FDA's Regulatory Perspective on Individualized Neoantigen-specific Cancer Vaccines

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CASSS Cell & Gene Therapy Products. Manufacturing, Quality and Regulatory Considerations

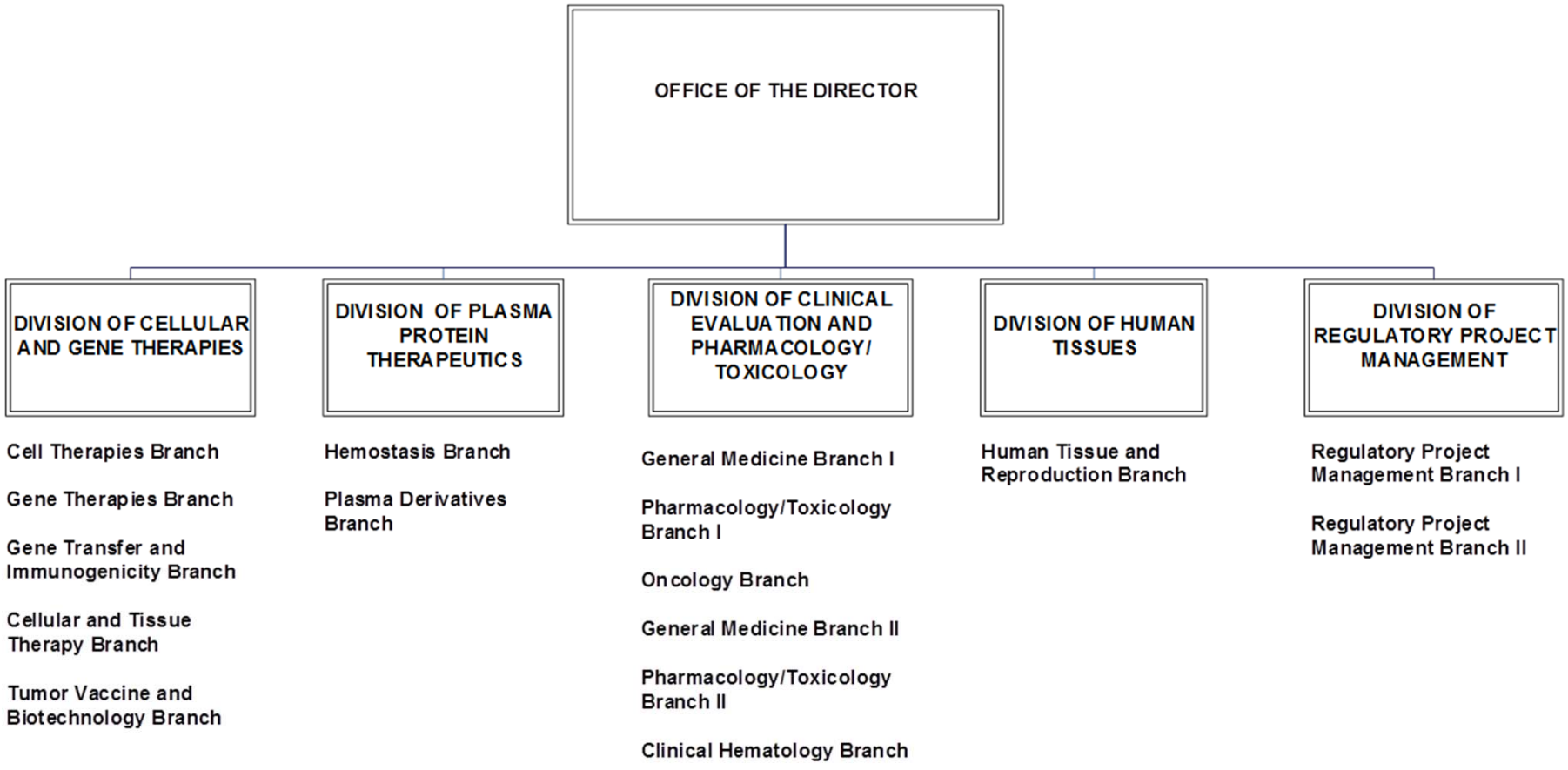
Disclosure

No financial relationships to disclose

Overview

- Office of Tissues and Advanced Therapies (OTAT), CBER
  - Organization and regulated products
- Cancer vaccines and immunotherapy products
  - General regulatory considerations for products
- Therapeutic peptide-based vaccines
- Personalized peptide vaccine and challenges
- Summary

