Clinical Development of Chimeric Antigen Receptor (CAR)-T Cell Therapy in Cancer

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Disclaimer

- My presentation is an informal communication and represents my own best judgment. These comments do not bind or obligate FDA

- I have no financial relationships or conflict of interest to disclose

Challenge Questions

1. **Which type(s) of meeting may occur prior to an IND submission?**

2. **Which primary endpoint(s) is (are) appropriate for a first-in-human study?**

Outline

1. Regulation of oncology products at FDA
2. Overview of CAR products and CAR design
3. Toxicities associated with CAR T therapies
4. Strategies to improve CAR design
5. Clinical considerations for early phase trials of CAR products
6. Communications with FDA

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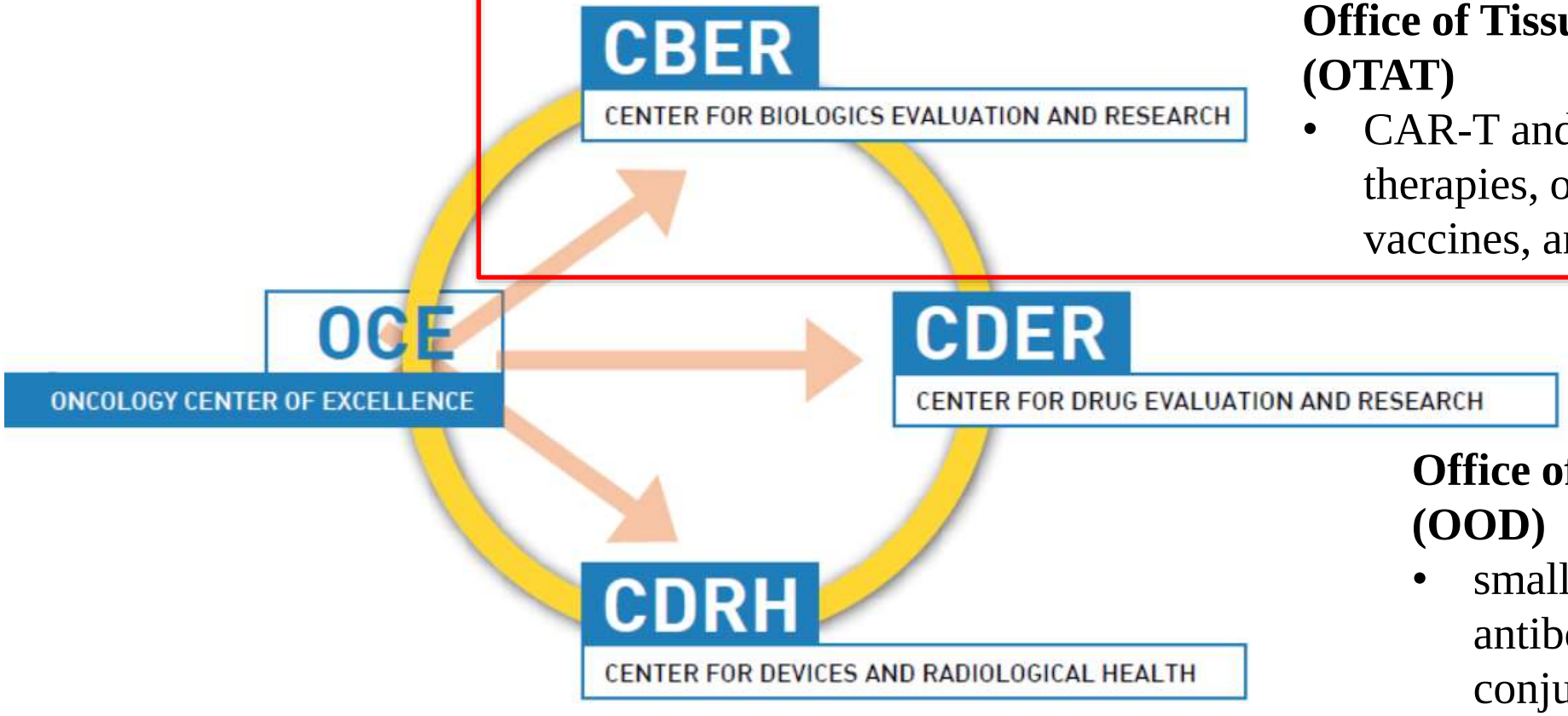
FDA Regulation of Oncology Therapies

The Oncology Center of Excellence fosters unified interaction between 3 FDA centers



Office of Tissues and Advanced Therapies (OTAT)

- CAR-T and other cellular therapies, gene therapies, oncolytic viruses, therapeutic vaccines, and microbiota

Office of Oncologic Diseases (OOD)

