U.S. FOOD & DRUG ADMINISTRATION

Scientific and Regulatory Considerations for Gene Modified T Cell Therapy

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Disclosures

We have no financial relationships to disclose.

Our comments are an informal communication and represent our own best judgment. These comments do not bind or obligate FDA.

Why gene modified T cells?

- Harness T cell immunity (cytotoxic functions, cytokine secretion, etc.) to attack tumor cells
- Conventional *ex vivo* expanded T cells targeting tumor antigens show some efficacy, but poor persistence
- Use gene transfer to improve functional properties of transduced T cells
  - Control of T cell specificity (recognition of defined tumor antigens)
  - Remove need for HLA specificity
  - Enhanced engraftment and proliferation
  - More potent effector function
- The above properties are encoded by the transgene

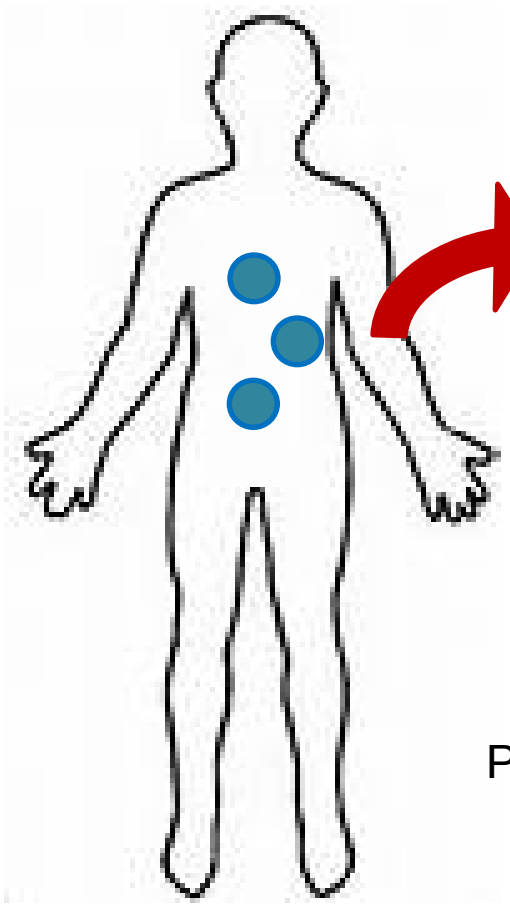
In US, gene modified T cell products are regulated by the Office of Tissues and Advanced Therapies in the FDA Center for Biologics Evaluation and Research

CAR T cells: a clinical reality

The London Bus theory of CAR T cell BLAs

- **Kymriah** – Novartis Licensed: 30th August 2017
  (CD19-CD3ζ-4-1BB) for pediatric relapsed/refractory B cell ALL
- **Yescarta** – Kite Pharma Licensed: 18th October 2017
  (CD19-CD3ζ-CD28) for adult relapsed/refractory DLBCL

Adoptive T cell immunotherapy: a basic overview



Cancer patient

T cell activation and transduction with gene transfer vector

Apheresis Product

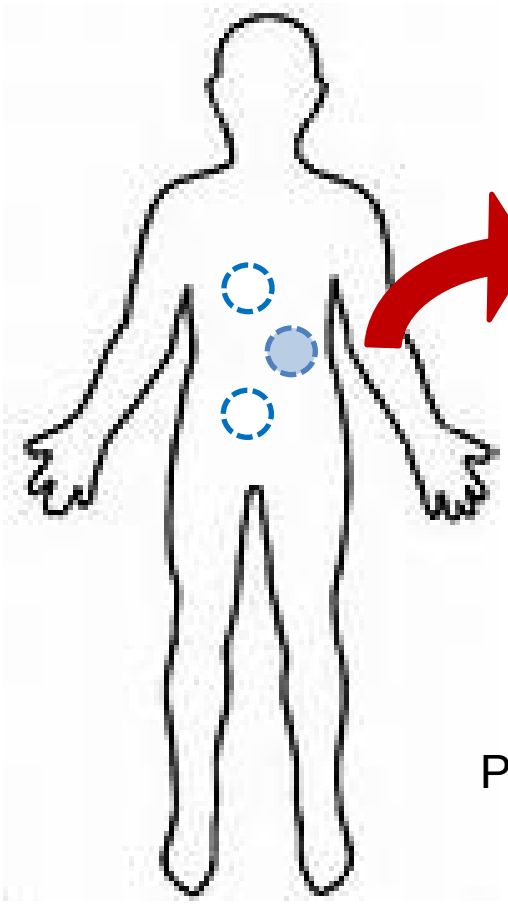
Expand in culture (CD3/CD28 stimulation ± IL-2 etc.)

Dose formulation
Product testing
Shipping

Gene modified T cell Infusion

Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post infusion

Adoptive T cell immunotherapy: a basic overview



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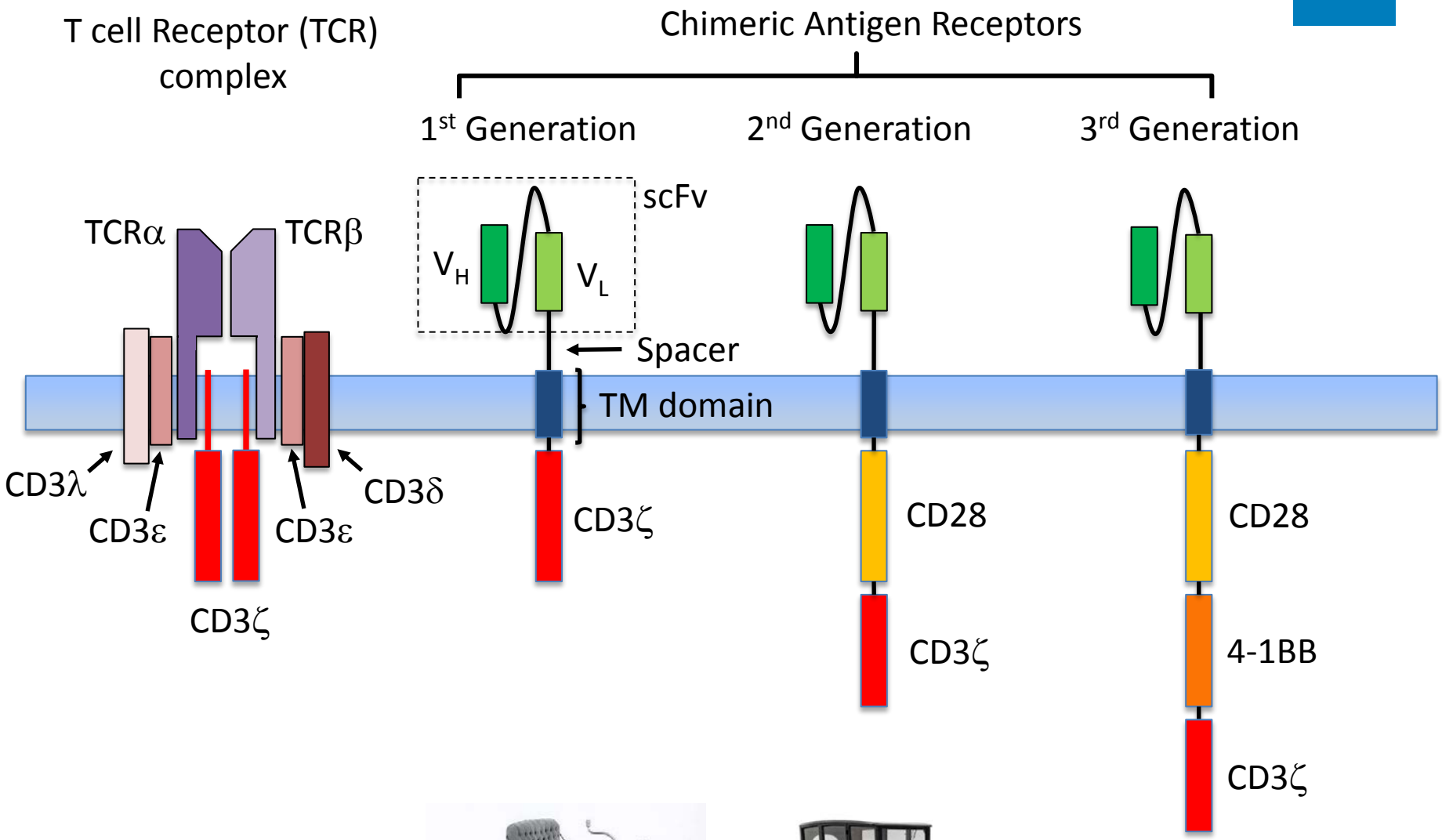
Gene modified T cells: characteristics

