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FDA Regulatory Considerations for Cancer Vaccines and Cellular Immunotherapy Products

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Outline

- FDA review of Oncology Products
- Approvals of cancer vaccines and cellular immunotherapy products
- Active areas of clinical research: personalized cancer vaccines and CAR-T cell therapy
- Regulatory considerations: manufacturing, pharmacology/toxicology and clinical
- Key considerations for CAR-T cell therapy
- Guidances

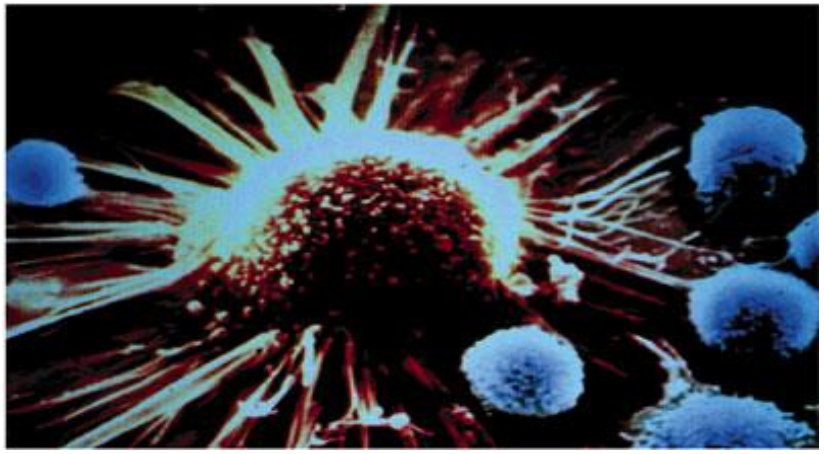
FDA Regulation of Oncology Products

- Oncology Center of Excellence (OCE)

- Office of Hematology and Oncology Drug Products (OHOP), CDER
  - Drugs (small molecules)
  - Biologics, including Monoclonal Antibodies, Therapeutic Proteins, Cytokines
- Office of Tissues and Advanced Therapies (OTAT) CBER
  - Cell therapies
  - Gene Therapies
  - Oncolytic viruses
  - Therapeutic vaccines and cellular immunotherapies
  - Microbiome based therapies
- Center for Devices and Radiological Health (CDRH):
  - Devices
    - Companion Diagnostics
    - Surgical and Delivery devices
    - Therapeutic devices

Cancer Vaccines and Immunotherapy Products – Evaluated by CBER OTAT

- Cells
  - E.g., dendritic cells, activated T lymphocytes (TIL, LAK), B cells, monocytes, cancer cells chemically modified or unmodified, *Ex vivo* gene modified cells (CAR-T cells)
- Tumor cell lysates
- Proteins, peptides
  - Mixed with adjuvants
  - Personalized vaccines
- Idiotypic and anti-idiotypic antibodies



Gene Therapy Products - Evaluated by CBER OTAT

- **Vectors Expressing Transgenes**
  - Plasmid DNA vectors
  - Replication defective viral vectors
  - Attenuated bacterial vectors

- **Gene Modified Tumor vaccines**
  - Non-viral and viral vectors expressing immunogenic molecules (e.g. TAA, TCR ligands, co-stimulatory molecules..)

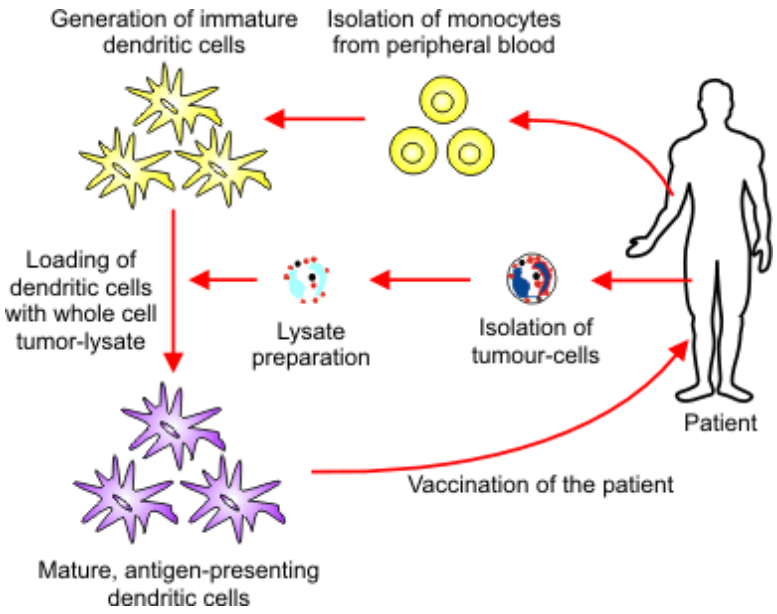
- **Gene Modified PBMCs and T cells**
  - Peripheral blood mononuclear cells (PBMCs) or purified T cells expressing chimeric antigen or T cell receptor