- small molecules, monoclonal antibodies, antibody-drug conjugates

Office of In Vitro Diagnostics and Radiological Health

- companion and complementary diagnostics

FDA Review Team

Pharmacology & Toxicology

Statistics

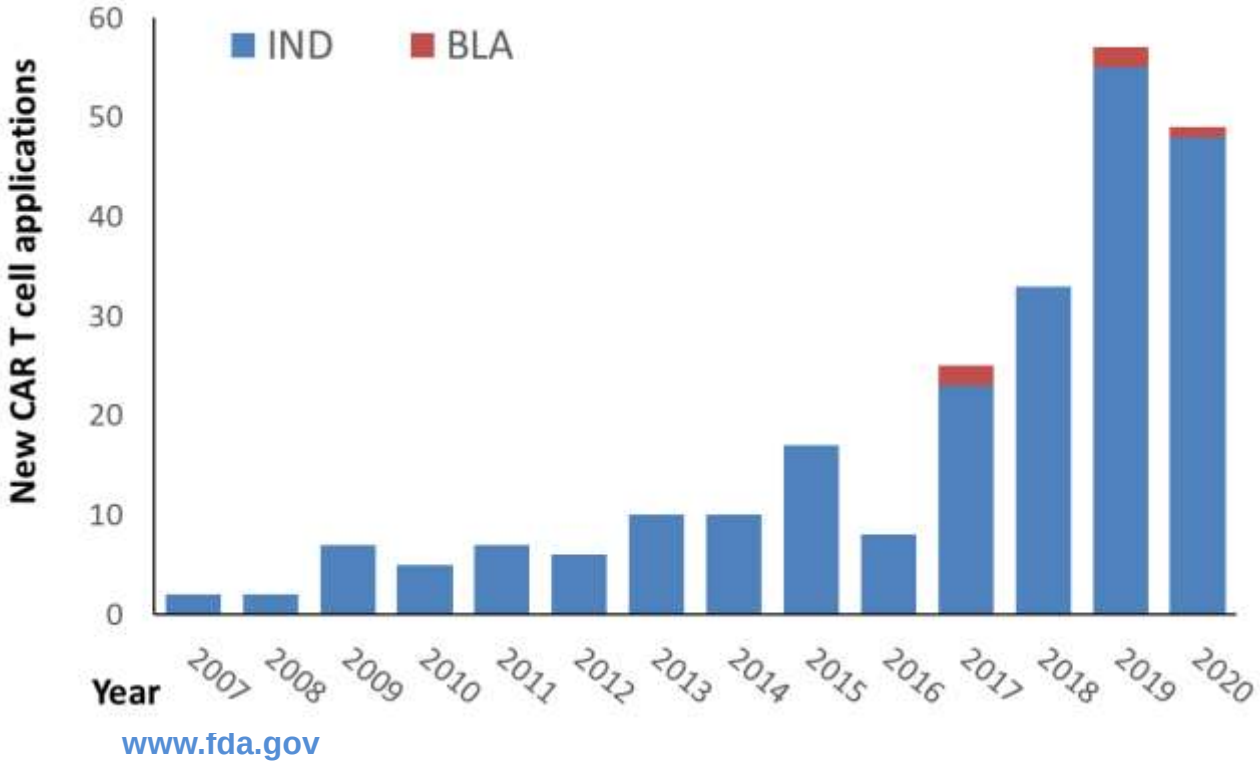
Regulatory Project Management

Clinical Pharmacology & Biopharmaceutics

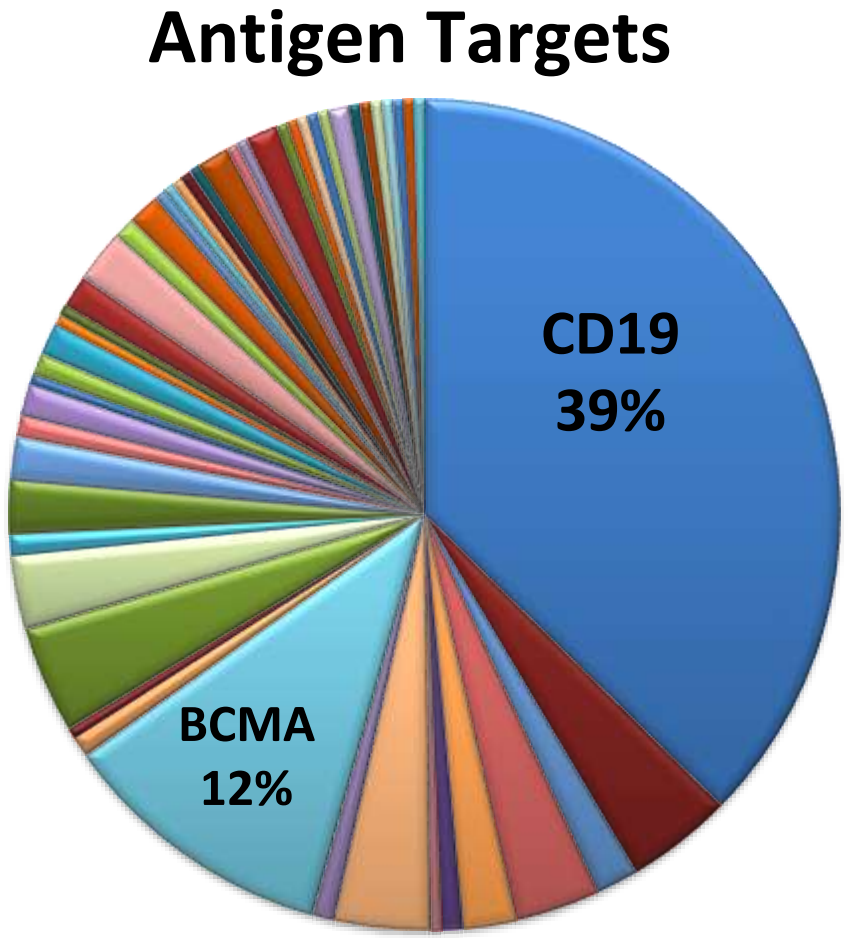
Clinical

Product Quality (CMC)

CAR T IND Applications in OTAT



www.fda.gov



- Approximately 231 CAR T cell INDs*
  - 68% are for hematologic malignancies
  - 86% are autologous products
- 5 licensed products approved in the U.S.