Office of Tissues and Advanced Therapies



Products Regulated by OTAT

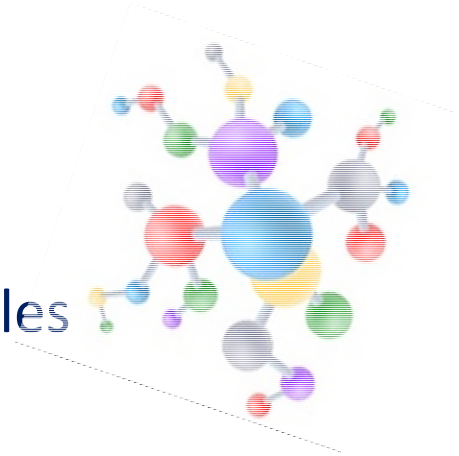
- **Stem Cells/Stem Cell-derived**
  - Hematopoietic, neural, mesenchymal
  - Placental, umbilical cord blood
  - Fetal, embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Somatic Cells**
  - Retinal pigment epithelial cells
  - Pancreatic islet cells
  - Chondrocytes
- **Gene Therapies**
  - Genetically-modified cells
  - Replication-competent vectors
  - Non-viral vectors
  - Viral vectors
  - Genetically modified organisms
- **Combination Products**
  - Tissue-engineered and regenerative medicine products
- **Cancer Vaccines/Cellular Immunotherapies**
  - Peptides
  - Protein-based products
- **Blood Products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulin
  - Snake venom antisera
- **Devices**
  - IVD, apheresis, PRP, cord blood, cell delivery, scaffolds seeded with cells etc.
- **Tissues**
  - Bone, skin, corneas, ligaments, tendons, dura mater, heart valves etc.

FDA's Regulation of Oncology Products

- **Office of Hematology and Oncology Drug Products, CDER**
  - Drugs (small molecules), Biologics including Monoclonal Antibodies Therapeutic Proteins, Cytokines
- **Office of Tissues and Advanced Therapeutics, CBER**
  - Cell Therapies
  - Gene Therapies
  - Oncolytic Viruses
  - Therapeutic Vaccines and Cellular immunotherapies
- **Center for Devices and Radiological Health (CDRH)**
  - Devices
    - Companion Diagnostics
    - Surgical and Delivery devices
- **Oncology Center of Excellence**
  - Oversees clinical review for all drugs, biologics, and devices used in medical oncology, a joint effort to create unified review policy approach

Cancer Vaccines and Immunotherapy Products

- Cell-based vaccines
  - e.g., dendritic cells, activated T lymphocytes (TIL, LAK), B cells, monocytes, cancer cells chemically modified or unmodified, *Ex vivo* gene modified cells.
- Tumor cell lysates
- Proteins, peptides
  - Mixed with adjuvants and/or nanoparticles
- Plasmid-based vaccines
- Virus-based vaccines
- Idiotypic and anti-idiotypic antibodies



Therapeutic Vaccines in OTAT

- More than 150 active clinical trials using peptide-based vaccines
- Most IND sponsors are investigators from academic institutions
- Peptides procured from contract manufacturer
- Often no Master File submitted from contractors
  - CBER highly recommends to submit DMF
  - Limited manufacturing information given by manufacturer
  - Incomplete/inadequate Certificate of Analysis submitted

Therapeutic Peptide Vaccines

- Most being used as cancer vaccines
  - Others for Neurodegenerative Diseases, Autoimmune Diseases, etc.
- Peptide or proteins that are tumor associated antigens (TAA)
  - Self-antigens, mutated self antigens (neoantigens), and tumor specific antigens
- Can be complex
  - Multiple peptides
  - Fused or mixed with adjuvants (e.g. KLH, Montanide etc.)
  - Combined with checkpoint modulators (e.g. anti-CTLA4, anti-PD1 antibodies etc.)
  - Other components (e.g. liposomes, polymers etc.)

Peptide Vaccine Characterization

In general, CMC expectations for therapeutic peptide 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 vaccines can use regulatory guidelines of other peptide/protein products

Peptide 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

Vaccine Product Safety Testing

- **Endotoxin** (LAL or equivalent)
- **Sterility** (21CFR 610.12: test must be appropriate for the test material and validated for the specific product). Revised as of April 1, 2018
- **Mycoplasma** (21CFR 610.30, PTC 1993 or cell substrate guidance), only for cell-based products (e.g. dendritic cells pulsed with peptides)

Personalized Peptide Vaccines

- Tumors being immunogenic elicit adaptive immune response, and peptide-based cancer vaccines can harness that immune response.
- Encouraging results from the first generation short peptide-based (9-10 amino acids) vaccines prompted exploration of next generation vaccines using longer peptides 20-35 aa.
- Lately, personalized vaccines tailored to match a patient's cancer mutations are developed for clinical translation.
- These tumor-specific neoantigens are antigens generated by somatic mutations that can be recognized by the host immune system for personalized cancer vaccines.