Property	Engineered TCR	Chimeric Antigen Receptor
Target recognition	α/β TCR (from human or mouse)	scFv from mAb
Increased potency	"affinity enhanced" TCR (often mutated for increased IFN-γ production)	Chimeric intracellular signaling domains (CD3ζ + CD28/4-1BB etc.)
Require tumor antigen derived peptide/MHC complex	Yes	No
Tumor antigen	Intracellular or cell surface	Cell surface only
Require co-stimulation	Yes (host antigen presenting cells)	No (provided by construct)

Transgene delivery commonly by retroviral or lentiviral vector

CAR development: A history



Construct considerations

- **What biological properties are desired?**
  - For CAR T cells:
    - which scFv? Mouse or "humanized" or human? Orientation (V_HV_L or V_LV_H)?
    - Spacer length?
    - which co-stimulatory domains to use (CD3ζ plus CD28 or 4-1BB or OX40 or….)?
  - For TCR cells
    - which TCR? Mouse or human?
    - affinity enhancement?
- **Persistence vs. immediate function?**
- **"Suicide" gene?** (e.g., iCasp9)
  - how fast/complete is cell depletion? Preclinical data useful
- **Marker gene?** (e.g., EGFRt)
  - allows selection (possibly also cell depletion post infusion)
- **Other functional attributes?**
- **Potential concerns**
  - Vector complexity
  - Immunogenicity

Pre-clinical considerations

- ***In vitro* studies**
  - killing/cytokine secretion/proliferation in response to target expressing tumor cell lines
  - lack of effect against non-target cells
- ***In vivo* efficacy models**
  - infuse cells into immunodeficient mice bearing human tumor xenografts
  - Show proof of concept only
- **No good animal models for safety**

Potential problems with CAR approach

- Requirement for Signal 1 + Signal 2 evolved to prevent autoimmunity
  - eliminating this checkpoint could “take the brakes off” T cell responses
- Differences in affinity for ligands:
  - endogenous TCR μM range
  - mAbs nM range (CD19 scFv 2.3 nM)
- T cells transfected with CAR still have endogenous TCR
  - we have no way of telling what these would be specific for – Viruses? Autoantigens?
- **Conservative clinical approach for first in human studies**

CAR T cell toxicities

- **Cytokine Release Syndrome / Macrophage Activation Syndrome**
  - "On target" toxicity
  - Cytokine storm as T cells expand and exert anti-tumor activity
  - What cytokines are important?
- **Neurotoxicity**
  - Reversible neurotoxicity common (aphasia)
  - Severe neurotoxicity has been seen (fatal cerebral edema)
- **Prolonged B cell aplasia (for CD19 CAR T cells)**
  - "On target, off tumor" toxicity
  - Manage with intravenous immune globulin
- **Can toxicity be dissociated from anti-tumor activity?**
  - If not, how best to manage toxicity?
    - Tocilizumab (blocks IL-6 receptor) – approved to treat CRS
    - Steroids? Potential interference with T cell activity/expansion
    - "Suicide" strategies? Do these deplete cells fast enough?
    - Monitoring and timing of interventions?

SAEs from autoreactive TCRs

- **TCRs may recognize self antigens and cause Serious Adverse Events**
  - Autoreactivity has always been a theoretical possibility, but actual SAEs led to:
    - Better understanding of risk factors
    - New strategies to screen for autoreactivity before using TCRs in clinical trials
  - Any TCR might be autoreactive, but risk is higher for certain engineered TCRs:
    - Non-human TCRs
    - Affinity-enhanced TCRs
    - Why is the risk higher for these? These TCRs have not been "self-educated" in thymus
- **National Cancer Institute** (Morgan *et al*. J Immunother. 2013 36(2); 680-8)
  - Mouse TCR targeted against MAGE-A3 / HLA-A*02
  - CNS toxicity due to unexpected expression of MAGE-A12 in CNS
    - MAGE-A3/12 epitopes are similar
- **University of Pennsylvania** (Cameron *et al*. Sci Transl Med. 2013 5(197); 197ra103)
  - Human affinity-enhanced TCR targeted against MAGE-A3 / HLA-A*01
    - (Also reacts against similar epitopes in MAGE-A6 and MAGE-B18)
  - Rapid cardiac toxicity due to unexpected "off target" TCR cross-reactivity with Titin (a muscle protein)
    - Steroid treatment didn't help

Preventing SAEs from autoreactive TCRs

Extensively characterize autoreactivity before first-in-human studies with new TCR-containing products

- Test for "on-target" autoreactivity against the antigen and highly-related antigens
  - Survey normal human tissues for the target antigen using sensitive methods
    - Literature survey may be insufficient
  - PCR for antigen mRNA is probably the most sensitive and practical method
    - Follow up positive mRNA hits with protein assays
  - If the antigen is from a family of closely-related proteins (e.g., MAGE antigens), then also look for TCR reactivity against similar epitopes in family members
    - If reactive, then survey human tissues for these family-member antigens

- Test for "off-target" autoreactivity against unexpected and unrelated antigens
  - Risk higher for animal derived or affinity enhanced TCRs
  - Screen for killing of cell lines
    - May need to use differentiated cells from various sources (e.g., iPSC-derived)
    - Product should kill only cell lines that express the intended antigen / HLA combination
  - Search human protein database for related epitopes
    - *In vitro* experimental approaches may be useful
    - **Basic BLAST search is insufficient**

One strategy to identify autoreactive TCRs

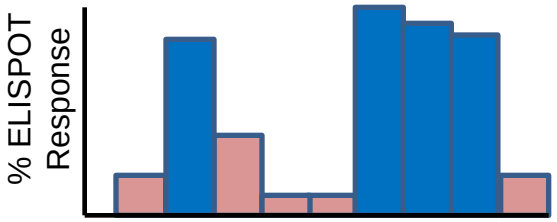
As described in: Cameron *et al*. Sci Transl Med. 2013 5(197); 197ra103

MAGE-A3 Epitope E-V-D-P-I-G-H-L-Y

Substitute each residue for alanine

A-V-D-P-I-G-H-L-Y
E-A-D-P-I-G-H-L-Y
E-V-A-P-I-G-H-L-Y
etc.

Test each peptide in ELISPOT assay with TCR expressing cells



"Core" Motif E-X-D-P-I-X-X-X-Y

If ELISPOT response drops significantly, the substituted residue is required for TCR recognition:
Use this data to define a "core" motif for the TCR

E-X-D-P-I-X-X-X-Y

Use core motif for database searches to identify potentially cross-reactive peptides

E-K-D-P-I-K-E-N-Y
E-F-D-P-I-Y-P-S-Y
E-S-D-P-I-V-A-Q-Y

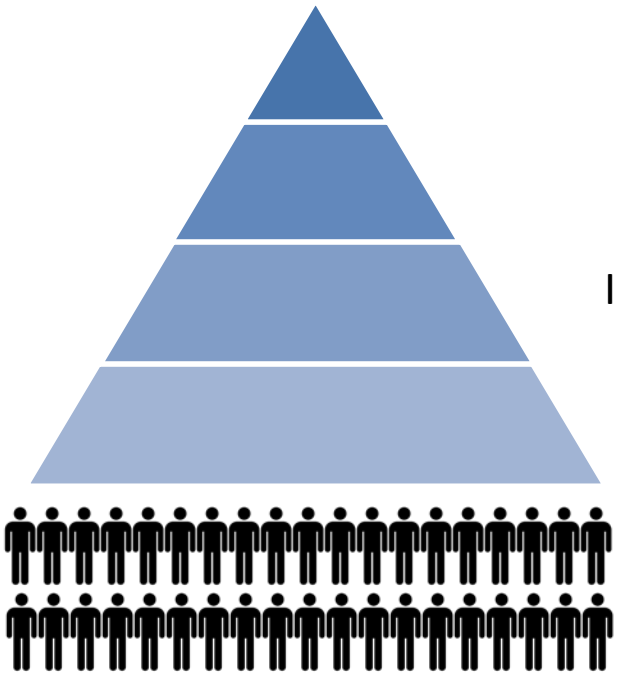
Test these peptides in ELISPOT assay with TCR expressing cells and/or MHC binding