*Current as of 01/01/2021

Courtesy of Dr Kim Schultz

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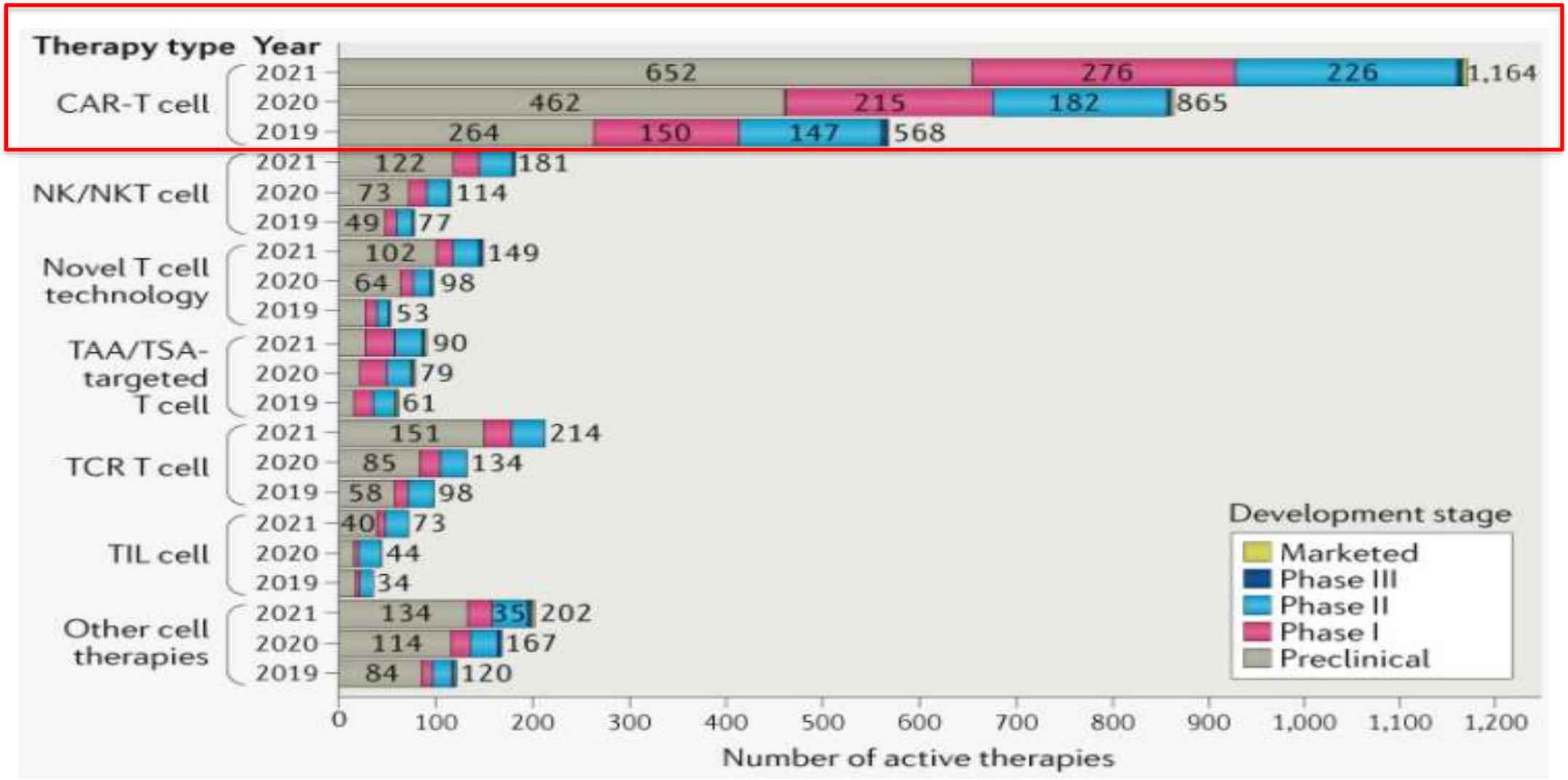