Oncology Gene Therapy Products contd..

- **Viral therapy (Oncolytic Virus) products**
  - Oncolytic viruses (OVs) - replication competent or attenuated viruses, e.g., adenoviruses, vaccinia, herpes simplex viruses, Newcastle disease virus (NDV) ….
  - OVs can be either naturally occurring or genetically modified, to achieve tumor-specific targeting and 'bystander' tumor cell killing, etc.

Cancer Therapy Products combined with other Biological Agents (e.g.,)

- Dendritic cells pulsed with tumor antigens, peptides, purified or recombinant proteins, cell lysates, nucleic acids or transduced with gene transfer vectors
- Cells cultured and expanded in growth factors or cytokines and administered as such or mixed with growth factors
- Tumor antigens or cells mixed with adjuvant (BCG, KLH, CPG, GM-CSF etc.) either injected separately or together
- Antibody, tumor antigen and adjuvant (anti-CTLA-4 Ab, peptide and montanide)



CBER Approved Oncology Products

- Provenge (sipuleucel-T) – Dendreon
- BCG Live (Intravesical) - TheraCys, Sanofi Pasteur Limited
- TICE® BCG (Intravesical) – Merck, Sharpe and Dohme Corp.
- Imlygic (talimogene laherparepvec) – Amgen
- Kymriah (tisagenlecleucel) – Novartis
- Yescarta (axicabtagene ciloleucel) - Kite

- HPC (hematopoietic progenitor cells), Cord Blood
  - Hemacord – NY Blood Center
  - Clinimmune labs, University of Colorado Cord Blood Bank
  - Ducord – Duke University
  - LifeSouth Community Blood Centers, Inc.
  - Allocord - SSM Cardinal Glennon Children's Medical Center
  - Bloodworks
  - Clevecord – Cleveland Cord Blood Center
  - MD Anderson Cord Blood Center

OTAT Regulated Products: Advanced Therapies at the Leading Edge

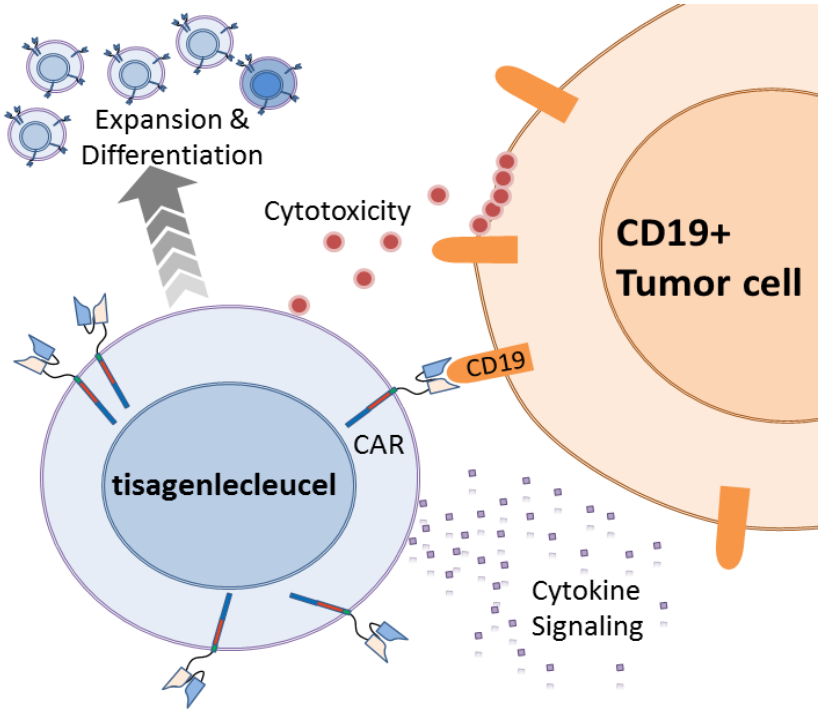
FDA News Release: FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia (Kymriah)

Yescarta is the second gene therapy product approved in the U.S.