Titin Peptide E-S-D-P-I-V-A-Q-Y

Personalized Medicine:
A different manufacturing paradigm

Conventional Drug/Biologic

1 product lot



Many patients

Raw materials

cGMP Manufacturing

In Process and Lot Release Testing

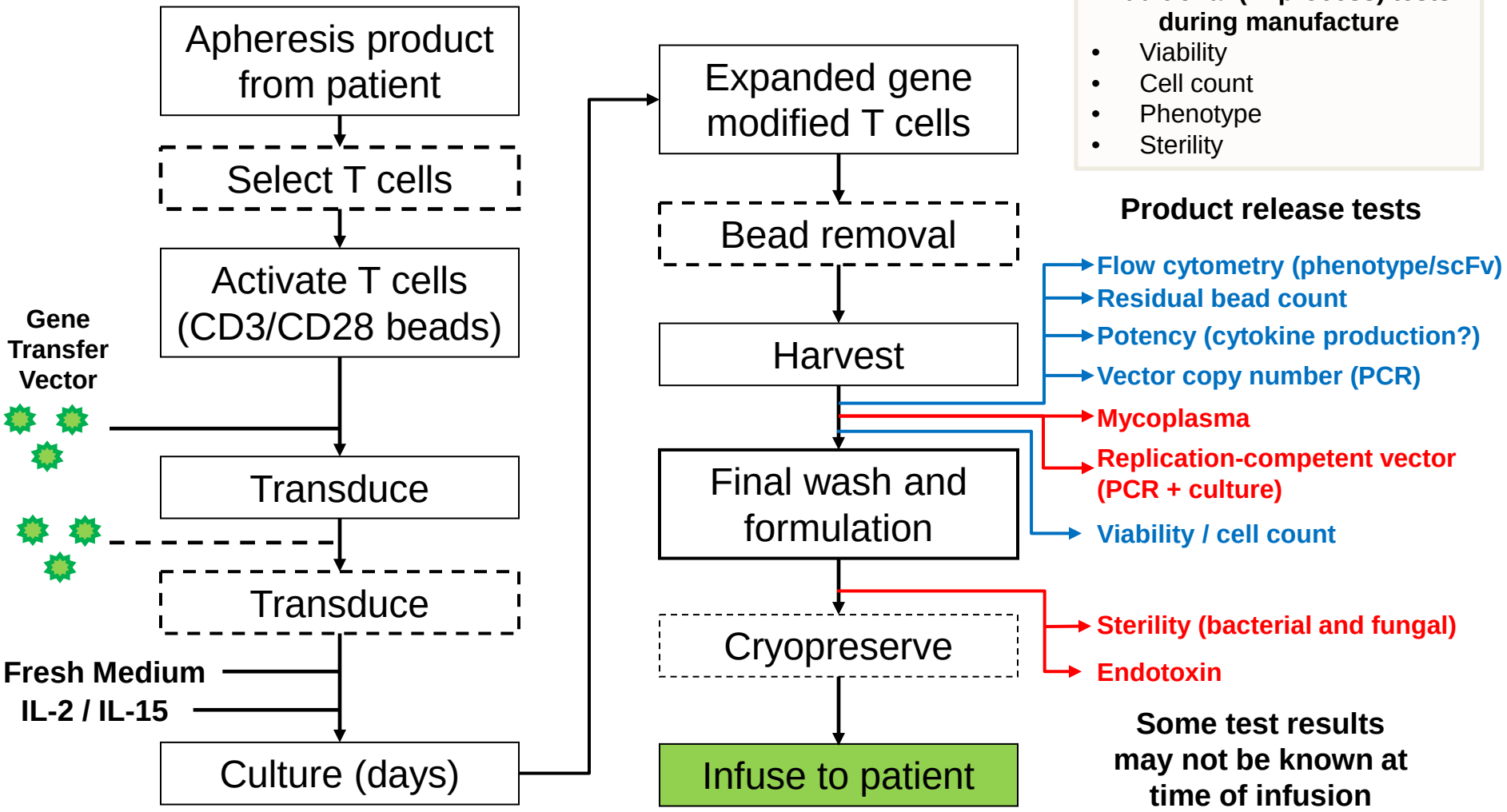
Distribution

CAR T cell

1 product lot

One patient

Gene modified T cell manufacture and testing



Vector manufacturing

- Construct usually delivered by Retroviral or Lentiviral vector
  - Stable virus producer cells (retrovirus)
  - Transient transfection (lentivirus)
- Vector often produced by contract manufacturer
- cGMP manufacturing required
- Cell banking system
  - requires extensive testing (adventitious agents)
- Initiate stability testing program (cell banks and virus)
- Vector lots must be tested for replication-competent virus (RCR/RCL)

Testing for replication-competent vector (RCR/RCL)

- **Culture based methods are "gold standard"**
  - Pro: Sensitive, detects wide range of RCR
  - Con: Expensive, time consuming, technically challenging
- **PCR-based methods** (e.g., detecting viral envelope gene)
  - Pro: Fast, inexpensive
  - Con: Might not detect all RCR, problems with false positive results
- **Test Master Cell Bank (MCB), each harvest of vector supernatant, and End of Production (EOP) cells for RCR using appropriate culture-based methods**
- **Test each *ex vivo* genetically modified product lot for RCR using culture- or PCR-based methods**

T cell manufacturing challenges

Supply chain vulnerabilities

- Many critical components from 3rd parties
  - Vector, media, serum, cytokines, stimulation reagents, consumables, test kits
  - Quality agreements with vendors
  - Material qualification and acceptance criteria to ensure suitability
  - Substitutes may not exist; if available, how will they affect product?

Product consistency

- Patient to patient variation in autologous T cell substrates
  - May depend on many factors including age, prior therapies
- Lot to lot variation in transduction efficiency
  - Standardization of Retro/Lentivirus vector stocks to give a constant multiplicity of infection (MOI)

Product tracking and labeling (chain of custody/chain of identity)

- Autologous products; critical to ensure patient receives the correct product

Manufacturing changes

Sometimes changes are unavoidable

- Scale up
- Facility changes
- Reagents or equipment changed/discontinued

Major changes require comparability testing

- New vector design, process changes, critical reagent changes etc.
- Comparability = similar product quality attributes pre- and post-change; no adverse impact on product quality, safety or efficacy
- Side by side studies of “old” vs. “new” product
- Use relevant biological and analytical assay methods

If comparability cannot be demonstrated FDA may require additional pre-clinical studies or clinical trials

Product testing challenges

In process testing

- Monitor cell proliferation/cell quality in real time
- Cell count, viability, (phenotype?)

Lot release testing

Parameter	Tests
Safety	RCR/RCL, sterility, endotoxin, mycoplasma, vector copy number per transduced cell
Identity	Presence of transgene sequence
Purity	Process and product-related impurities (residual BSA, antibiotics, etc.)
Dose	Number of viable T cells expressing CAR/TCR
Potency	Cytokine production, tumor cell killing, phenotype, etc.

Personalized products; time window for release testing may be limited

- Especially if products are to be given “fresh”

Choice of potency assay

- **Guided by proposed mechanism of action and pre-clinical proof of concept data**
- **Conduct product characterization studies throughout product development**
- **Evaluate multiple measures of product potency**
  - Can choose one assay for product release while continuing to collect data on other assays
  - Sometimes a single measurement may not be fully informative and a matrix approach may be needed
- **Assays should be chosen based on successful test method qualification using the product**
- **Validate assay performance prior to licensure**

Scientific Challenges

Testing for potency

- What potency assays are most appropriate?
  - Cytokine production, proliferation, or lytic activity when incubated with target cells?
  - Phenotypic characteristics by flow cytometry?
  - Does potency correlate with transduction efficiency?
    - Not necessarily (cells expand in patient post-infusion)

Is there an "optimal" T cell population?

  - Optimal for what? Persistence? Cytotoxicity? Cytokine production? Tumor homing? Safety (i.e., lack of toxicity)?
  - $CD4^+$ vs. $CD8^+$? $\gamma\delta$ or NKT? Effector vs. Naïve vs. Memory?
  - Select at start of culture or end of culture

What product attributes reflect product performance?

