TGA considerations for preclinical studies of cell therapy products

Asanka Karunaratne, PhD
Toxicologist
Toxicology Section
Scientific Evaluation Branch

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• Cell therapy is a broad field:
  – Large range of applications/indications
    ▪ E.g. Bone marrow transplants, neural cell replacement, heart repair, cartilage and/or bone replacement or cancer treatment (CAR-T-cells)
  – Large range of cell types:
    ▪ E.g. If stem cells: Mesenchymal Stem Cells (MSCs), Haematopoietic Stem Cells (HSCs), Neural Stem Cells (NSCs), Embryonic Stem Cells (ESCs), Induced Pluripotent Stem Cells (iPSCs), or large range of progenitor or differentiated cell fates
    – Each indication and/or each cell type carries unique and context-related challenges

• Cell therapy is multidisciplinary:
  – Therefore, difficult to take issues in isolation

• Cell therapy is fast paced and dynamic
Challenges: Preclinical Evaluations (Overview)

• Knowledge gap:
  – Multidisciplinary convergence
  – Dynamic, fast-paced clinical development (increases gap between fundamental and translational research)
  – Complacency

• Suitability of animal models:
  – Immunological response; can impact on safety and efficacy
    ▪ Even in absence of immune response, susceptible to species specific differences
  – Biological context; cells are live entities, therefore understanding biological context important for their utility
Challenges: Preclinical Evaluations (Overview)

• Biologically active dose
  – Identification of biological active dose complicated; influenced by factors such as:
    ▪ Indication (location)
    ▪ Mechanism of action (often, not well characterised)
    ▪ Type of cell therapy (i.e. differentiated cell fates, progenitor cells or naïve stem cells)
    ▪ Stochastic nature of cell proliferation and differentiation (depends on final resting position of cells)
    ▪ Stochastic nature of distribution (post infusion/transplant)
    ▪ Stochastic nature of cell survival (post infusion/transplant)
The Knowledge Gap
The ‘Knowledge Gap’

Multidisciplinary convergence

**Molecular Biology**

**Cell culture**

**Proteomics**

**Developmental Biology**

**Immunology**

**Genomics**

‘Convergence’
The ‘Knowledge Gap’

• So what is a knowledge gap (in the context of cell therapies)?
  – It is essentially ‘gaps’ in knowledge between the disciplines
  – The ‘knowledge gaps’ have implications for safety and efficacy assessments
    ▪ Often incumbent on the nonclinical evaluator to accommodate the ‘knowledge gaps’ when performing an evaluation

• Reason for the ‘knowledge gap’
  – Different rates of progress between fields
  – Different rates of progress within fields
    ▪ i.e. fundamental to translational research transitions are out of step
  – Insufficient technological progress
    ▪ Analytical/detection methods
    ▪ Tissue culture techniques
The ‘Knowledge Gap’

• Reason for the ‘knowledge gap’ (continued)
  – Complacency
    ▪ Due to convergence of entire disciplines it is sometimes “just too hard” to cover *all* essential aspects
      • “just too hard” = cost prohibitive?
  – Over-reliance on limited published data to bridge gap between “therapeutic potential” → clinical application
    ▪ Most published data demonstrate “potential”, but lack sufficient depth in safety and efficacy findings
  – Over-reliance on evolutionarily conserved cellular response
    ▪ Cells demonstrate robust survival and differentiation potential many circumstances
      • E.g. in bone marrow transplants
    ▪ Other circumstances require precise handling and manipulation of cells to achieve desired results
      • Where this is not possible, the field as a whole, tends to imply the cells can ‘compensate’ for precise handling and manipulation (i.e. “The cell knows what to do”)
The ‘Knowledge Gap’

The notion of “The cell knows what to do” is insufficient to bridge knowledge gap and thoroughly evaluate safety and efficacy aspects of pre-clinical studies.
The ‘Knowledge Gap’

Exampled 1: Using the ‘homing’ potential of Mesenchymal Stem Cells (MSCs) to treat various diseases:

• Published evidence of ‘homing’
• Homing mechanisms not extensively characterised or clearly defined
• When ‘homing’ does occur, characterisation is limited:
  – i.e. Quantification within target tissue, distribution relative to damaged cells/tissue sections, long-term integration and/or propagation or phenotype characterisation
• The fact that ‘homing’ happens is often assumed to be sufficient for clinical application
  ▪ However, in the absence of accurate MOA, quantification and characterization, non-clinical evaluation of safety and efficacy is challenging.
The ‘Knowledge Gap’

Exampled 2: Cell replacement therapies (e.g. diseases of the central nervous system)

• Published evidence of limited replacement potential
• Replacement mechanisms not extensively characterised (in vivo)
  – Number of cells requiring replacement
  – Appropriateness of neural connections
  – Longevity of replaced cells/neurons
• Lack of characterisation sometimes due to technological limitations
  – Quantification of cells and connections within target tissue difficult
  – Assessing accuracy of replacement connections difficult
    ▪ Since original connections haven’t necessarily been appropriately resolved
• Therefore, difficult to reconcile animal model outcomes with histology data
Appropriate Animal Models
Appropriate animal models

• **Common issue; immunogenic responses (with clinical product)**
  - Can use immune compromised animals
    ▪ However, doesn’t always allow for appropriate disease model to be used

• **Often overlooked; biological context in which model is used**
  - Classical toxicological studies – consider pharmacology, pharmacodynamics, ADME, carcinogenicity etc
  - In cell therapies – concepts such as molecular signalling also need to be considered