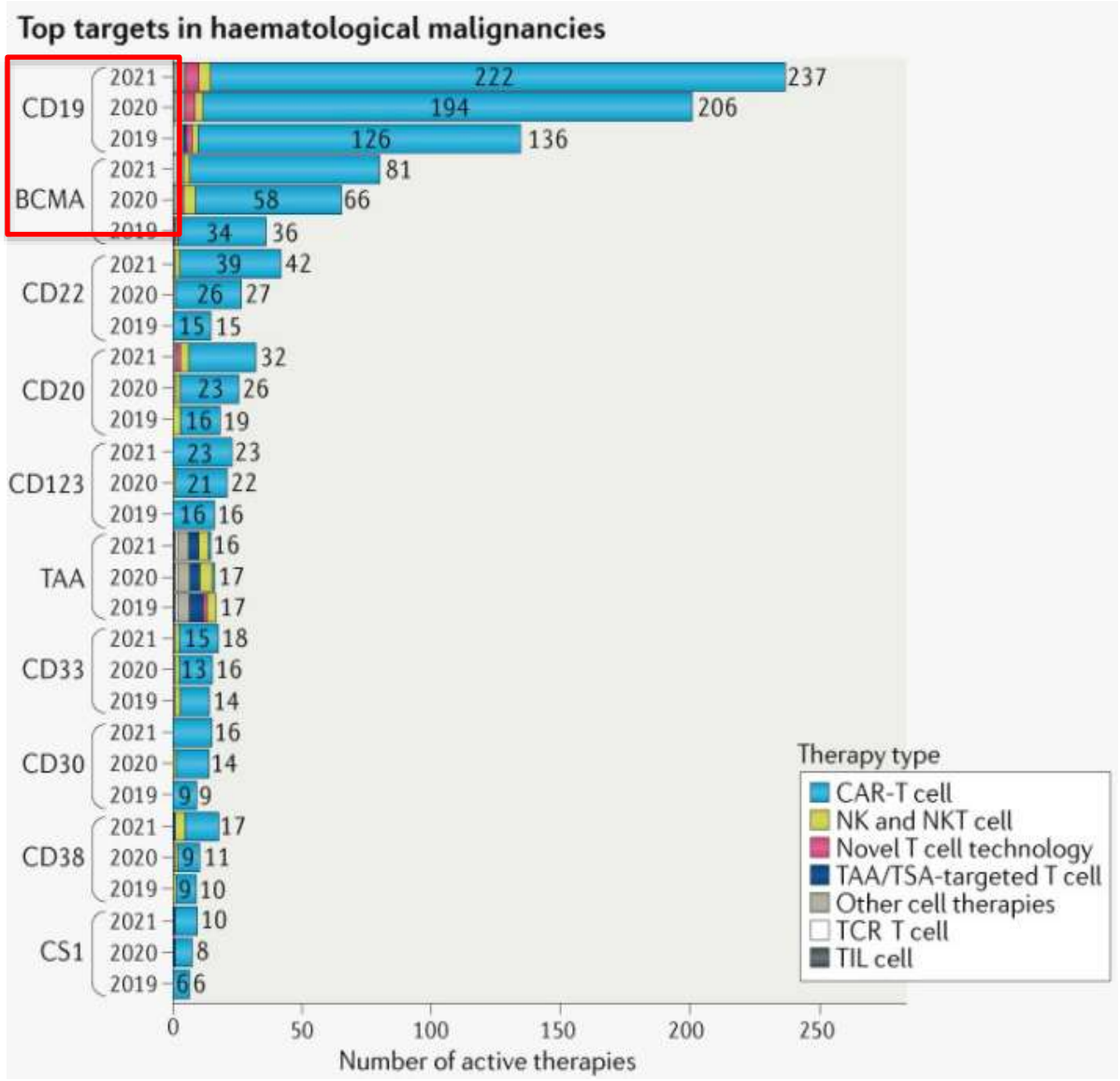
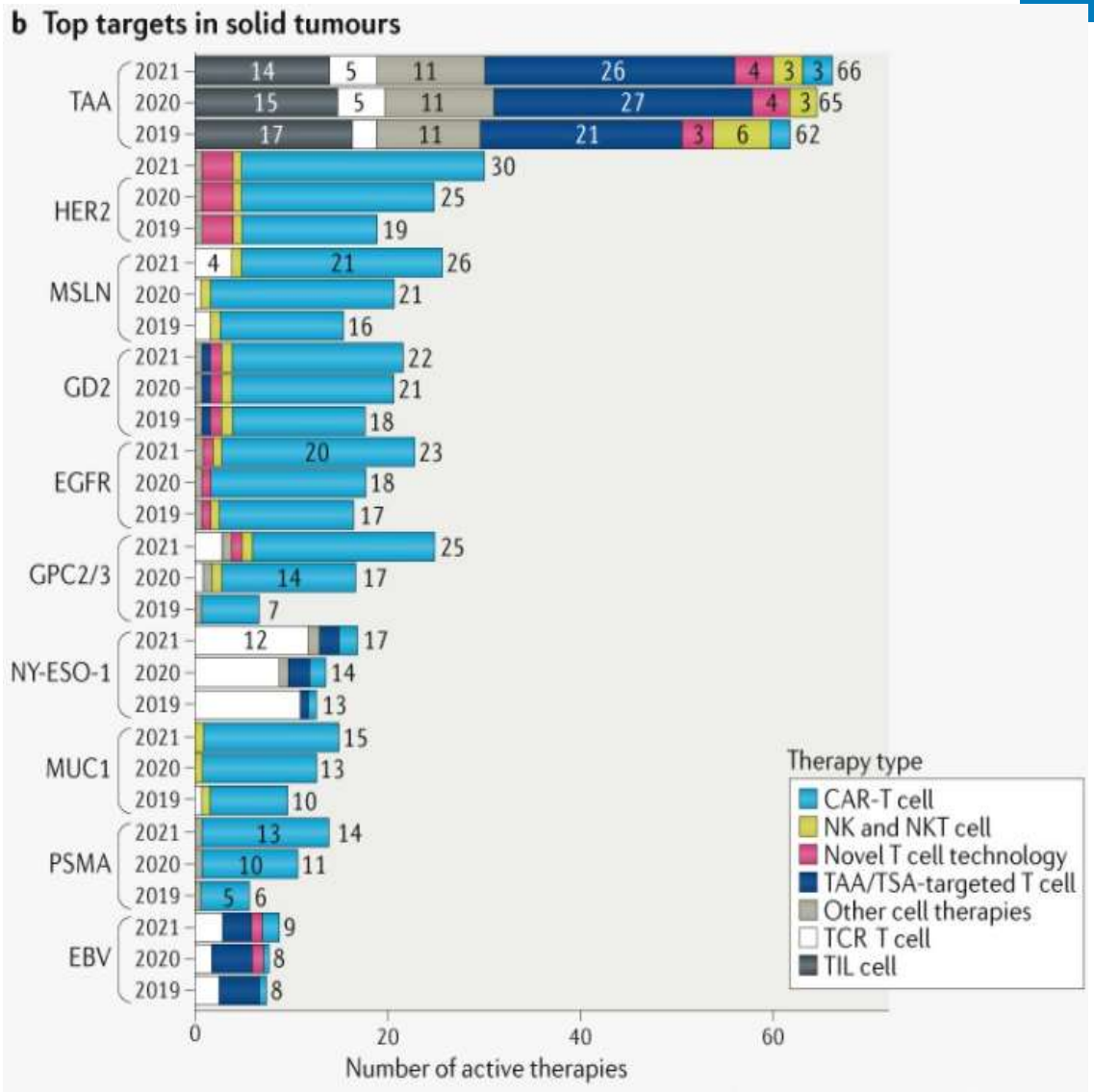
CAR-T Cell Therapies Dominate Cell Therapy Pipeline