Early phase INDs: challenges

Preclinical studies

- *In vitro* specificity/characterization studies
- Animal studies of efficacy (where feasible and informative)
- Show proof of concept
- Comparing new products to previous iterations may be useful

Manufacturing

- Ensure quality of all product components (vector, reagents, cells)
- Develop manufacturing experience, show feasibility
- Make changes where necessary
- Develop and begin to refine tests
- Continual product characterization studies to inform testing

Engage with regulators early

- Pre-IND meeting

Pathway to licensure: challenges

Access to key reagents/ IP issues

- Need materials/reagents adequate for product manufacture
- Certain reagents often only available from a single supplier

Move from academic to industrial manufacturing settings

- Manufacturing capacity (patient-specific products: manufacturing currently labor intensive)
- Central manufacturing facilities?
- Comparability studies needed if manufacturing methods/sites changed between early and late stage studies
- Product characterization is critical

Summary

- **Gene modified T cells show promise for cancer therapy**
  - Chimeric antigen receptor (CAR) T cells
  - T cell receptor (TCR) modified T cells
- **Products moving rapidly from lab to clinic**
- **Products are complex**
  - Many subcomponents: Construct, vector, autologous cells
- **Complex manufacturing and testing**
- **Toxicity is a concern**
- **Scientific questions remain**
  - What construct elements dictate optimal product performance?
  - Better pre-clinical evaluation methods needed
  - What tests predict product performance?
- **Upcoming products likely to be even more complex**

FDA 101: CLINICAL REGULATORY CONSIDERATIONS AND APPROVAL PATHWAYS FOR (CAR-T) CELL & GENE THERAPIES

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Center for Biologics Evaluation and Research

Stanford/UCSF CERSI Lectures
November 2017

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- CD 19 CAR T Cell Safety Database pilot research project
- Resources and Contact Information

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FDA Regulation of Oncology Products

CDER

Office of Hematology and Oncology Drug Products (OHOP)

- Drugs (small molecules)
- Biologics
  - Monoclonal Antibodies
  - Therapeutic Proteins
  - Cytokines

CBER

Office of Tissues and Advanced Therapies (OTAT)

- Cell therapies
- Gene Therapies
- Oncolytic viruses
- Therapeutic vaccines and immunotherapies

CDRH

Office of In Vitro Diagnostics and Radiological Health (OIR)

- Companion Diagnostics

Oncology Center of Excellence (OCE)

Reviews require multidisciplinary input

Pharmacology & Toxicology

Statistics

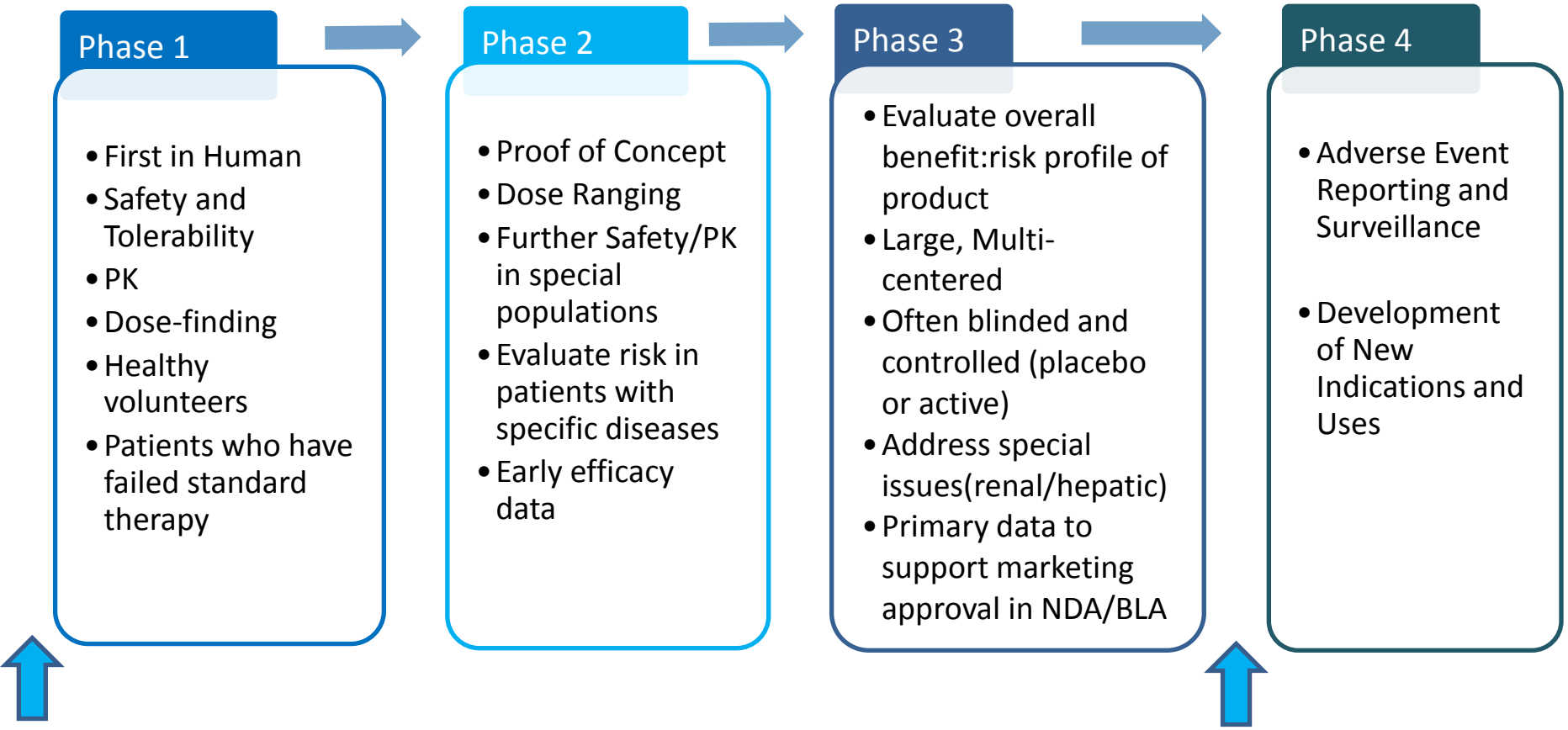
Clinical Pharmacology & Biopharmaceutics

Regulatory
Project
Management

Clinical

Product Quality (CMC)

Traditional Drug Development Progression

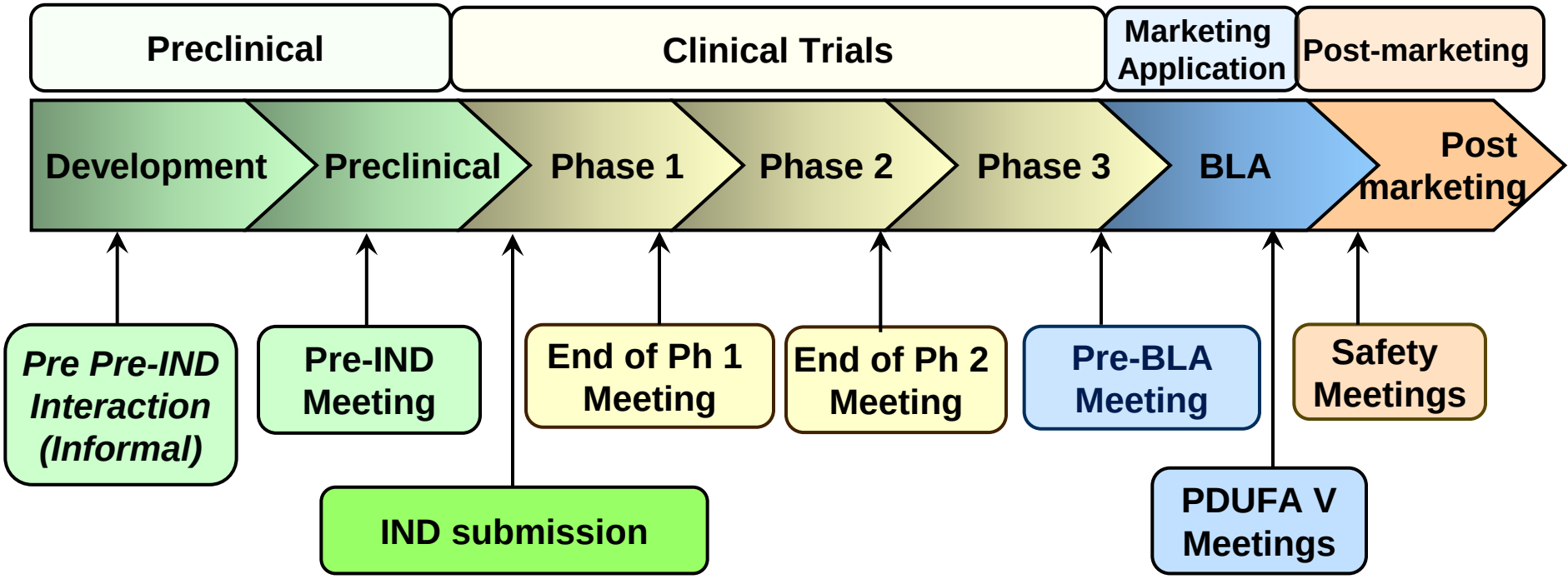


IND deemed safe to proceed

But distinctions between Phase 1, Phase 2, and Phase 3 trials are often blurred in today's environment

NDA/BLA approval

When to Approach FDA for Product Development Discussions



https://www.fda.gov/downloads/drugs/guidances/ucm153222.pdf

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What happens after you submit your IND to FDA?