For Immediate Release

October 18, 2017



Oncology Product Approvals in 2017

- Kymriah (tisagenlecleucel)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - For treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
  - For adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma (May 2018).

- Yescarta (axicabtagene ciloleucel)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Potential Applications of Genome Editing in Oncology Therapies

- Repairing genetic defect by insertion of a functional gene-coding sequence at a defined genomic location
- Disruption or removal of deleterious genes or sequences
  - Huntington's disease
  - Microbial genome
  - Potentially whole chromosome(s)
- Inactivation of normal genes for disease prevention and treatment
  - Infectious diseases (HIV)
- Gene modification of cell therapy product for improved therapeutic effect
  - Engineered T cell therapies

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Two active areas of clinical research in oncology

Personalized Neoantigen Vaccine

- Complex Manufacturing Steps
  - Tumor tissue source
  - Sequencing – various techniques
  - Bioinformatics
    - Identification of mutations of interest
    - Epitope prediction algorithms
    - Epitope selection and peptide design
  - Cross-reactivity with endogenous proteins
  - Rationale for antigen selection for minigene or peptide synthesis
  - Peptide and minigene synthesis, pooling & fill/finish, release

Challenges in Personalized Vaccine

- Every patient product is different
- Manufacturing steps are lengthy and time-sensitive
- Conventional Pharm/Tox studies may not be feasible
- Accuracy of prediction algorithm needs to be improved
- Neoantigen identification, and prediction that these molecules will induce protective immune response
- Autoimmunity remains a concern (vaccine cross-reactivity with endogenous protein)

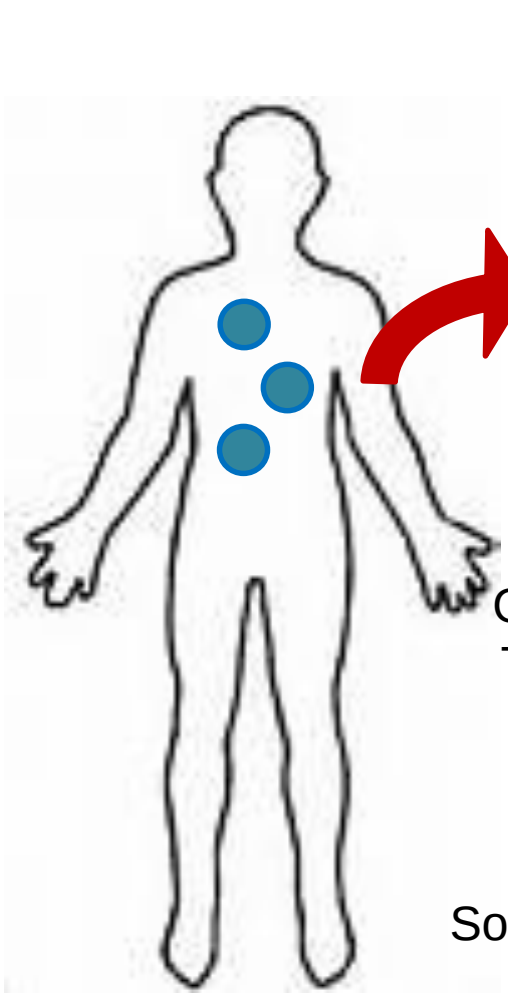
Peptide and plasmid Vaccine Product Quality

- Identify appropriate targets of therapies
- Safety, identity, purity and potency testing should provide meaningful information about the product prior to its release/use
- Appropriate tests and standards are critical
- Greater product knowledge (mechanism of action, characterization, etc.) will aid in developing meaningful assays and/or novel approaches for product characterization

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 (low affinity?)
- 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