• **Temporal regulation, not discussed in cell therapy models**
  - Concept especially relevant to stem/progenitor cell therapies
  - Lack of consideration of temporal regulation by-product of the ‘knowledge gap’
    ▪ Not necessarily a shortcoming of animal models *per se*
    ▪ However concept required addressing when using animal models
Appropriate animal models

Temporal regulation

• Gestation periods of common pre-clinical animal models:
  – Mouse 19 days (~85% genome conservation with humans)
  – Rat 21-23 days
  – Canine Av 61 days
  – Monkey 164 days (95% genome conservation with humans)
  – (Humans 259-280 days)

• Increased gestation time likely due to increased cell count in larger animals
  – There is also increased molecular signalling coordination required with increasing size
    ▪ This process requires additional time
    • This is an example of temporal regulation
Appropriate animal models

Temporal regulation (Carnegie staging of development)

- Staging of development not based on size, but on evolutionarily conserved structures
  - i.e. same signals, same structures formed at different times during gestations
Appropriate animal models

Temporal regulation (CNS patterning as an example)

• Duration of molecular signals important for final cell fate

Cell autonomy and temporal patterning
Appropriate animal models

Temporal regulation

- Following xeno-transplant, which temporal mechanisms take precedence?
  - The host (animal model) or donor (clinical product)?
    - Data on such temporal regulatory mechanisms limited

- Is understanding temporal regulation relevant?
  - Yes it is! Because…
    - May have implications for duration of safety studies
    - May have implications for efficacy studies
      - Will human cells be less efficacious in animals models as opposed to the clinic.
    - May have broader implications in naïve stem/progenitor studies *cf.* differentiated cell fates
Appropriate animal models

Temporal regulation

• Can temporal regulation be accommodated in animal models?
  – Not in all circumstances
    ▪ Most developmental processes follow linear-non repetitive time-line
      • Therefore, difficult to replicate host developmental signals in cell-replacement models (e.g. CNS)
  – There is no accommodation of developmental timelines in most cell replacement models
  – It is often ‘implied’ the naïve cells can compensate for variations in developmental signals
    ▪ i.e. “The cell knows what to do”
      • This notion is likely fueled by the presence of differentiated stem cells in adult models
        – Due to random differentiation or
        – Secondary (but limited) differentiation pathways
          ▪ In the absence of verified MOAs, remains speculative
Biologically Active Dose
Biologically active dose

• Selection of biologically active dose is context dependant
  – Indication/application (local/systemic)
  – Choice of cells; differentiated cells (local/systemic transplants) or naïve stem cells (local/systemic)
    ▪ Differentiated cells; need to consider proliferative potential (intrinsic/extrinsic regulation)
      • E.g. Immune cells transplants (chimeric antigen receptor T-cells (CAR-T cells) in cancer therapies)
    ▪ Naïve stem/progenitor cells: differentiation and proliferative potential
      • Regulation of differentiation potential (intrinsic/extrinsic regulation)
      • Proliferative potential (intrinsic/extrinsic regulation)
        – E.g. MSCs in GVHD or NSCs in neurodegenerative diseases
        – Due to proliferative potential, biologically active dose can significantly increase over time

• Selection of biologically active dose is influenced by cell survival rates
  – Cell therapy transplants/infusions are often associated with high levels of cell death
    ▪ Usually a by-product of misaligned biological context (which cells die is a random process)
Biologically active dose

• Influenced by residual cell phenotype
  – Related to differentiation potential
    ▪ Balance of target cell phenotypes Vs residual cell phenotypes can impact safety and efficacy
      • Quantification and characterisation difficult due to limitations of lineage tracking capabilities
        – Technological limitation
• Complicated by need for mixture of cells
  – Cell replacement not always ‘1:1 replacement’ of single cell fates (active cells Vs support cells)
  – Support cells secrete trophic factors
    ▪ Impact of trophic factors difficult to quantify
      • Effect can be influenced by distance from target cells/tissues
      • Effect can be influenced by signalling from local environment
Biologically active dose

• Influenced by location/final resting position of cells
  – Important in therapies where cells administered systemically or locally, but require homing and/or migration to reach target site
    ▪ Appropriately differentiated cells may not be ‘biologically (therapeutically) active’ if
      • Not ‘replacing’ diseased cell or
      • Providing trophic support for diseased cells/tissues (requires close proximity)
  – Final resting position is a random process
    • i.e. difficult to quantify homing/integration mechanisms
      – e.g. “MSC homing” or neural cell transplants to CNS(technological limitation)
Biologically active dose

• Influenced by biological context
  – Using cell replacement in neurological disorders as an example:
    ▪ Neural replacement only successful if appropriate connections are established & maintained
      • Local environment should be conducive to differentiation (i.e. appropriate molecular signals)
      • Assuming appropriate differentiation, accurate neural connections requires establishment
        – i.e. Transplantation of stem cells with differentiation potential alone is insufficient
  – Using homing as an example (assuming cells migrated to damaged tissue)
    ▪ Infiltration of target tissue required
      • Either infiltration in sufficient numbers or through proliferation post integration
      • With target tissue, local migration required to elicit action according MOA
        – Must be assessable or quantifiable

• Biologically active dose is a dynamic value
Summary
Challenges for preclinical studies of cell therapy

• Knowledge gap:
  – Causes and examples

• Animal models
  – Suitability based on compatibility and biological context

• Biologically active dose
  – Intricacies of defining dose as it pertains to cell therapies
“...What gets us into trouble is not what we don't know. It's what we know for sure that just *ain't* so...”

Mark Twain