The 30-day IND safety review

Regulatory Decision: Hold or Proceed

- FDA determines whether the following criteria are met in order for the IND to be considered "safe to proceed"
  - The study does not pose an unreasonable or significant risk of illness or injury
  - The study is adequately designed to meet its stated objectives

https://www.fda.gov/RegulatoryInformation/Guidances/ucm240323.htm

For Safety, Context is Important

- Who are the subjects?
  - Healthy volunteers
  - Patients with chronic disease
  - Patients with life-threatening cancer
  - Patients with potentially curable cancer
- Is there prior clinical experience with the drug/product?
  - Is this first-in-human (FIH), first-in-class (FIC)?

https://www.fda.gov/RegulatoryInformation/Guidances/ucm240323.htm

Eligibility Criteria

FDA considers

- Available therapies
- Seriousness of the disease
- Known toxicities and / or toxicity in animals
- Special populations (e.g., age, pregnancy)

Patient Monitoring

- Provide a calendar of events and ensure consistency with protocol and consent form
- Animal studies may be informative, e.g.:
  - ECGs if QTc concern
  - MUGA if cardiomyopathy is a concern
  - PFTs if pneumonitis is a concern
- Consider half life of drug
  - mAbs may require longer-term monitoring
- FIH studies may need frequent monitoring and labs due to unknown toxicities

Dosing / Dose Escalation

- Is the dose safe?
  - Based on toxicology data?
  - Prior human experience (this product, like product)?
- In a phase 1 study, what is the *next* dose?
  - Generally consider:
    - Half-log increments for biological drugs (log is generally aggressive)
    - Percentiles for small molecules (100% is generally aggressive)
- Intra-patient dose escalation typically not allowed for biologics for FIH
- Staggering of treatment between subjects / dose cohorts

Dose Limiting Toxicity

- Prevents excess toxicity during dose escalation
- Context important
  - Healthy volunteer versus late stage cancer
- Ensure *clear* definition
  - e.g., for cytotoxic drugs: Grade 4 (life-threatening) hematological toxicity or ≥ Grade 3 non-hematological toxicity (except alopecia or Grade 3 nausea, vomiting, or diarrhea lasting less than 48 hours).
- Provide justification for non-standard rules and exceptions
- For continuous dosing or long half-life: consider extension of DLT period of observation or incorporation of additional rules
- Early dose-escalation studies frequently find a recommended Phase 2 dose (RP2D) that is overly toxic (just by chance)

Study Stopping Rules

- Temporary pause in enrollment and treatment of additional subjects to prevent excess subjects from experiencing toxicity
  - Death
  - Increased incidence of expected toxicity
- Dose escalation studies usually consider DLTs
  - 3 + 3 or rolling-6 design
  - Bayesian or Continuous Reassessment Method (CRM) design
  - Other
- Recommend stopping rules for safety after dose-escalation phases
  - Can be based on severe / serious toxicity
  - Higher than expected cumulative incidence of a known toxicity
  - DSMB oversight may be sufficient

Dose Modification / Interruption

- Ensure clear and internally consistent rules
- Ensure rules are reasonable (e.g., interrupt / delay for life threatening cardiomyopathy, infection, etc.)
- Dose reduction may be appropriate following resolution of toxicity
  - For severe / life threatening diseases
  - For dose-related toxicities (e.g., neutropenia with a cytotoxic antibody)

IND Rules of Thumb

- **DO**
  - Provide justification for dose
  - Provide adequate monitoring plan
  - Expect comments from FDA that need a quick turn-around (~ 2-7 days)
  - Consider requesting a pre-IND meeting if trial / product is complex
- **DON'T**
  - Go "off the grid" after submitting an IND (without providing a contact who can be easily reached)
  - Copy/Paste irrelevant or incorrect information from other protocols

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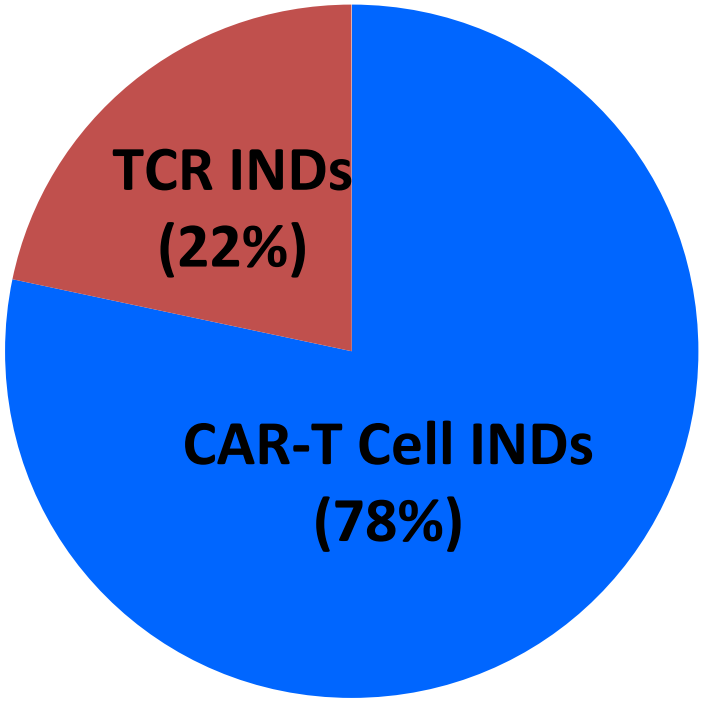
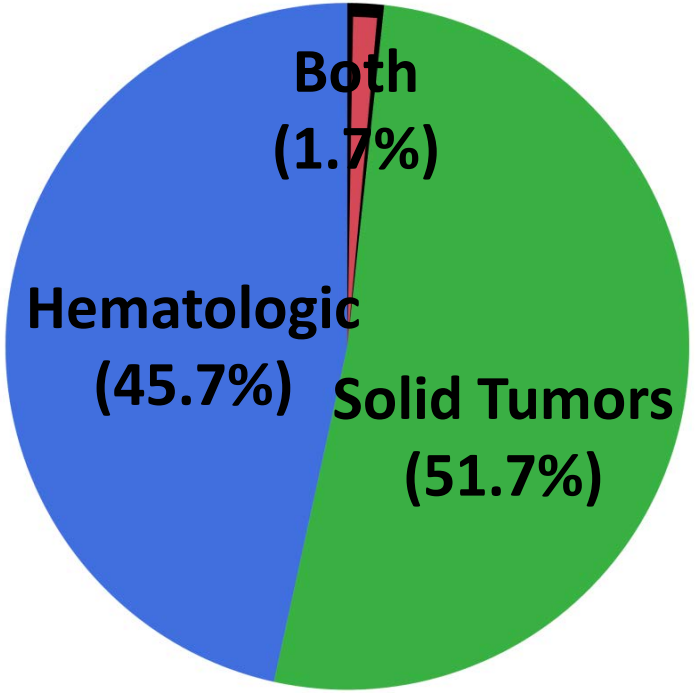
TCR and CAR-T cell products under CBER review





A total of ~140 TCR / CAR-T Cell INDs regulated by OTAT/CBER

As of October 2017

Regulatory Considerations

Patient Population

- Challenges in enrolling patients with different tumor histology (targeting a specific antigen regardless of tumor type)
  - Prior treatment requirements
  - Patient performance and organ function
  - Disease stage or severity
    - Risk-benefit considerations – most severely affected should not be the default choice
    - Lack of other treatment options
- Companion diagnostic for target identification
- Enrolling pediatric subjects / conducting pediatric studies

Regulatory Considerations

Treatment Plan

- Dose Selection
  - Role of preclinical data (allometric scaling for CGT products may be less precise than for small molecules)
  - Previous clinical experience with related products might be helpful
- Dose Description
  - Products mixture of various cell types
  - Variable gene transduction rates
  - Variable *in vivo* expansion
- Repeat administration
  - Staggering doses

Regulatory Considerations

Trial Design / Efficacy Endpoint

- Single-arm trial
  - Tumor response rate
  - Magnitude of the treatment effect
  - Duration
- Randomized controlled trial
  - Time to event (overall survival, progression-free survival)
  - Appropriate control
- Impact of concurrent treatments
  - Lymphodepletion
  - Chemotherapy tailored to patients with different tumor types
- Other factors confounding study results