Upadhaya S, et al., The clinical pipeline for cancer cell therapies. Nat Rev Drug Discov. 2021 Jul;20(7):503-504

Top Targets in Hematologic Malignancies and Solid Tumors

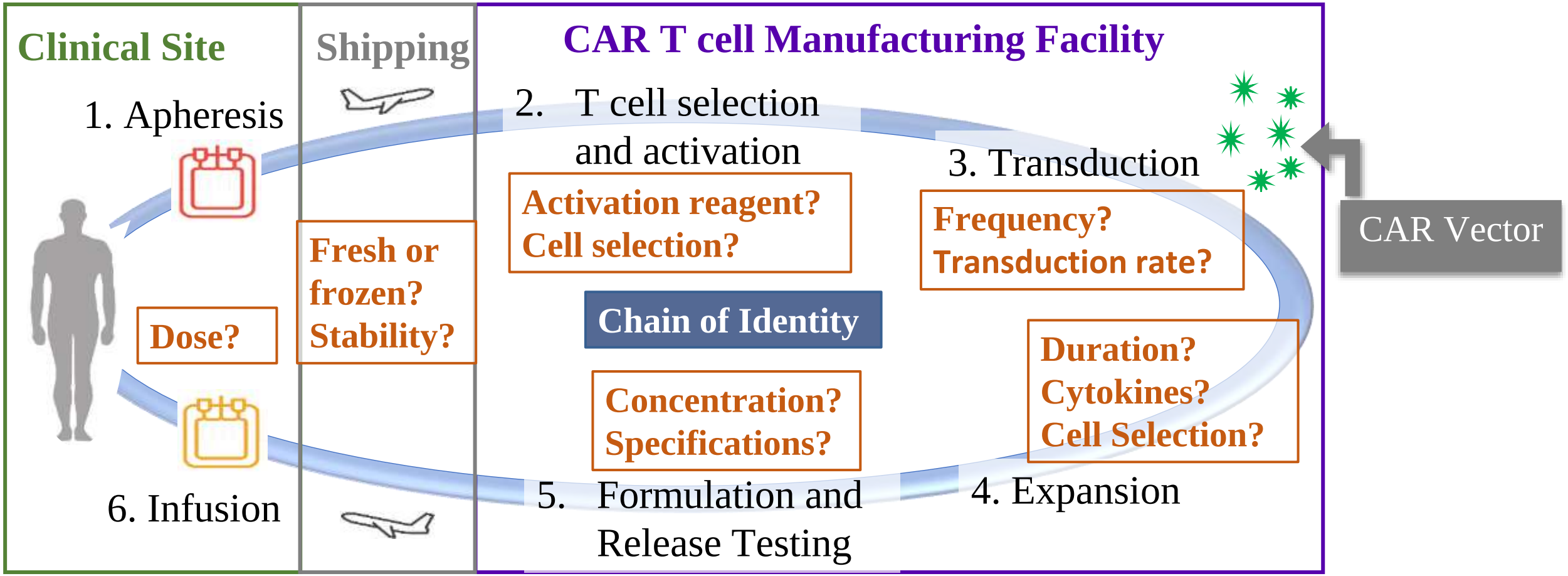




Upadhaya S, et al., Nat Rev Drug Discov. 2021 Jul;20(7):503-504

Autologous CAR-T Cells

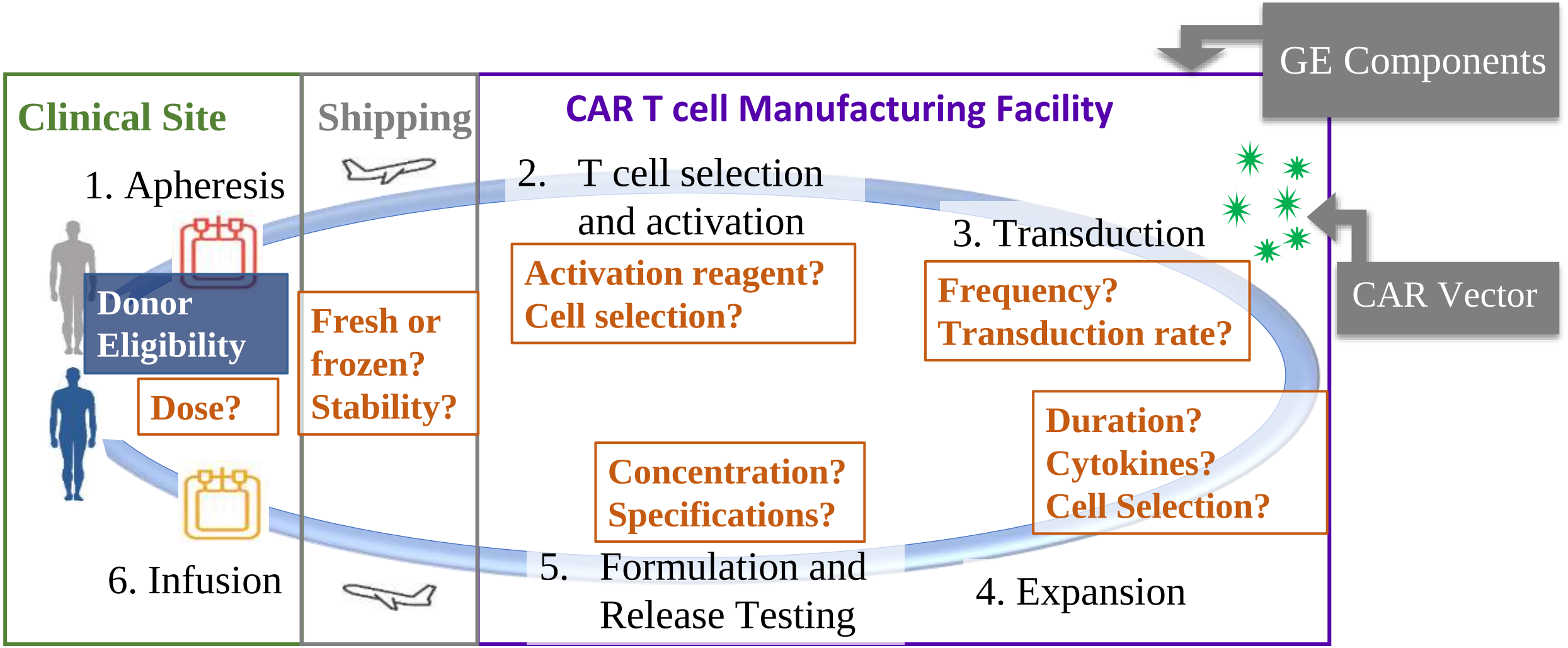
- Main components: patient's cells & CAR vector
- Aseptic process, no terminal sterilization