T cell immunotherapy: Basic overview



Cancer patient

Apheresis Product

T cell activation and transduction with gene transfer vector

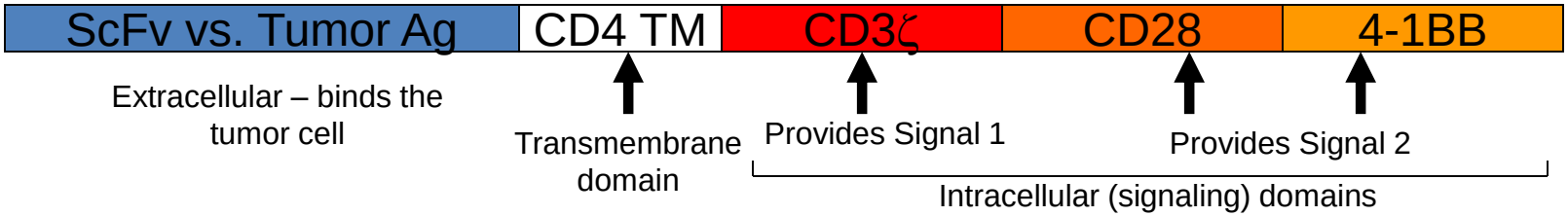
Expand in culture CD3/CD28 beads ± IL-2 / IL-15

Dose formulation Product testing

Gene modified T cell Infusion

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

Typical Chimeric Antigen Receptors (CAR) construct



- Antigen recognition via ScFv from a monoclonal antibody targeting Tumor Antigen (eg. CD19, Her2/neu, mesothelin, IL-13Rα2 or CEA)
- After ScFv binding to Tumor Antigen, the initial signal ("Signal 1") for transduced T cell activation is via CD3ζ intracellular domain
- Co-stimulation ("Signal 2") via CD28 and/or 4-1BB intracellular domains
- Signal 1 + Signal 2 triggers CAR T cell cytolytic function, cytokine secretion and proliferation

T Cell Therapies: T Cell Receptors (TCRs) vs. CARs

TCRs

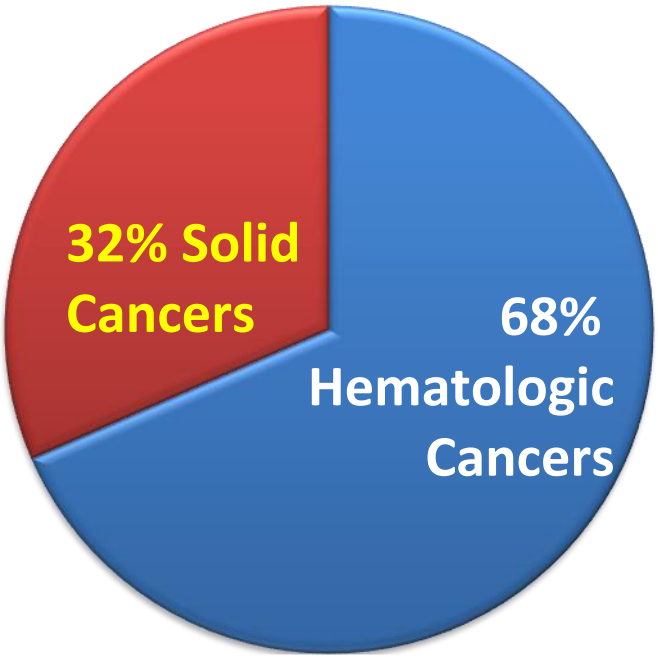
- Recognize intracellular proteins via the MHC system causing T cell activation and proliferation
- Despite having lower affinity and expression levels, TCRs may be more sensitive than CARs.
- Target specific antigens: NY-ESO-1, MART-1, etc.
- HLA restricted