Regulatory Considerations

Toxicities – 1

- Infusion reactions
- Cytokine release syndrome
  - Specify criteria used (CTCAE not sufficient)
  - Importance of monitoring cytokine levels
- Neurotoxicity
  - Type
  - Evaluations
    - Baseline
    - During Toxicity
    - End of treatment
- Other (cytopenias, cardiac)
- Optimal management for toxicities
  - Consideration for specific algorithms, hospital admission

Regulatory Considerations

Toxicities – 2

- On-target / off-tumor effects
- Off-target effects
- Long-Term safety concerns
  - Monitoring cell persistence over time
- Optimal management for toxicities
  - Short-term vs. long-term

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Regulatory Standard for FDA Approval of New Treatments

- Requires substantial evidence of effectiveness derived from adequate and well controlled investigation (1962 amendment to Food, Drug and Cosmetic act)
  - Clinical benefit demonstrated by showing an improvement in survival or quality of life, or an established surrogate for either (regular approval)
  - "An effect on a surrogate endpoint that is reasonably likely… to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." (accelerated approval)

Kefauver Harris Amendment –FD&C Act § 505(d), 21 USC 355(d) (1962)
See Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998

Requirements for BLA/NDA Approval

- Substantial evidence of effectiveness with acceptable safety in adequate and well-controlled investigations
- FDA examines the evidence in the context of the disease state, available therapy, study design, endpoints selected, and strength of the evidence
- Ability to generate product labeling that:
  - Defines an appropriate patient population
  - Provides adequate information to enable safe and effective use

Federal Food, Drug, and Cosmetic Act, Section 505

Expedited Development Programs

- Fast Track (FT)*
- Breakthrough Therapy (BT)*
- Regenerative Medicine Advanced Therapy (RMAT) Designation*
- Accelerated Approval (AA)
- Priority Review (PR)

* FT, BT, and RMAT may be rescinded if the product ceases to qualify under these categories

Comparison of Expedited Programs

Criteria

Fast Track	Breakthrough Therapy	RMAT	Accelerated Approval	Priority Review
-**Serious condition** AND -Nonclinical or clinical data demonstrate the *potential* to address unmet medical need Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-**Serious condition** AND -Preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	-**Serious condition** AND -It is a regenerative medicine therapy - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	-**Serious condition** AND - Meaningful advantage over available therapies - Demonstrates an **effect on** either: a **surrogate endpoint or an intermediate clinical endpoint**	-**Serious condition** AND -Demonstrates potential to be a significant **improvement in safety or effectiveness**

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Comparison of Expedited Programs

Features

Fast Track (FT)	Breakthrough Therapy (BT)	RMAT	Accelerated Approval (AA)	Priority Review (PR)
Frequent meetings Frequent written communication Eligibility for *: ✓ **Accelerated Approval** ✓ **Priority Review** ✓ **Rolling Review** *if relevant criteria are met	**All of FT Features** **+** ✓ **Intensive guidance** on an efficient drug development program, beginning as early as Phase 1 ✓ Organizational commitment **involving senior managers**	**All of BT Features**	Approval based on surrogate or intermediate clinical endpoints ✓ **Save valuable time** in the drug approval process. ✓ **Reduce waiting period to obtain clinically meaningful benefit.**	✓ **Short Review Clock** ✓ **FDA will Take action on an application within 6 months** (compared to 10 months under standard review).

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- **CD19 CAR T Cell Safety Database pilot research project**
- Resources and Contact Information

Pilot CAR T-Cell Database

- Assess feasibility of systematically collecting, storing and analyzing safety data from CAR T cell products to enable cross-study / cross-IND analysis.
- Develop predictive models to identify safety issues, leading to the development of risk-mitigation strategies.
- Two interactive databases:
  - Clinical Safety Database
    - CDISC / SDTM to facilitate safety data submission
  - CMC Information Database
    - impact of the manufacturing process on product quality
    - determine how critical product attributes contribute to safety

Contact Information

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  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber

Useful FDA Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- OTAT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

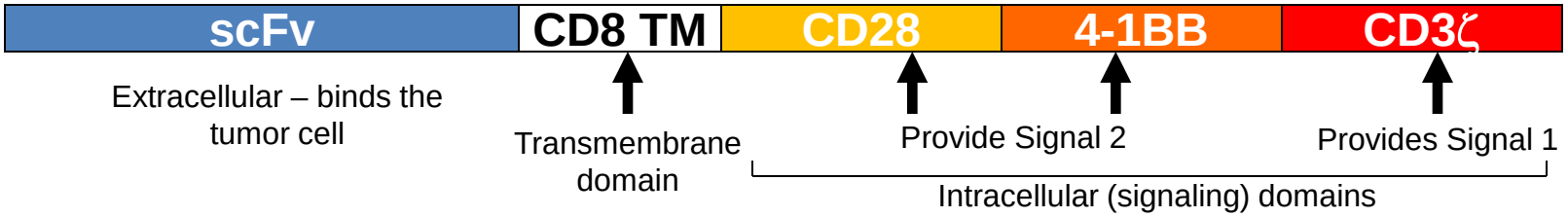
- Cell and Gene Therapy Guidances
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/

- Expedited Programs Guidance:
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Back Up Slides

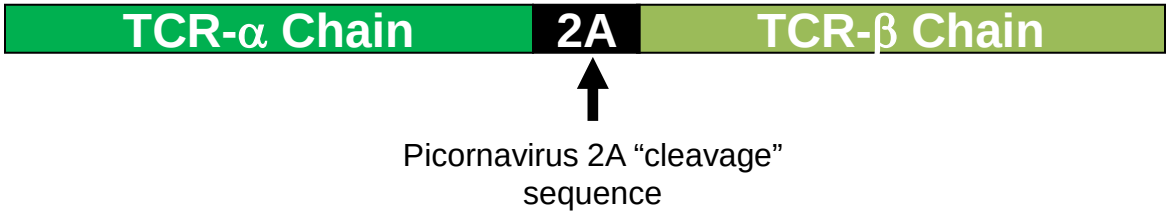
Basic construct design

CAR T cell construct



Constructs can include other elements (marker genes, “suicide” genes etc.)

TCR construct



TCR constructs can contain point mutations
(confer enhanced affinity to peptide-MHC complex, increased cytokine production etc.)

Future products: new targets

- **CAR T cells**
  - Currently mostly for hematologic malignancies
  - CD19 (2 licensed products), CD20, CD22, CD30, BCMA
  - Solid tumors?
    - Neuroblastoma (GD2)
    - Mesothelioma (mesothelin)
    - Glioblastoma (IL-13R, EGFRvIII)
    - Prostate (PMSA)
- **TCR products**
  - None licensed
  - Investigational products mostly target cancer testis antigens (MAGE-A3, MART-1, NY-ESO-1)
  - New methods to identify desirable TCRs and targets
  - Other cancer targets? Infectious diseases? Autoimmune diseases?

Future products: new constructs

- **Third and fourth generation CARs and beyond**
  - More (different?) intracellular domains
  - Auto-costimulation (co-express stimulatory ligand [e.g., 4-1BBL] with CAR) – "Armored CAR"
  - Co-expression of cytokines (e.g., IL-12) – "TRUCK" (T cells redirected for universal cytokine killing)
- **"Trojan horse" constructs**
  - Chimeric receptors fusing inhibitory receptor exodomain to stimulatory receptor intracellular domain (e.g., Mohammed *et al*. 2017; Mol Ther 25: 249)
  - Co-express with antigen specific CAR or TCR
  - Subvert immunosuppressive tumor microenvironment to promote T cell killing
- **Limitation of "on target, off tumor" toxicity**
  - Combinatorial targeting
  - Co-express inhibitory CAR (based on PD-1 or CTLA-4) that binds antigen expressed on non-tumor cells but **not** on tumor cells (Federov *et al*. 2013; Sci Trans Med 215ra172)

Future products: new combinations

- **Multivalent CARs**
  - Multiple scFvs to target different antigens simultaneously
  - Prevent tumor escape?
- **Checkpoint inhibitors/chemotherapy**
  - CTLA-4, PD1/PD-L1 inhibitors?
  - IDO inhibitors?
  - Promote T cell survival and function in tumor microenvironment
- **Engineered chemotherapy-resistance**
  - Protect T cells from concomitant cytotoxic drug treatment
- **Improved suicide genes/deletion methods ("Safety switches")**
  - Inducible caspases
  - Antibody deletion targets (e.g., tCD19 or EGFRt)
  - Might allow "tuning" of response