Courtesy of Dr Kim Schultz

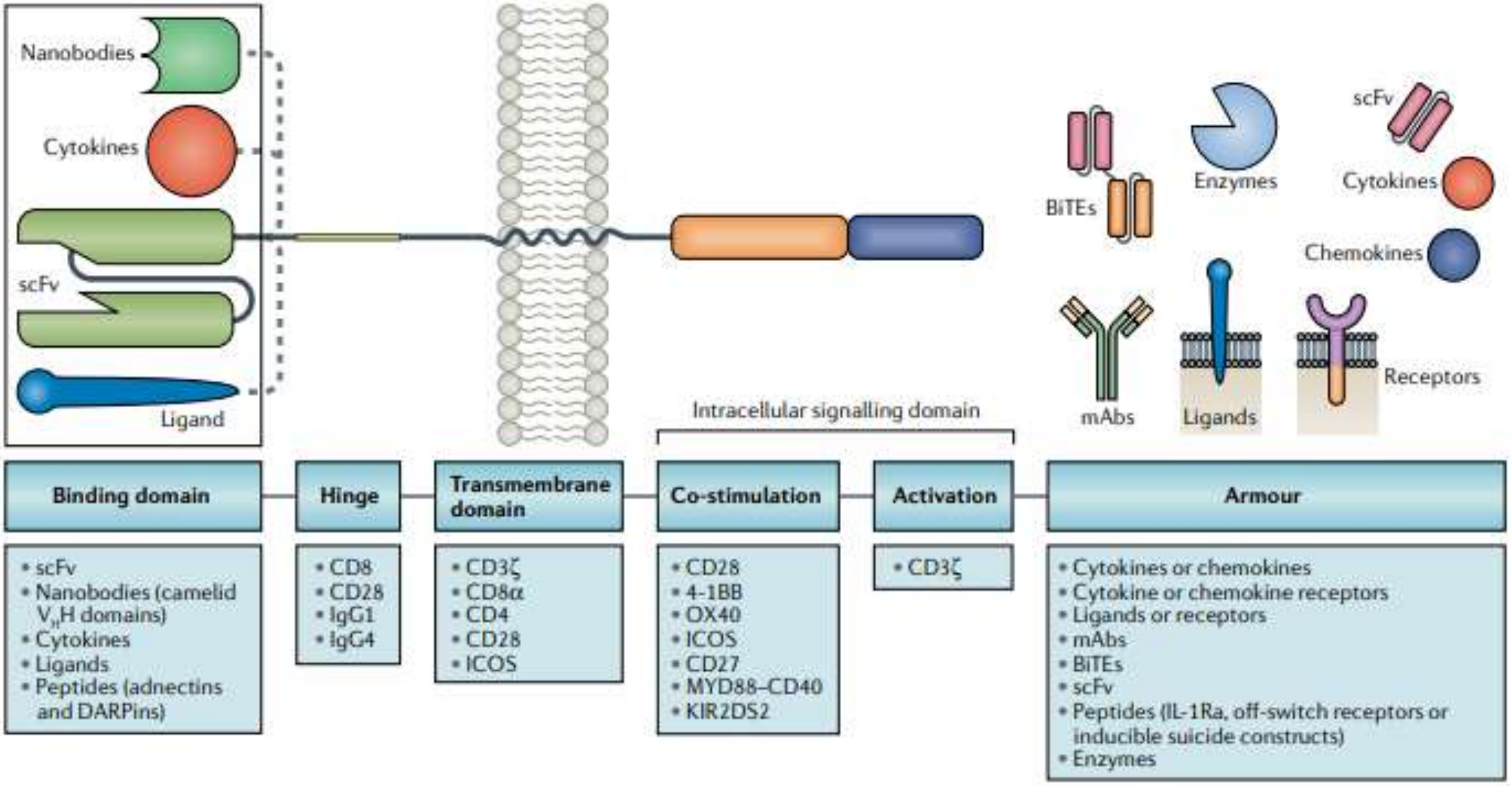
Allogeneic CAR-T Cells

- Main components: donor cells, TCR disruption, & CAR vector
- Aseptic process, no terminal sterilization



Courtesy of Dr Kim Schultz

Blueprint of CAR Design



Rafiq S, Hackett CS, Brentjens RJ. Nat Rev Clin Oncol. 2020 Mar;17(3):147-167.

FDA Approved CAR T Cell Therapies

- Tisagenlecleucel (Kymriah) *
  - Refractory B-cell ALL, 2017; Refractory DLBCL and high-grade FL, 2018
- Axicabtagene ciloleucel (Yescarta) *
  - Refractory DLBCL, 2017; Refractory FL, 2021
- Brexucabtagene autoleucel (Tecartus) *
  - Refractory Mantle cell lymphoma, 2020; Refractory B-cell ALL, 2021
- Lisocabtagene maraleucel (Breyanzi) *
  - Refractory B-cell NHL, 2021
- Idecabtagene vicleucel (Abecma) ^
  - Refractory multiple myeloma, 2021

*CD19-directed CAR-T cells; ^ BCMA(CD269)-directed CAR T cells

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Toxicities Associated with CAR-T Therapies

Boxed Warnings and Risk Evaluation and Mitigation Strategy

- Cytokine release syndrome (CRS)
- Neurotoxicity

Warnings and Precautions [Prescribing Information Section 5]

- Infusion-related reactions/hypersensitivity
- Serious infections
- Prolonged cytopenia
- Hypogammaglobulinemia and B-cell aplasia
- Risk of secondary malignancies

Other Adverse Reactions [Prescribing Information Section 6]

- Tumor lysis syndrome
- On-target/off-tumor toxicity

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Overcoming Toxicities

1. Suicide genes (e.g., iCasp9, intrinsic ability to neutralize relevant cytokines)
2. On/Off switches on administering small molecular agents
3. Direct antagonist of systemic cytokines (e.g., knock out cytokine genes or expression of cytokine antagonists)

Improving Efficacy

1. Target multiple antigens
2. Enhance in vivo persistence
3. Increase tumor homing and penetration
4. Overcome immunosuppression in tumor microenvironment (TME)

Rafiq S, et al., Nat Rev Clin Oncol. 2020 Mar;17(3):147-167.

