Suicide genes (such as inducible caspase, iCasp9), to inactivate unexpectedly developed toxicity**

Front Immunol. 2018;9:283.

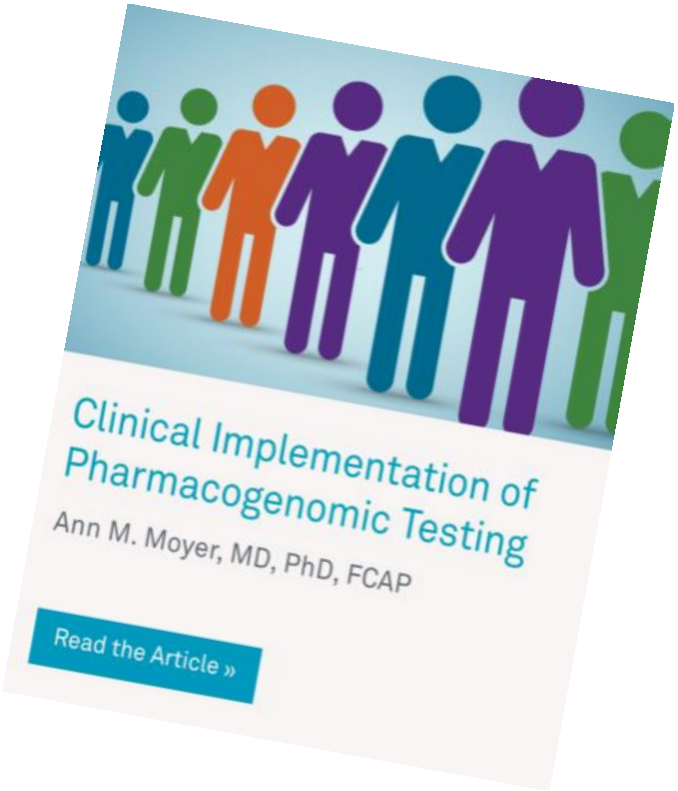
Conclusions

- **CAR-T Therapy has entered the clinical world as an *ex vivo* genetically modified human cellular therapy**
- **FDA-approved CAR-T therapy is extremely effective in producing response in CD19+ BALL and certain lymphomas**
- **There are many ongoing CAR-T trials covering a multitude of cancers**
- **There are many considerations in administration of CAR-T therapy**
- **CAR-T is expensive and not without adverse side effects**
- **CAR-T will now be reimbursed under Medicare**
- **Allogeneic products are being investigated**
- **Pathologists must be involved in CAR-T administration and be up-to-date in our understanding of genetically-modified therapies**

CAP's Precision Medicine Webpage

- **The webpage includes brief, relevant articles by CAP members that enable the reader to gain a better understanding of a particular area of precision medicine.**
  - **Examples include pharmacogenetics, immune response genes, and the latest in the molecular drivers of cancer.**
  - **Access them www.cap.org >**

    Member Resources > Precision Medicine



Short Presentations on Emerging Concepts (SPECS)

- **Pathology SPECs are:**
  - **Short PowerPoints, created for pathologists**
  - **Focused on diseases where molecular tests play a key role in patient management**
- **Recent topics include:**
  - **Microbiome**
  - **Biomarkers in Lung Cancer**
  - **MDS**
  - **Other emerging topics**
- **Access them at www.cap.org > Resources and Publications**

CAP's Pathology Resource Guide: Precision Medicine

- **The CAP has created the Pathology Resource Guides to assist pathologists in understanding key emerging technologies.**
  - **Printed guides are now available for members ($39) and non-members ($69)**
  - **The digital copy of the Resource Guides are a complimentary member benefit**
  - **Access them www.cap.org > Resources and Publications**

See, Test & Treat® brings cancer screenings to women in need!

- See, Test & Treat is a CAP Foundation-funded program that brings free, same-day cervical and breast cancer screening, diagnoses and follow-up care to women in medically underserved communities across the U.S.

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THANK YOU!

Thank you for attending our webinar, "CAR-T Therapy: What Does it Mean for Pathologists?" by

Allison Cushman-Vokoun, MD, PhD, FCAP

For comments about this webinar or suggestions for upcoming webinars, please contact phcwebinars@cap.org.

NOTE: There is no CME/CE credit available for today's free webinar. The PDF of the presentation will be sent out in a week.

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