Roundtable Session 2 – Table 7 - Advancing Stem Cell Therapy Development: Overcoming Challenges and Expanding Horizons

Facilitator: Elaine Shults, *Genentech*

Scribe: Abbygail Foster, *Genentech*

Abstract:

Stem cell (SC) therapies offer promising avenues for treating an array of diseases and injuries. Since the first successful bone marrow transplant in 1956, the field has burgeoned, leveraging the unique regenerative potential of stem cells to address various healthcare needs. Stem cells encompass three main categories: adult stem cells, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs).

Based on FDA Guidance and reflected similarly in other regions, the main criteria for determining the level of regulatory framework that applies to stem cell products are whether they are "minimally manipulated" and intended for "homologous use."

Accelerating stem cell therapy development must address obstacles like neoplastic propensity, genetic instability, and immune rejection. Challenges also arise from scarce ethically sourced human embryos and manufacturing standard discrepancies. Among stem cell types, iPSCs offer scalable and less controversial cell generation. However, transitioning iPSC-based therapies from the lab to clinics demands addressing multifaceted manufacturing and quality control challenges, including safety, potency, genetic stability, and cost considerations.

Discussion Questions:

1. How do different stem cell reprogramming methods influence differentiation, immune response and tumorigenic potential?
2. How do growth factors and post-translational modifications affect the scalability and therapeutic effectiveness of stem cells?
3. Can gene editing technologies enhance stem cell differentiation towards specific cell lineages, and enhance safety profiles?
4. How does next-generation sequencing contribute to the overall development and genomic characterization of stem cells?
5. What are the pros and cons of autologous vs. allogeneic SC therapies?
6. Where is regulatory clarity and/or global harmonization most needed to foster SC development?
7. How can the industry overcome the high manufacturing costs associated with stem cells?

8. What advancements in stem cell manufacturing are currently being explored to overcome manufacturing hurdles?
9. What organizational setup best facilitates advancing stem cell products?

Notes:

- What are the biggest challenges and sticking points in advancing the development of stem cell therapies?
    - Developers have significant challenges with scaleup. Additionally, you cannot expand undifferentiated stem cells in vivo
        - Example: HSCs in particular cannot expand like T cells
    - There is a lot of effort/drive to minimize losses, but this is difficult
    - Analytical Challenges
    - Improving the quality of the starting material
    - Genentic modification (potential for mutations)
    - Limited product understanding

<u>Exploring specific challenges</u>

- How do we improve stem cell expansion?
    - Some developers have optimized immobilization using plerixafor mobilizing agent
    - There is not as much understanding outside of iPSCs
    - 2D expansion (bioreactors with microcarrier based expansion, cell stacks, etc)
        - Important to consider consistency/reproducibility
        - Potential for operator-induced variability
        - Cell stacks are limited but there is no major challenge when we have desired cell types and can move to bioreactors
- Considerations around improving the quality of the starting material
    - Varying the direct input in your process helps - this includes investigating washing steps, reagent staining concentration, etc.
    - Recovery and selection of CD34+ cells especially with cryopreservation can lead to yield changes of +/- 50%
- Analytical challenges in Advancing Stem Cell Development:
    - It is important to understand what state the cells are in and it is difficult to tie analytical methods to the ultimate function
    - Materials for development are scarce and there are often long timelines
    - Markers of differentiation are not well known and characterized. One the more successful strategies may use single cell analyses - find a marker or two that correlates well with the product
    - Off target editing is a critical challenge, as well as a costly and complex process
        - Important to develop assays to understand what is happening with the product
    - In process sampling (difficult/ not possible to do this continuously)

        - Important to design the sampling plan to get a better understanding of the product
        - Important to understand impact of cryopreservation and thaw
- Genetic modification
    - With genetic modification there is a need to understand if there are mutations that are present after editing
    - Potential genomic instability - chromosomal abnormality in the bank that is tied to a lot of batches
        - Important to perform extensive characterization to understand the product
        - Utilize bioinformatics data and lean on as many in vitro systems as needed to gain more understanding
        - Ok to not exactly know the exact thing your product looks like
- Product understanding
    - Developers should identify adequate reference materials to support the definition of the correct basal state
    - Important to understand what is the expected phenotype/what is phenotypically conserved to support the selection
    - Development should work backwards from the TPP

<u>Additional questions:</u>

- .Is there a potential for artificial intelligence to support a lot of the data analyses?
    - Trajectory-inference single-cell RNAseq analysis could be a possibility but would be difficult to introduce in manufacturing because it would be difficult to implement in a QC setting
        - Potential to use this to guide the strategy for future manufacturing or characterization of the product
- How do we engineer around poor recovery during certain unit operations?