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Clinical Considerations

Early Phase/First-in-Human Trials with CAR Therapies

IND Application Contents
21 CFR 312.23(a)

(1) Cover sheet (Cover letter)

(2) A table of contents

(3)* Introductory statement and general investigational plan

(5)* Investigator's Brochure

(6) Clinical protocols

(7) Chemistry, Manufacturing and Control information

(8) Pharmacology and Toxicology information

(9) A summary of previous human experience with the investigational drug

(10) Additional information (e.g., dependence and abuse potential, information related to radioactive drugs)

(11) Other relevant information (e.g., reference to previous submissions or other IND applications)

* 21 CFR 312.23(a)(4) is not listed

Trial Objectives

- Safety - primary objective
- Dose exploration
  - Dose escalation
  - Maximum tolerated dose (MTD)
  - Optimal dose
- Assessment of manufacturing feasibility
- Preliminary anti-tumor activity assessment

Eligibility Criteria

- Relapsed/Refractory to available therapies
- Comorbidities should be considered
- Pediatric studies *21 CFR 50, Subpart D*
- Specific target may require an in-vitro companion diagnostic (IVD)
  - Antigenic target
  - HLA restriction
- IVD assay may require an investigational device exemption (IDE)
  - Does the IVD forego or delay treatment known to be effective?
  - Could the use of IVD expose subjects to safety risks?

Study Design: Endpoints, Controls, and Confounders

- Single arm trial
  - Safety, optimal dose finding
  - Objective response rate (ORR), duration of response (DOR)
- Randomized controlled trial
  - Time-to-event (overall survival, progression-free survival)
  - Appropriate control required – discuss with FDA
  - May not be feasible for these products in a refractory population
- Potential confounding factors of concurrent treatments
  - Lymphodepletion
  - Addition of checkpoint inhibitors
  - Bridging therapies

Starting Dose / Dose Escalation

- Starting dose for first in human (FIH) study
  - May be based on toxicology data
  - Prior human experience with similar construct (empirical dose)
  - Dose may be based on transduced cells per unit weight (or BSA), or flat dose
  - Justifications for starting dose (preclinical data or clinical experience)
- Dose escalation scheme
  - Classic 3+3 design
  - Half-log increments for biological drugs (1 log escalation is generally considered aggressive)
  - Continual reassessment of dose escalation design using Bayesian adaptive design
  - Intra-patient dose escalation not recommended
  - Staggering of treatment between subjects / dose cohorts
  - Anticipated toxicities
  - Anticipated cell expansion in vivo

Dose Limiting Toxicities (DLTs)

- Examples of DLTs associated with CAR T therapies
  - Treatment-emergent Grade 4 Cytokine Release Syndrome (CRS)
  - Treatment-emergent Grade 3 CRS that does not resolve to ≤ Grade 2 within 7 days
  - Treatment-emergent autoimmune toxicity ≥ Grade 3
  - Grade 4 infusion-related reactions
  - Grade 3 or greater major organ toxicities, not pre-existing, occurring within 30 days of cell infusion
  - Death within 30 days of CAR T cell infusion unless clearly due to disease progression
  - Grade 3 or higher encephalopathy
  - Seizure
- Grading CRS and Neurologic Toxicity Associated with Immune Effector Cells (ICANS)
  - American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading [1]
- Confounded by toxicities of conditioning lymphodepletion regimens

[1]Lee DW et al. Biol Blood Marrow Transplant 2019;25:625-638

Management of CRS

- Include an algorithm for assessment (grading) and management
- Rule out other causes of fever (sepsis, infusion reactions)
- Management of CRS
  - Tocilizumab (IL-6 receptor antagonist)
  - Steroids – Potential interference with T cell activity/expansion
  - Supportive care (ICU) Intubation, vasopressors, etc.
- Specify cytokine sampling requirement and monitoring
- Patients should remain in reasonable proximity to the treating institution in case of delayed toxicities

Safety Monitoring

- Duration of monitoring for adverse events
  - Sufficient to cover expected duration of effect
  - Depends on information from preclinical studies, and experience with related products
- Safety Assessments and schedules (cover acute, subacute and delayed safety events)
- Long term follow-up may be required[1]
  - 15 years of follow-up for integrating viral vector-based products
  - Clinical development can continue while long-term follow-up is ongoing

[1] FDA Guidance: Long Term Follow-up After Administration of Human Gene Therapy Products (2020)
https://www.fda.gov/media/113768/download

Study Pausing/Stopping Rules

- Temporary pause/suspension/stop in enrollment and dosing of additional subjects to limit the number of study subjects exposed to unreasonable risk
  - Death within 30 days of infusion
  - Death possibly related to the protocol treatment
  - Increased incidence of expected toxicity (e.g., > 33% DLTs)
- Specify conditions for temporary suspension of enrollment and dosing until a safety evaluation is performed by the study safety oversight committee
- Protocol revision may be warranted
  - Eligibility criteria, dose, monitoring plan
- Not intended to terminate a study