Future Products: Genome engineering

- **Allogeneic T cell platforms**
  - "off the shelf" platform therapy (not bespoke/patient specific)
  - Potential for Graft versus Host Disease (GvHD)
    - Genome engineering (CRISPR/Cas or Zinc-Finger Nucleases) to remove/suppress endogenous TCR?
  - Potential for rejection
    - Circumvented by immunosuppression?
    - Genome engineering to remove allo-MHC?
  - Possibly allow large batch manufacture
- **Increased potency, longer function**
  - Remove/suppress inhibitory receptors (e.g., CTLA-4, PD-1, TIM-3, LAG-3)
- **Challenges to genome engineering**
  - Off target effects?
  - Potential immunogenicity?
- **Non-viral transduction methods**
  - mRNA electroporation?
  - Plasmid/transposon-based systems

Future manufacturing

- **Automated manufacturing**
  - Product-dedicated cGMP facilities expensive
  - T cell manufacturing labor-intensive
  - Increasing interest in automated manufacturing systems
    - Self-contained
    - Disposable, closed system design
    - Automated processing steps
    - Built-in cell purification, culture/feeding, harvest
  - Increased manufacturing capacity
  - In process monitoring and controls still needed
  - Lot release testing still required
  - Replace dedicated facility? Probably not

Back up Slides – Expedited Programs

Regenerative Medicine Advanced Therapy (RMAT) Designation

- 21st Century Cures Act: Title III, Sections 3033-3036
  - Section 3033: Accelerated Approval for Regenerative Advanced Therapies
  - Creates program for designation as a regenerative advanced therapy
- A drug is eligible for designation if:
  - It is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, gene modified cell therapy, or any combination product using such therapies or products
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

https://blogs.fda.gov/fdavoice/index.php/2017/03/this-is-not-a-test-rmat-designation-goes-live/
https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Regenerative Medicine Advanced Therapy (RMAT) Designation

- Benefits of RMAT Designation
  - Early interactions with FDA to discuss any potential surrogate or intermediate endpoints to support accelerated approval
  - Interactions as specified for products granted breakthrough therapy designation
  - May be eligible for priority review
  - May be eligible for accelerated approval, as agreed upon during product development, based on:
  - Surrogate or intermediate endpoints reasonable likely to predict long-term clinical benefit, or
  - Reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate

https://blogs.fda.gov/fdavoice/index.php/2017/03/this-is-not-a-test-rmat-designation-goes-live/
https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Back up Slides – Expanded Access

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- FDA: Basics and overview
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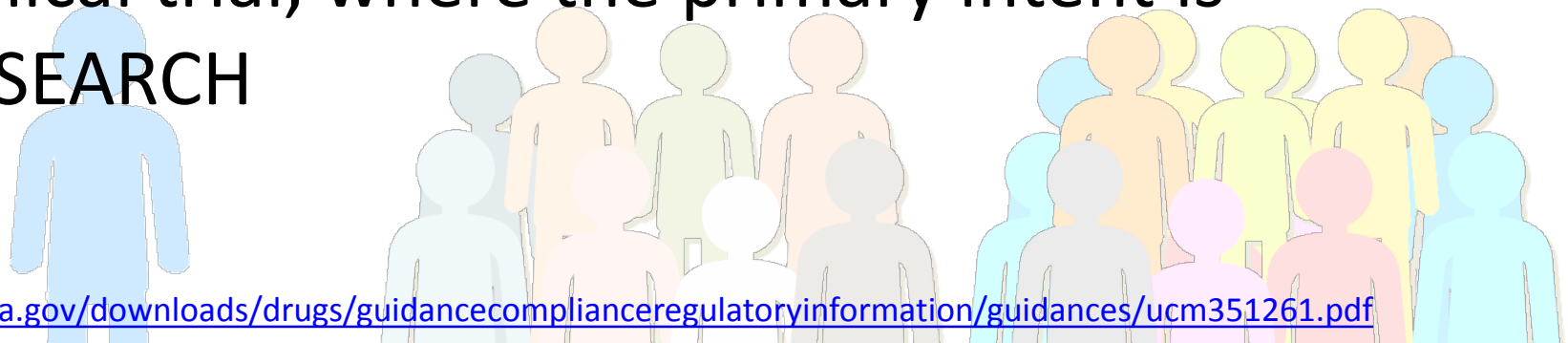
- **Expanded Access Program**
- CD 19 CAR T Cell Safety Database pilot research project
- Questions / Discussion
- Resources and Contact Information

What is Expanded Access?

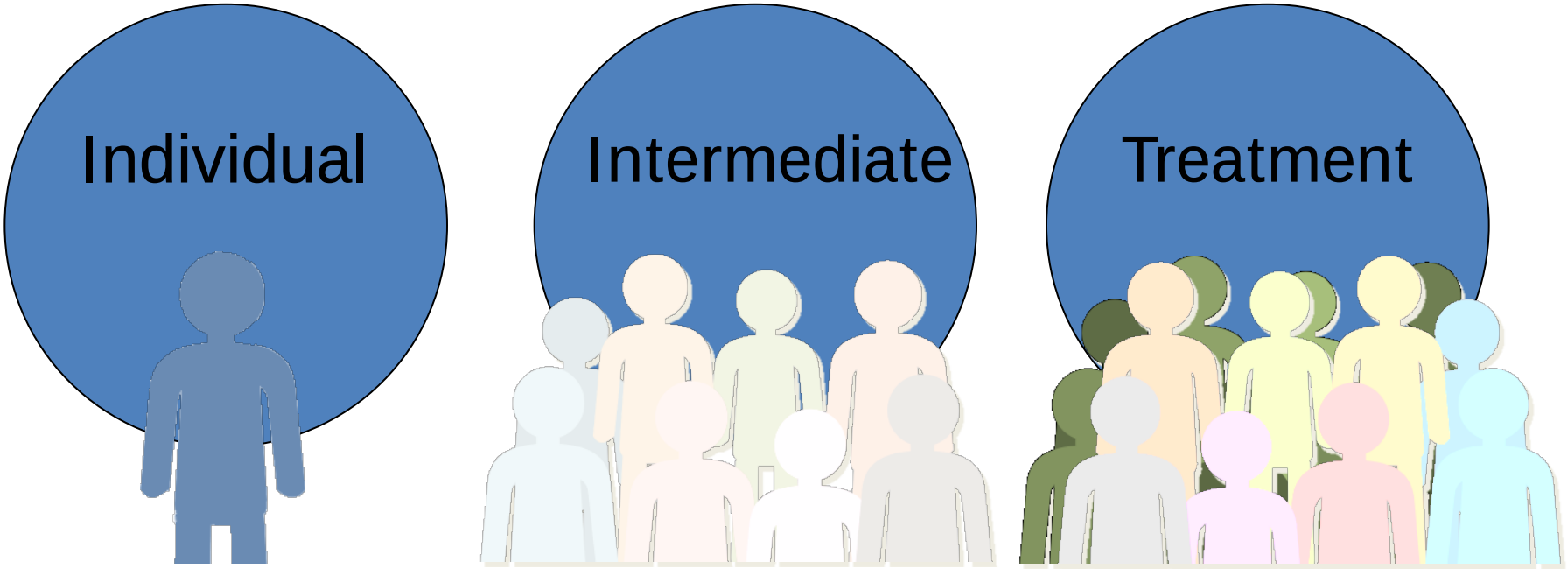
- Use of an investigational drug to treat a patient with a serious disease who has no other satisfactory options
- Intent is TREATMENT; also called "Compassionate Use"
- Contrast with using an investigational drug in a clinical trial, where the primary intent is RESEARCH



https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Types of Expanded Access Programs (EAPs)

There are three types of EAPs defined in the code of federal regulations:



https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Requirements for all EAPs

21 CFR 312.305

- Serious or immediately life-threatening illness or condition
- No comparable or satisfactory alternative therapy
- Potential benefit justifies the potential risks of the treatment (risks are not unreasonable in the context of the disease / condition being treated)
- Providing drug will not compromise product development

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Human Subject Protections Apply to <u>All</u> EAPs

Drugs used in EAPs are *investigational drugs*, and they are subject to the following requirements from 21 CFR:

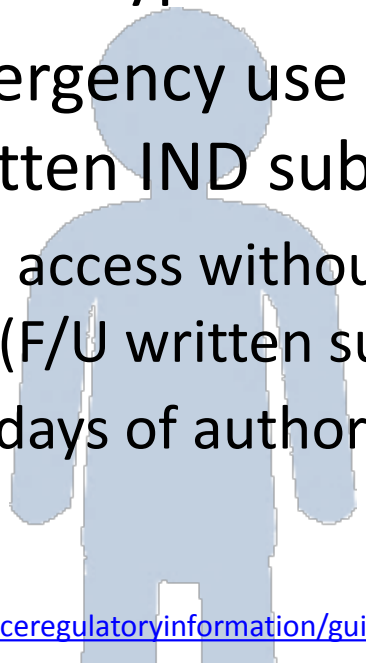
- Part 50 - Protection of Human Subjects (informed consent)
- Part 56 - Institutional Review Board
- Part 312 - including Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Individual Patient EAPs