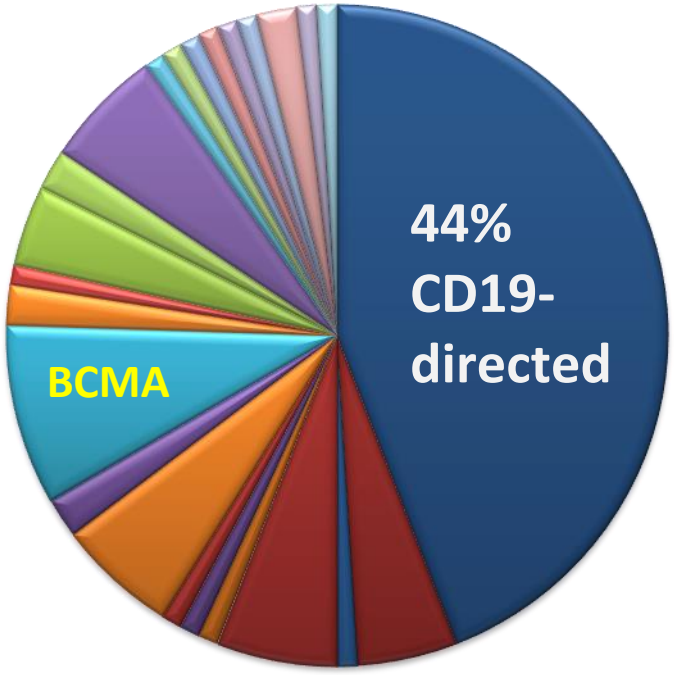
CARs

- Respond to cell surface antigens independent of MHC
- Synthetic constructs
- Higher affinity
- Generally single-chain antibody fragment
- Possible to construct bispecific CARS with multiple scFv fragments, each fused to different signaling domains for T cell activation

CAR T cell Targets

111 active CAR T cell investigations in OTAT as of 6/30/18





CD19:

- Expressed on B-cells
- Targets hematologic cancers

BCMA:

- B-cell maturation Antigen
- Expressed on malignant plasma cells

Key considerations for Product Characterization

- Importance of product characterization
  - To ensure lot to lot consistency, integrity, stability, demonstrate comparability
  - Quality of all product components (e.g., growth factors, cells) should be demonstrated
  - In process & final product testing (e.g., sterility, purity)
  - Sterility, safety, purity, potency of final product
  - Products with multiple active components- identity and potency

Key considerations for Product Characterization

- Greater product knowledge (mechanism of action, characterization) will aid in developing meaningful assays and/or novel approaches for product characterization and comparability

- Potency and identity testing would provide meaningful information about the product prior to its release/use – consider applying modern technologies

- For personalized products (autologous tumor vaccines and cellular immunotherapy); time window for release testing may be limited

CAR-T Cell Manufacturing Challenges

- **Product tracking and labeling**
  - Chain of custody/chain of identity
  - Autologous products must be tracked from apheresis to administration
- **Product consistency**
  - Patient to patient variation in autologous starting material
  - Control of manufacturing process, Shipping
  - Develop final specifications prior to efficacy studies
- **Changes in late stage development**
  - Comparability studies required to evaluate impact of manufacturing changes on product quality, safety or potency

Preclinical Considerations with CART therapies

- May not be a suitable animal model – need for specific preclinical studies determined on case by case basis
- Tissue cross-reactivity data should be provided to assess the potential for both on-target and off-target toxicity of novel targets
- **2nd genetic modifications**
  - Option to introduce a 2nd genetic modification from the beginning, vs. first establishing safety of unmodified CAR T cells – need to discuss rationale with preclinical branch
- **TCR vs. CAR preclinical requirements**
  - May vary depending on specific product and target
  - Case by case
  - Pre IND and “Pre Pre IND” advice

Clinical Considerations with Cancer Vaccines and Immunotherapy Products

- Patient enrollment - based on science
  - Known expression of target antigens in normal and tumor tissue
  - Preclinical evidence of activity in specific tumor
  - Stage of disease
    - Advanced disease may reach endpoint sooner
    - Earlier disease may be more immune competent
      - Vaccine may potentiate subsequent therapy

Clinical Considerations with Cancer Vaccines and Immunotherapy Products

- Distinct product mechanism of action requires different trial design
  - Defining optimal biologic dose (OBD) rather than maximum tolerated dose (MTD), proof of concept
  - Consideration of unique toxicity profiles and monitoring – may need long term follow-up
- Demonstrate Early evidence of activity/efficacy
- Estimate effect size for phase 3 planning
  - Consider randomized phase 2 studies

Clinical Considerations with Cancer Vaccines and Immunotherapy Products

- Measurement of Immune response is critical – Correlate kinetics of immunological and clinical responses
- Biomarkers
  - Support proof of concept
  - Immunological monitoring
  - Determine analytical properties of assays used to determine eligibility for enrollment

Clinical Considerations with CAR-T Cell Therapies

- CAR-T cell studies may enroll patients with different tumor histologies – "basket" design
  - Prior treatment requirements
  - Patient performance and organ function
  - May need companion diagnostics for identifying targeted antigen(s)
- DLT definitions based on expected toxicities
- Endpoints: Safety, optimal dosing, response rates
  - Randomized studies may not be feasible
  - Role of CAR-T therapies in earlier-stage disease?