Advantages of Targeting Neoantigens

Tumor-Associated Antigen

- Self antigen
- Expressed in multiple tumors
- Higher risk of self-tolerance
- Susceptible to immune-selection
- Antigen loss variants common
- Higher risk of autoimmunity

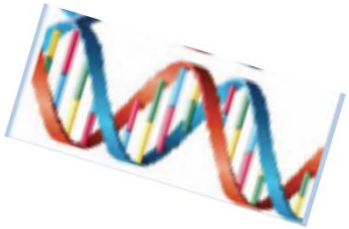
Neoantigen

- Non-self antigen
- Unique to individual tumor
- Lower risk of self-tolerance
- Resistant to immune-selection
- Antigen loss variants less common
- Lower risk of autoimmunity

Zhang *et. al.* Vaccine, 2017

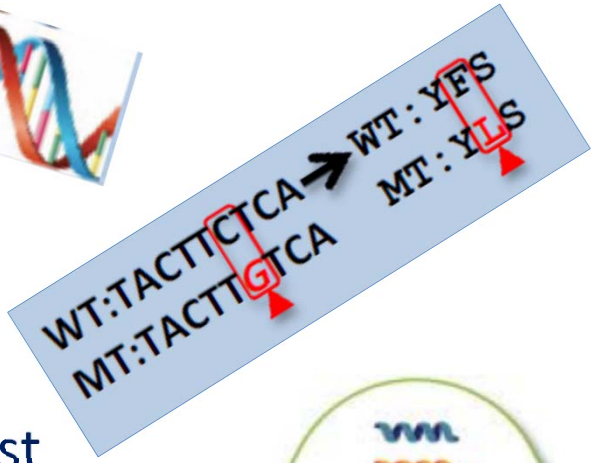
Personalized Neoantigen Vaccine

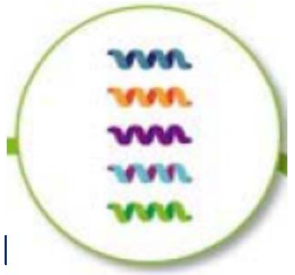
Individual peptides are manufactured matching the patient's cancer mutations



Manufacturing Steps

- Tumor tissue source
- Sequencing – which technique
- Bioinformatics
  - Identification of mutations of interest
  - Several thousand mutations/tumor
  - Prioritize for immune targeting using computer based prediction algorithms for HLA binding
  - Candidate epitope selection and peptide design

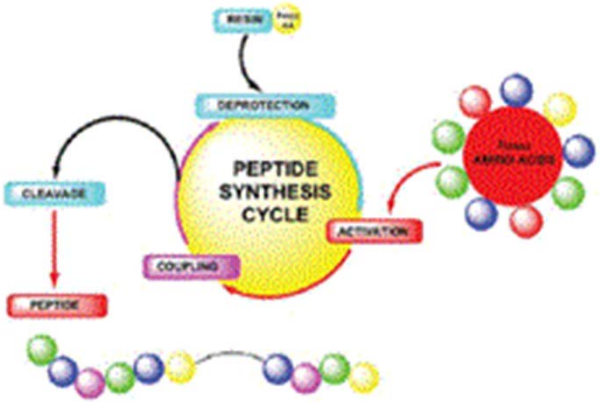




Personalized Neoantigen Vaccine

Manufacturing Steps – cont'd….

- Cross-reactivity with endogenous proteins
- Rationale for neoantigen selection for peptide synthesis
  - Predicted binding can be validated and ranked by *in vitro* binding of neoantigen with HLA allele of interest
- Peptide synthesis
- Pooling & fill/finish
- Release



Challenges in Personalized Peptide Vaccine

- Every patient product is different
- Manufacturing steps are lengthy and time-sensitive
  - Purity and yields could be production issues
  - de novo DS production feasible but challenging
- 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)

Typical CoA of Peptide Drug Product

Test	Method	Specifications	Results
Lot #		XXX-12-017	-
Date of manufacture		November 17, 2017	-
Appearance (cake)	Visual	White solid	White solid
Moisture	Karl Fisher	<3%	0.7%
Appearance (liquid)	Visual	Clear, colorless solution	Clear, colorless solution
pH	pH Meter, USP<791	3.5 to 5.5	4.6
Identity	RP-HPLC, MS	Conforms to standard	conforms
Peptide concentration	RP-HPLC	0.61 – 0.82 mg/ml (for each peptide)	Peptide 1: 0.48 mg/ml Peptide 2 : 0.97 mg/ml Peptide 3: 0.87 mg/ml Peptide 4: 0.77 mg/ml
Purity	RP-HPLC	90%	97.0%
Osmolality	USP<785>	244-364 mOsm/kg	300 mOsm/kg
Sub-visible particles	HIAC – liquid particle counting system	10 mm counts: ≤8000 per container 25 mm counts: ≤600 per container	10 particles per container 1 particles per container
Endotoxin	USP<85>	≤500 EU/mL	<6.0 EU/mL
Sterility	USP<71>	No growth	Pass