21 CFR 312.310

- Physician must determine probable risk from drug does not exceed that from disease
- FDA must determine that the patient cannot obtain access under another type of IND
- Procedures for emergency use (when there is not time to make a written IND submission)
  - FDA may authorize access without submission, with very quick turn-around (F/U written submission required within 15 working days of authorization)



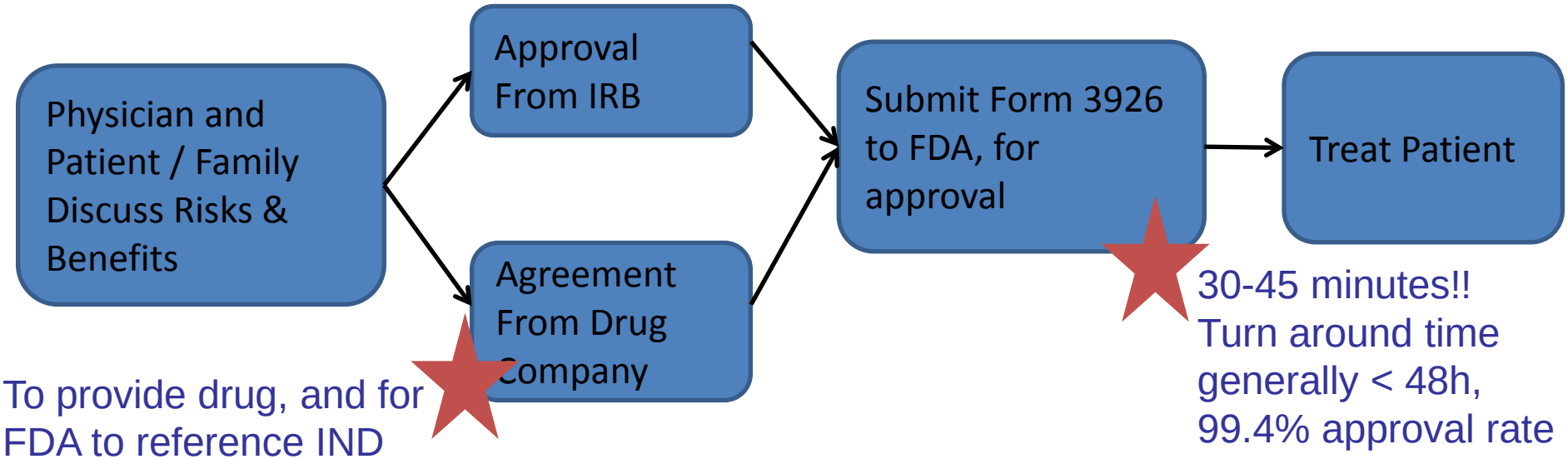
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Individual Patient Expanded Access

- Usually multiply-relapsed, refractory patients
- Reasons for requesting expanded access may include:
  - Promising evidence of activity with a similar molecular target or histology
  - Previous benefit from a clinical trial
  - Ineligible for clinical trial, but potential benefit is thought to outweigh potential risk
  - Clinical trial is closed to accrual
  - Drug is not currently being developed

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Obtaining a Single Patient IND

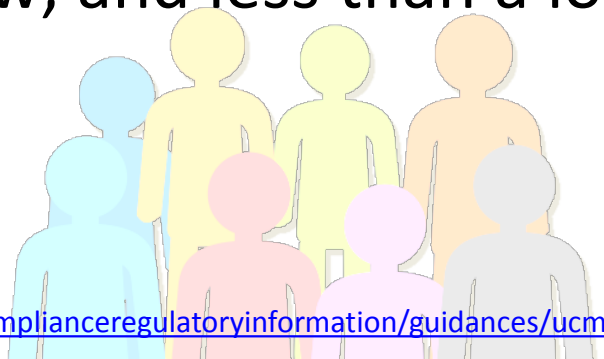


- Form 3926 is 2 pages and includes:
  - Brief medical history and rationale for trying drug
  - Proposed treatment plan with safety /efficacy monitoring
- Also submit:
  - Letter of authorization from sponsor
  - Investigator qualification statement / Form 1571

Intermediate Size Population

21 CFR 312.315

- Intended for situations where multiple patients with the same condition might benefit from a particular investigational product
- No set numerical parameters – meant to be practical
  - more than a few, and less than a lot

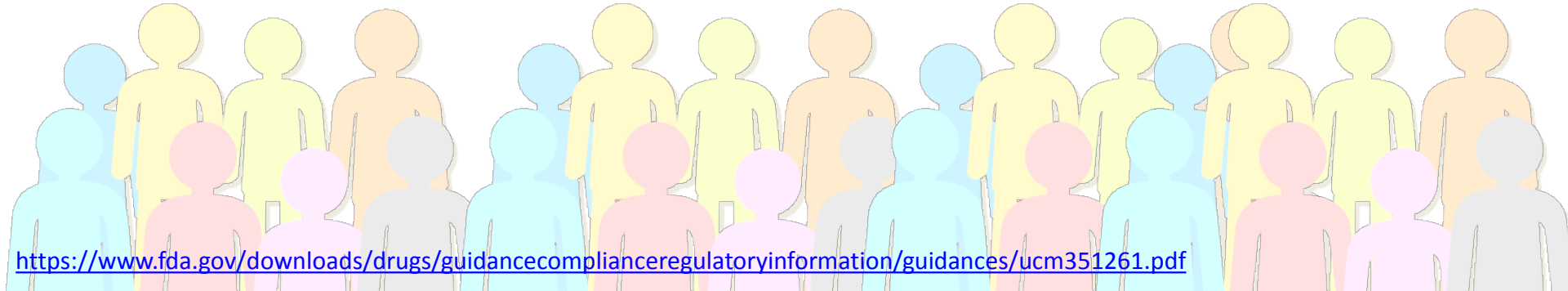


https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Treatment IND

21 CFR 321.320

- Drug is being investigated in clinical trial designed to support marketing, or trials are complete
- Company is actively pursuing approval
- Sufficient evidence of safety & effectiveness



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Back up Slides – Questions and Answers with Guidance Documents Referenced

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Question 1:

Concern: Cancer immunotherapeutics cannot rely solely on traditional toxicology studies for safety predictions.

Can the Agency provide guidance on the appropriate toxicology studies needed for proper safety predictions?

A: Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm376136.htm

Also consider a pre-pre IND or pre-IND meeting

Question 2:

The cost of opening a small cell production facility in order to produce cells for phase I trials is extremely high. Can the Agency provide more guidance on the core requirements of a cell production facility?

Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for **Human Gene Therapy** Investigational New Drug Applications (INDs) 4/2008

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm

Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for **Human Somatic Cell Therapy** Investigational New Drug Applications (INDs) 4/2008

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm

Question 3:

Clarify the regulatory guidance for cellular therapies for malignant and non-malignant hematology diseases and hematologic verses solid tumor indications. How does the FDA regulate cell-based therapies aimed at treating malignant versus non-malignant hematologic diseases? Is the regulatory path the same for both or is it different?

Answer : In general, the regulatory "paths" are the same for both malignant and non-malignant diseases. However the risk and benefit analysis will differ depending on the disease.

*In fall 2016, CBER underwent restructuring resulting in a new office, OTAT, which now includes a Clinical Hematology Branch, in addition to the Oncology Branch.

Question 4:

Repeat dosing - much needs to be learned about repeating dosing, and the patient's tolerability of each dose – this seems like a process that should be warranted and encouraged.

Why does the FDA discourage repeat dosing of cellular products on clinical trials?

Answer: The FDA does not discourage repeat dosing of cellular products. In fact the FDA would like encourage dose exploration in early clinical trials. However, for a first-in-human product, repeat dosing is not initially allowed. Once there is human safety experience, Sponsors should contact the agency to discuss exploring different dosing options.

Question 5:

Does the agency have any guidance regarding how to implement cost recovery of novel cell therapeutics after FDA approval to obtain cost recovery for a product manufactured under IND has been granted?

SOPP 8203: Evaluation of Cost Recovery Requests for Investigational New Drugs and Investigational Device Exemptions

https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/ucm336287.htm