INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

25 September 2023

Foundation for the National Institutes of Health
11400 Rockville Pike
Suite 600
Bethesda, MD 20852

Re: Request for Information (RFI 2032-002) Inviting Comments and Suggestions from Stakeholders on Cell-Based Therapies for use in Developing an Accelerating Medicines Partnership Cell-Based Therapy Consortium

Submitted electronically to: Kira Gillett, Program Manager, Cell and Gene Therapies (kgillet@fnih.org)

The International Society for Stem Cell Research (ISSCR) appreciates the opportunity to provide feedback to the Foundation for the National Institutes of Health (FNIH) to support the development of an Accelerated Medicines Partnership (AMP) for cell-based therapies. Founded in 2002, the ISSCR is an independent, global, nonprofit organization that promotes excellence in stem cell science and applications to human health. The ISSCR represents 4,500 scientists, educators, ethicists, and business leaders across 80 countries. The ISSCR shares the desire of the AMP program to bring together public, private, and nonprofit stakeholders to work towards a common goal of accelerating new and effective therapies to patients.

The rapid advances in stem cell research have created opportunities for the promise of regenerative medicine and cell-based therapies, including allogeneic cell therapy products such as therapeutic cell products derived from pluripotent stem cells (PSCs). The defining characteristics of PSCs, self-renewal and pluripotency, make them an ideal starting material for Regenerative Medicine products. However, these same characteristics are also associated with safety concerns such as genetic stability and tumorigenicity. Development of starting materials, platform technologies, and assays that streamline the demonstration of safety for these products will help to accelerate these important products to patients.

To strengthen the translational and clinical pipeline of allogeneic cell therapies, we must enable researchers to move faster by eliminating pain points, which in turn could help with lowering costs. To do so, the ISSCR recommends that a cell therapy AMP focus on one, or several, of the following areas:

- **Creating a bank of clinical PSC cell lines** for researchers would facilitate translation by eliminating the time-consuming process of generating, optimizing and validating clinical cell lines in individual labs. Providing researchers with complete documentation (or Letter of Authorization to a Drug Master File) for these lines could also accelerate IND submissions for individual researchers. A source of stable, well-characterized, and documented clinical iPSC lines would assist and accelerate the development of cell products relevant to specific patient populations and therapeutic applications.
- **Reducing genomic heterogeneity** is a priority to mitigate risk at the genome level in translating stem cell applications to clinical therapies. While our ability to detect and quantify mutations is growing rapidly, our ability to discern functional consequences is not keeping pace. There is a need to establish which genomic mutations are of concern and what level of allelic frequency is acceptable.

Development of predictive assays to determine if specific genetic mutations are associated with safety risks would accelerate the development of these important therapies, while simultaneously reducing risk.

- **Developing safe, hypoimmune therapies** is critical for the large-scale manufacturing of allogeneic cell-based therapies. But achieving hypoimmunity without compromising the therapeutic benefit of a cell-based product is challenging, especially at scale. These products will require multiple edits and demonstration of durability after delivery. Developing technologies and assays that readily assess the hypoimmune status of the product will accelerate and de-risk development of these therapies.
- **Developing *in vitro* alternatives to animal models** to assess safety and efficacy would save considerable time and money for developers of cell-based therapies. Animal studies can stretch to years and are quite costly. The development of sensitive, robust, and predictive *in vitro* assays to test for, e.g., tumorigenicity, could shorten the timeline for the development of these products. An added benefit is that *in vitro* alternatives satisfy the 3R's principle that governs research with animal models (Reduce, Replace, Refine).

Lastly, to be most effective, the AMP's initial disease targets for drug design should be focused in number and include diseases for which there is recent, robust clinical data that shows promise for the development of a cell-based therapeutic. Several targets that fit this profile are Type 1 diabetes, Parkinson's disease, and macular degeneration, among others. Successful development of technologies for these initial disease targets can then be applied to a broad range of diseases.

Thank you for the opportunity to comment. The ISSCR looks forward to working with FNIH and other stakeholders as the development of the AMP moves forward. If you have any questions, please feel free to contact Tyler Lamb, JD, ISSCR Policy Director (tlamb@isscr.org).

Respectfully,

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