Lessons Learned from CD19

- Cytokine release syndrome (CRS)
  - Importance of monitoring cytokine levels
  - Persistence of CAR-T cells
  - Proactive use of Tocilizumab
  - Neurological Toxicities
  - Need for uniform DLT grading system
  - Cardiopulmonary evaluation and monitoring to recognize and treat CRS quickly
- Potential for off-target effects
  - Pre-clinical studies may not be informative
  - Clinical monitoring and cautious dose escalation
  - DLTs based on potential tissue cross reactivity

Off Target Toxicities (with TCRs)

- CNS Toxicity
  - 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

    (Morgan *et al*. J Immunother. 36(2); 680-8, 2013)

- Cardiac Toxicity
  - Human affinity-enhanced TCR targeted against MAGE-A3 / HLA-A*01 (Also reacts against similar epitopes in MAGE-A6 and MAGE-B18)
  - Rapidly fatal cardiac toxicity due to unexpected “off target” TCR cross-reactivity with Titin (a muscle protein)

    (Cameron *et al*. Sci Transl Med. 5:197 2013)

CAR-T Therapy for Solid Tumors

- Challenges
  - Target identification, distinguishing from normal tissue, avoid off target effects
  - CAR-T trafficking and homing to tumor site to mediate cytotoxicity despite immunosuppressive microenvironment
  - Solid tumor antigens may be expressed in cytoplasm, less accessible to CARTs
  - Thus far, CART in solid tumors less successful than for hematologic malignancies

- Opportunities
  - Application of knowledge gained from CAR-T for hematological malignancies
  - Enhance CART function with genetic modifications to recognize novel antigens, multiple antigens
  - Expression of cytokines to avoid immunosuppressive microenvironment
  - Potential to address unmet medical needs

Kakarla S, Gottschalk S, Cancer Journal (20:2) 2014

Future:
CAR-T Cell Products

- **Allogeneic CAR T cells**
  - "Off the shelf" platform therapy (not patient specific)
  - Potential for Graft versus Host Disease (GvHD)
    - Genome editing (e.g., CRISPR/Cas9) to remove/suppress endogenous TCR?
  - Potential for rejection
    - Requirements for immunosuppression?
- **Suicide genes/deletion methods**
  - Inducible caspases, antibody deletion targets
  - Allow control of severe toxicities
- **Non-viral transduction methods**
  - mRNA electroporation?
- **Fresh vs. cryopreserved cells**
  - More time for release/characterization testing
  - Delay pre-conditioning until a product passing release tests is available
  - Allow re-dosing?

Facilitating Cancer Therapeutics Product Development: Collaboration with NCI & Professional Societies

- Interagency Oncology Task Force (IOTF)
  - Facilitates interagency collaboration
  - Supports FDA/NCI joint fellowship training program
    - NCI supported training in cancer-related scientific research and regulatory review
    - http://iotftraining.nci.nih.gov/index.html
- Joint workshops with NCI and Professional Societies
- FDA Liaison to SITC, AACR, ASCO, Patient advocacy groups)

CBER Guidances

- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines 2009
- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products 11/2013
- Guidance for Industry: Considerations for the Design of Early Phase Clinical Trials of Cellular and Gene Therapy Products 6/2015
- Guidance for Industry: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines and Related Recombinant Viral or Microbial Products 3/2015.
- Guidance: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products. 8/2015

Summary

- Numerous cancer vaccines and cellular immunotherapy products are in various stages of product development
- Cancer vaccines and cellular immunotherapy products have unique scientific and regulatory challenges
- CAR T cell science is a moving target and maintaining regulatory flexibility as knowledge improves is key to effective drug development.
- FDA has published various guidance documents that are helpful for cancer vaccines and cellular immunotherapy product development
- Communication with the FDA throughout product development is recommended

Useful FDA Information

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

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

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Peptide and plasmid Vaccine Characterization

In general, CMC expectations for therapeutic peptide or plasmid vaccine quality are similar to other therapeutic products of the same type and class of the products, e.g.,

- Cell-based vaccines can mostly follow quality attributes of other cell-based products
- Peptide and plasmid vaccines can use regulatory guidelines of other peptide/protein and plasmid products