RAPS 2021 Convergence

T-cell Therapies – A Primer

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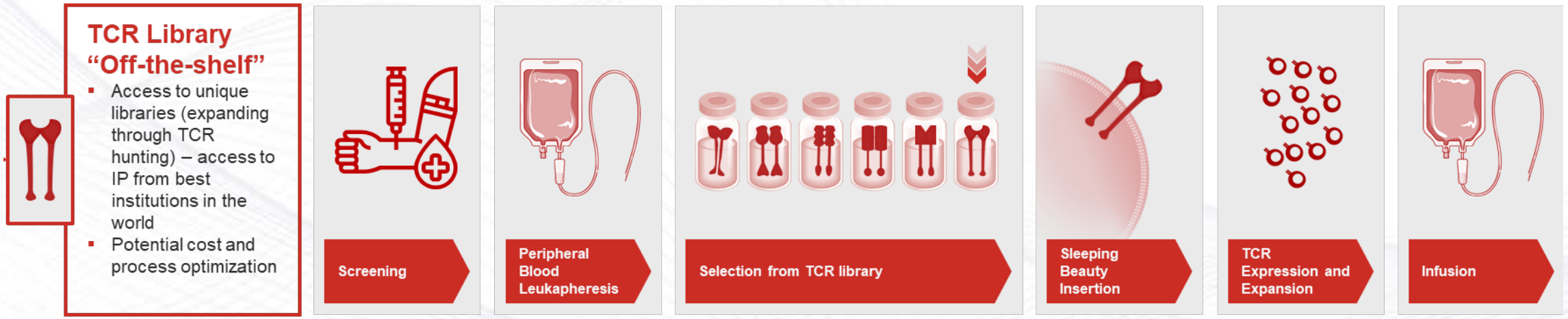
Outline

- Ziopharm's Cell Therapy Program
- Gene/cell Therapy Products and Regulatory Considerations
- Development Considerations
  - Nonclinical
  - CMC
  - Clinical
  - Agency interactions
- Key Takeaways

Cutting-Edge Ziopharm Programs for TCR-T Cell Therapy in the Treatment of Epithelial Cancers



Ziopharm is the first and currently only commercial group evaluating library TCR-T cells targeting shared "hotspot" neoantigens in the non-viral setting.

Product Uniqueness and Regulatory Considerations

- Regulatory Principles
  - Identity, purity, potency, etc.
  - Nonclinical assessment of safety – representative of clinical product
  - Adequate well controlled studies
  - Overall benefit/risk
- Tell Your Story
  - Module 2
- Regulatory Pathways
  - Orphan Drug Designation (ODD)
  - Accelerated / Conditional approval
  - Breakthrough Designation (BTD) / Priority Medicine (PRIME) / Regenerative Medicine Advance Therapy (RMAT)

Development Considerations

- Nonclinical
  - Toxicology and animal models
    - If no relevant animal models, pharmacology / *in vitro* package need to address potential safety concerns
  - Key aspects
    - Anti-tumor effect
    - Potential toxicities
      - On-target off-tumor
        - e.g., in-silico sequence homology and *in vitro* data
      - On-target on-tumor
        - e.g., cytokine release syndrome (CRS), neurotoxicity, etc.
    - Potential risk of cell transformation
      - Vector copy number (VCN)
        - Need to tie into manufacturing data
      - Integration site analysis

Development Considerations

- CMC
  - DS
    - Plasmids and vectors – same level of details as DS; Module 3.2S
      - Highest quality material
      - Lot-to-lot consistency
  - DP
    - Health donor vs. patients' cells
    - All reagents for cell selection and growth
    - Development runs versus GMP runs – representative material
    - Media runs to demonstrate aseptic processing
    - Vector copy number (VCN) – tie it to nonclinical data
    - Fresh vs frozen product
      - Sterility testing

Development Considerations

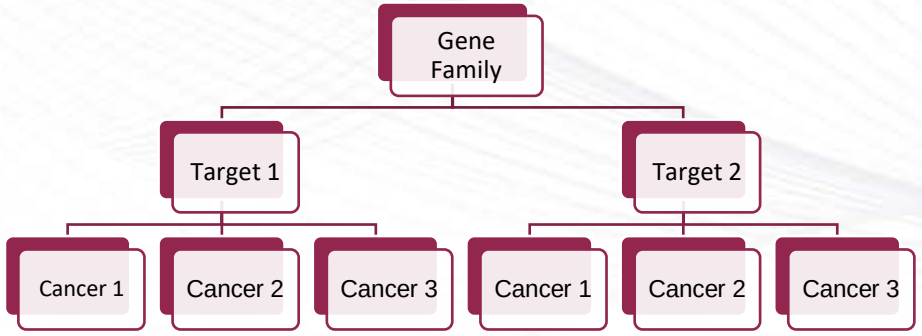
- CMC (cont'd)
  - Potency*
    - Process consistency – runs with similar and different donor cells
    - Matrix and progressive approach
      - Multiple assays
        - Mechanism of action and biological activity
        - Qualitative vs quantitative
      - Stages of development

*Final Guidance for Industry - Jan. 2011: Potency Tests for Cellular and Gene Therapy Products.

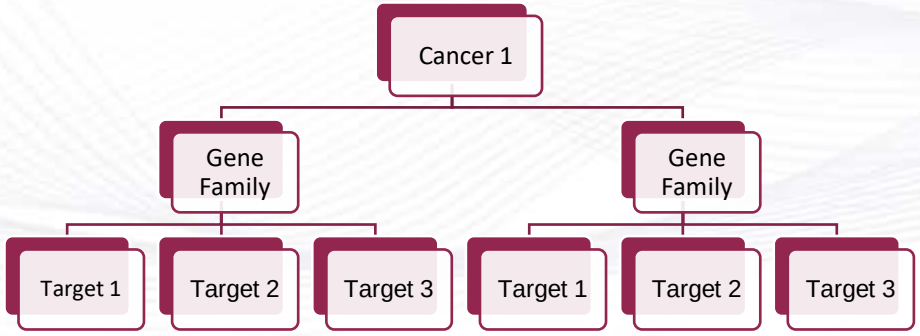
Development Considerations

- Clinical
  - Development strategy mostly driven by targeted therapy portfolio and indications of interest
  - Possible frameworks for targeted therapies

Basket Framework



Umbrella Framework



Development Considerations

- Clinical (cont'd)
  - Identification of targets and HLA alleles (if applicable)
    - CLIA certified labs and validated methods, e.g., NGS
  - Chain of identity throughout the process
  - Eligibility criteria needs to be specific
  - Rationale for dose selection
  - Clear study pausing/stopping rules

Agency Interactions

- INTERACT meeting
  - Leverage it for new innovative technology
  - Pre-IND still an option following INTERACT meeting
- Align with EU CA and/or EMA early even if clinical trials not initially conducted in Europe
  - Particularly if entering Phase 2 in US only that may lead to expedited approval pathways
- Timely feedback on CMC specific topics if progressing into late-stage development

Key Takeaways

- Gene/cell therapy products unique but regulatory principles and pathways still apply
  - Remember the “case-by-case” rule
- Nonclinical
  - Robust *in vitro* package particularly in the absence of animal models
  - On-target off-tumor toxicities
  - Risk of cell transformation
- CMC requires extra strategic and operational planning
  - Characterization
  - Potency
  - Phase readiness to support clinical development
- Clinical plan mostly driven by:
  - Targeted therapy portfolio
  - Indications and unmet need congruent with therapeutic hypothesis
- Leverage Agency interactions to facilitate development