

Common Factors Impacting the Utility and Commercialization of Any Cell Therapy

There is no denying that cell therapy has the potential to be one of the most powerful therapeutic options one can administer. Cell therapy can take several forms and serve many purposes. A cell therapy may be used to alter normal cell response, stimulate or reset a native signaling cascade, perform a missing metabolic function, restore lost tissue, or change the normal course of repair into true regeneration. Designing and implementing a plan for commercialization can take many paths, each with their own set of biological, technical and regulatory considerations. However, there are some common factors that will impact the clinical success and commercialization of any cell therapy. This brief overview outlines a few of the basic factors that will determine safety and efficacy.

Robustness

Robustness, used here, refers to the strength of the process that gets you to a functional cell therapy. Robustness speaks to: 1.) The reproducibility of the source, 2.) The predictability of a cell population's behavior, 3.) Its ability to eventually form what you want it to and 4.) Your ability to determine and assure that it does so. In your development, try to define what *in vitro* parameters can be used as predictable measures of what will happen post-implantation. These parameters will define your product and they should have a biological basis. Robustness of the process also extends to the implant's behavior post-implantation. Safety and efficacy will depend on how long the cells survive post-transplantation, your ability to deliver them to the site, their ability to stay in place and their growth and functional regulation once *in situ*.

Stability

Stability relies on robustness in part, but is not the same thing. While stability impacts effectiveness, the primary concern here is safety. Demonstration of growth control mechanisms and the cell population's ability to differentiate and naturally senesce are all parameters that can be used to add confidence that the cell therapy will be safe. Added assurance of stability can come both from *in vivo* and *in vitro* testing. Demonstration of the cell therapy's responsiveness to normal mechanisms of growth control is particularly important if the therapy will persist for an extended period of time.

It is fairly obvious that delivery to a patient requires some assurance that the cells will perform the desired task, and only that task. Although the generation of cell banks requires a certain lack of differentiation to maintain desirable growth properties, ultimately, the process reaches a point where function and control are important, either before, or after, implantation. Demonstration of stability will be particularly important the farther one diverges from the natural cell source.

Another practical but important point irrespective of the cell source is that while *in vitro* immortalization and transformation in human cells are very rare events, they can and do happen. On rare occasion, it will develop into changes that will limit the functionality of the cell source and in the extreme – pose a risk to the patient. As more data is accumulated, we may one day be able to define the genetic parameters that result in a predisposition for instability without having to undergo functional testing. For now, *in vitro* and/or *in vivo* biological tests can be designed to demonstrate the safety of your process and the stability of the cell populations (strain or line) you put through your process. Like any medical treatment, the level of risk will always be weighed against the benefit to the patient. What may be considered acceptable risk for a debilitating condition will be different than what may be considered reasonable for a cosmetic application.

Functional Capacity

Functional capacity of the cells relates directly to efficacy. If cells are injected to deliver dopamine, then highly differentiated dopaminergic neurons will have more functional capacity than neuron-like cells that express some dopamine or a cell population where only a percentage of the cells achieve the desired functional status. Whether you begin your process with embryonic stem cells, adult stem cells, more differentiated cells (like transit amplifying cells), or “transdifferentiated” cells, in the end, all roads meet somewhere on the molecular path of development that gives rise to functional differentiation. Not all paths will be capable of delivering the same level of functional differentiation. Administering a few cells with a naturally high capacity will be stronger biologically, than a lot of cells with limited functional capacity. Administering a larger numbers of cells to make up for either a low functional capacity or a low percentage of conversion, has the potential to compound your issues of robustness and stability, while not delivering the efficacy you need – the way you need it. As you develop your process, it is a good idea to test the cell populations for changes in their functional capacity as the process evolves. It is important to have as part of your research and development plan, assays and models *in vitro* and *in vivo* that can give you a good sense of functional

capacity so you can design a process that selects for it. *In vivo* implantation is not a panacea. Functional capacity may improve dramatically but it can also not improve or even digress, particularly if one is using cells outside their natural path of development.

All cell therapies, even those that are not meant to persist, will rely on functional capacity for their effectiveness. Ultimately, if the cell population you introduce is able to recapitulate developmental differentiation and retain a capacity to naturally renew like native tissue, the implant could maintain a high functional capacity for a very long time starting with relatively few implanted cells. This could lead to a life-changing curative therapy in some indications. The functional capacity of the cells in your process may be more pivotal than the cell population's capacity for expansion.

Influence of the recipient

The cell implant will not function in a vacuum. Patient conditions will be variable. The more robust, stable and functional your product is, the better it can weather the influence of varying patient physiological and medical conditions, including ones that will be factors in all patients like inflammation and the native fibrotic response. Consider even simple procedures like wound bed preparation, or companion therapies that might assist your implant. Something as simple as an aspirin might make a difference, and preclinical as well as pilot Phase I studies can be designed to help you understand what conditions might deter or assist your implant's functionality.

Robustness, stability and functional capacity are all achievable if one addresses these issues on an ongoing basis during the research and development process. Achieving them can place your product squarely in the win column for patients and your company.

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