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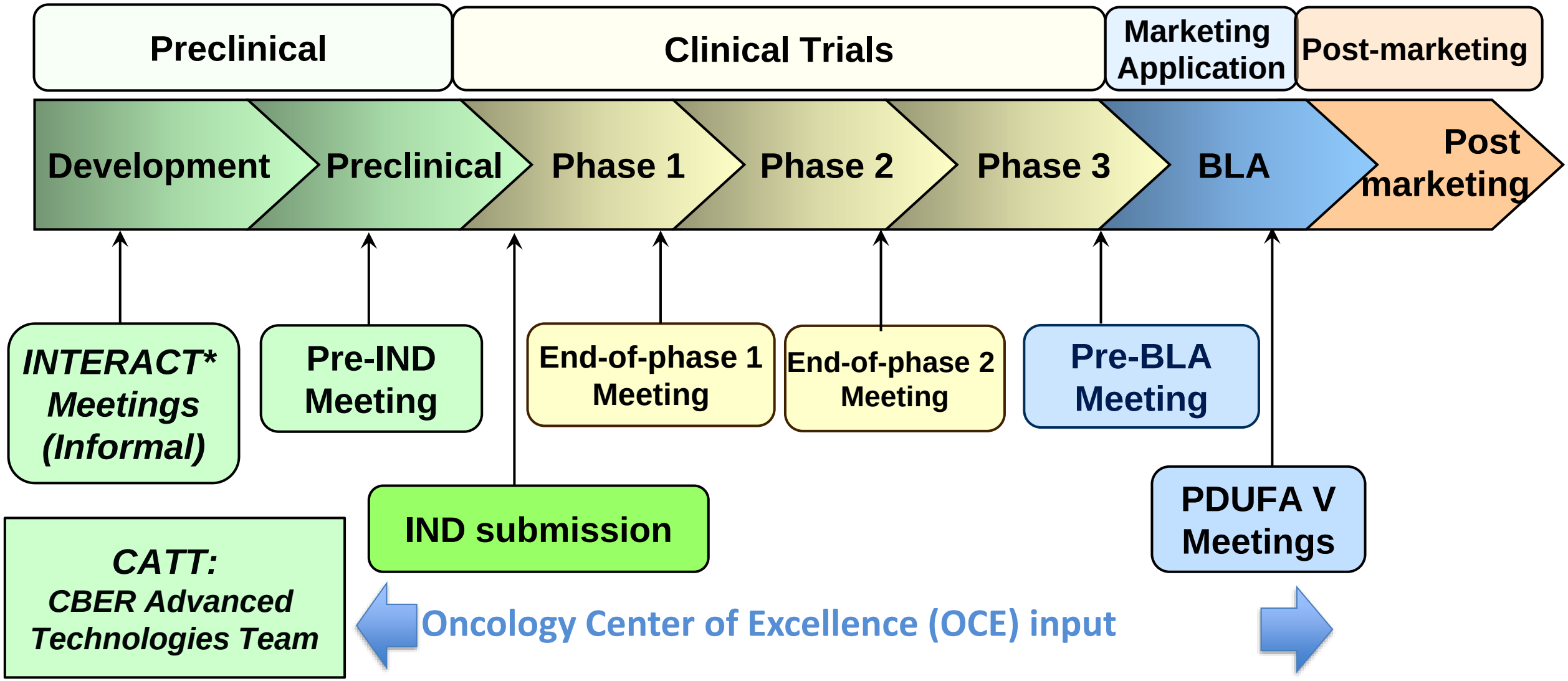
When to Approach FDA for Product Development Discussions



*INitial Targeted Engagement for Regulatory Advice on CBER producTs

Resources for Meetings

FDA Guidance Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products 2017

https://www.fda.gov/media/109951/download

Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT program):

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings

CATT program

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

Guidance for Industry

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), January 2020. https://www.fda.gov/media/113760/download
- M4Q: The CTD – Quality, August 2001 (Final). https://www.fda.gov/media/71581/download
- CGMP for Phase 1 Investigational Drugs, July 2008. https://www.fda.gov/media/70975/download
- Potency Tests for Cellular and Gene Therapy Products, January 2011 (Final).https://www.fda.gov/media/79856/download.
- Preclinical Assessment of Investigational Cellular and Gene Therapy Products, November 2013 https://www.fda.gov/media/87564/download
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry, January 2020 (Final). https://www.fda.gov/media/113790/download.
- Long Term Follow-up After Administration of Human Gene Therapy Products, January 2020 (Final) https://www.fda.gov/media/113768/download
- Expedited Programs for Serious Conditions—Drugs and Biologic, May 2014 (Final) https://www.fda.gov/media/86377/download
- Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency https://www.fda.gov/media/145301/download
- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (Final) https://www.fda.gov/media/134731/download

Guidance for Industry (Continue)

- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, June 2015 (Final) https://www.fda.gov/media/106369/download
- Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, August 2007 (Final) https://www.fda.gov/media/73072/download
- Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, July 2020 (Final) https://www.fda.gov/media/123745/download
- Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings, June 2021 (Draft) https://www.fda.gov/media/150244/download
- Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry, October, 2019 (Final) https://www.fda.gov/media/112605/download
- Evaluating Cancer Drugs in Patients with Central Nervous System Metastases, July 2021
- https://www.fda.gov/media/141507/download
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial (Draft), September 2021 https://www.fda.gov/media/152536/download
- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry, December 2017 (Draft) https://www.fda.gov/media/109951/download
- References for the Regulatory Process for the Office of Tissues and Advanced Therapies http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Cell and Gene Therapy Guidance access via https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

Summary

- FDA has approved several CAR T therapies for the treatment of hematologic malignancies
- CAR product development for solid tumors remains challenging
- Newer CAR-T constructs have been focused on reducing toxicity and improving efficacy
- FDA clinical review has been focused on safety specific to the type of CAR construct and dosing regimens
- FDA encourages communications
  - Pre-IND meetings
  - INTERACT meetings
  - CBER Advanced Therapies Team (CATT)
  - IND meetings (End-of-phase 2, pre-BLA, etc.)

Challenge Question #1

Which type(s) of meeting may occur prior to an IND submission?

A. INTERACT meeting

B. Pre-BLA meeting

C. Pre-IND meeting

D. CATT meeting

Challenge Question #2

Which primary endpoint(s) is (are) appropriate for a first-in-human study?

A. Overall Survival

B. Safety/Feasibility/ Dose finding

C. Landmark Progression Free Survival Rate

D. Objective Tumor Response Rate

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Thank you!

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- **OTAT Learn Webinar Series:**

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