Nonclinical Considerations for Cell-Based Products

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Cell-based products regulated by CDE

- Stem cell-derived cells
  - Adult (hematopoietic, mesenchymal, cardiac, neuronal, adipose)
  - Perinatal (placental, umbilical cord blood)
  - Fetal, (amniotic fluid, neuronal)
  - Embryonic
  - Induced Pluripotent Stem Cells (iPSCs)
- Functionally mature / differentiated human cells (i.e. chondrocytes, islet cells,hepatocytes, neuronal cells, variousimmune cells,etc.)
- Cell-based Vaccines:DC vaccines,neoantigen vaccines
- Genetically modified cells: CAR-T/NK、TCR-T、iPSC、Cell-based products derived from genome editing

Safety Concerns

- Ex vivo manipulation (i.e. expansion, genetic modification)
- Potential inflammatory / immune response to the administered CT (i.e. allogeneic)
- Inappropriate cell proliferation (i.e. tumor formation)
- Inappropriate cell differentiation (i.e. ectopic tissue formation)
- Cell migration to non-target sites / tissues
- Gene modification
  - Vector insertion/intergration/transformation
  - Unintended immune responses to vector or transgene
  - Transgene effects

Strategy for nonclinical Evaluation

- Case by case，product by product

  No “one-size-fits-all”

- Guidelines
  - Guideline on quality, non-clinical and clinicalaspects of Cellular Therapy Products , 2017.12
  - Guideline on non-clinical aspect of medicinal products containing genetically modified cells（draft）,2021.3
- Genetically modified cell products regulated as cellular therapy products
- Review on benefit : risk profile

Nonclinical Testing Program

- Proof-of-concept (POC)

  in vitro and in vivo

- Cell fate

- Safety
  - System toxicity
  - Tumorigenicity
  - Special considerations for genetically modified cells

Data Supporting IND submission

- GLP-compliant toxicology studies
- Proof-of-concept studies
- Pharmacokinetics studies
- Published data in peer-reviewed journal
- Detailed clinical study reports from clinical trials

Communication With CDE

- Pre-pre IND
  - Non-binding
  - early communication, discussion of specific issues
- Pre-IND
  - Non-binding, formal, scientific discussion
  - Preclinical data package (all completed preclinical studies), to support the use of specific product in a specific patient population

Challenges for nonclinical Evaluation

- Tumorigenicity assessment of cell-based products and timing
- The selection of animal species and disease/Injury model，and the predictability of the non-clinical data
- The evaluation of potential off-target editing in cell-based products derived from genome editing
- The evaluation of potential off-target toxicities of TCR modified immune cells and CAR-T cells

Thank You

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