Common Deficiencies at the End-of-Phase 2 Studies

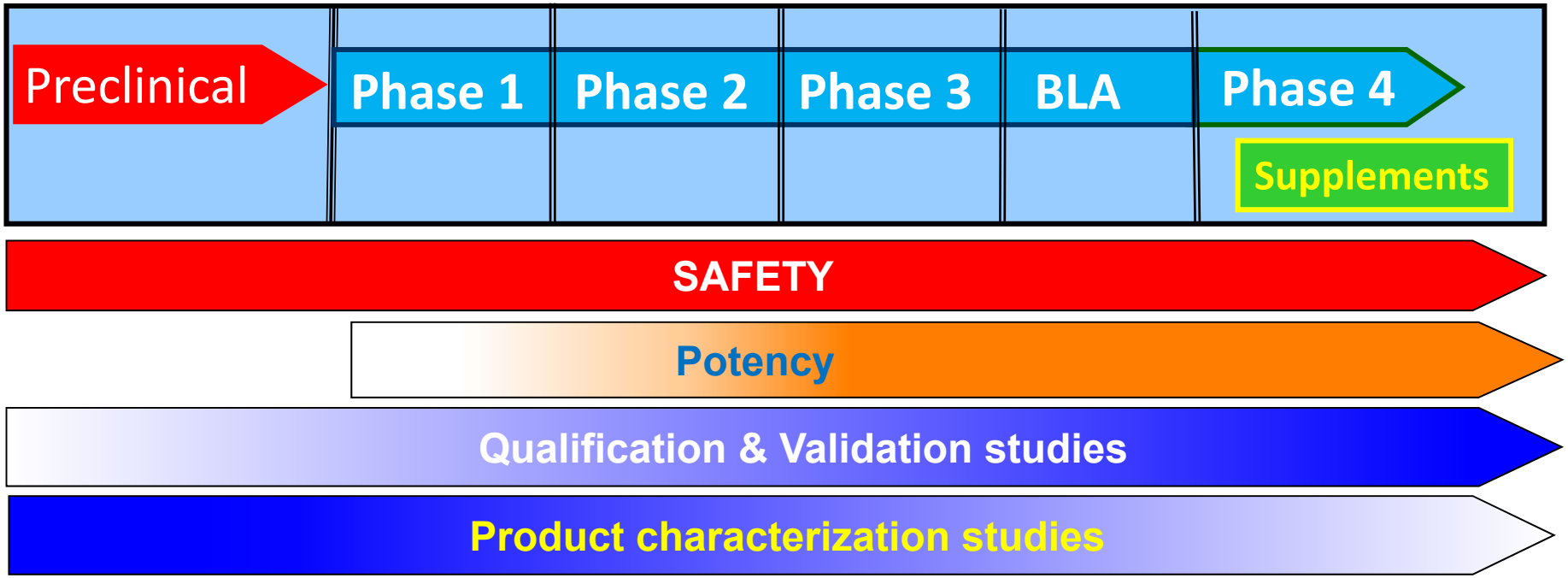
- Stability protocols not fully developed
- Stability data missing
- Potency assay qualification and validation
  - The word potency is interpreted to mean the specific ability or capacity of the product…to effect a given result. (21 CFR 600.3(s)
  - Tests for potency shall consist of either *in vitro* or *in vivo* tests, or both, which have been specifically designed for each product so as to indicate its potency (21 CFR 610.10)
- Comparability studies, if applicable

Lot Release Specifications are Interrelated

We recommend you to choose them carefully and apply them where needed.

Phases of Clinical Investigation

The stage of product development guides the review concerns, with safety always being the primary concern at all stages.



- Product characterization occurs throughout the lifecycle but critical details should be determined early
- Some qualification studies are required for phase 1 to ensure safety, but most qualification/validation studies typically do not occur until late in the lifecycle
- Some properties (e.g. stability, purity, identity, etc.) overlap both safety and potency

Summary

- Vaccine development is a complex and challenging process
- Personalized vaccine provides advantages over conventional peptide vaccines, but needs improvement
- Feasibility is demonstrated, clinical effects encouraging but small sample size
- Recommends sponsors to perform right level of product characterization to ensure product quality
- Lot release specifications should be carefully considered
- Encourage sponsors to communicate early with the FDA/OTAT

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

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

- Guidance for Industry Clinical Considerations for Therapeutic Cancer Vaccines
  https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm278673.pdf

- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products at
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf

- Draft Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptides Drug Products that Refer to Listed Drugs of rDNA Origin
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andas-certain-highly-purified-synthetic-peptide-drug-products-refer-listed-drugs-rdna-origin

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