Developing Induced Pluripotent Stem Cell-Based Therapy for the Masses

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SUMMARY

The discovery of induced pluripotent stem cells and the ability to manufacture them using clinically compliant protocols has the potential to revolutionize the field of regenerative medicine. However, realizing this potential requires the development of processes that are reliable, reproducible, and cost-effective and that at the same time do not compromise the safety of the individuals receiving this therapy. In the present report, we discuss how cost reductions can be obtained using our experience with obtaining approval of biologic agents, autologous therapy, and the recent approval of cord blood banks.

SIGNIFICANCE

For therapy to be widely available, the cost of manufacturing stem cells must be reduced. The steps proposed in the present report, when implemented, have the potential to reduce these costs significantly.

PERSPECTIVE

In the United States, the manufactured biologic agents used to treat individuals are regulated by the Center for Biologics Evaluation and Research Division of the Food and Drug Administration (FDA) under a Biologics Licensure Application (BLA) license process. This BLA process is similar to an initial new drug application and requires the provision of documentation of the safety and efficacy of the product and evidence that the product can be manufactured reliably and reproducibly, ensuring lot-to-lot consistency. This process of approval has worked well to date, and several products have been approved using this BLA approval process [1–3].

The increase in the complexity and variety of regenerative medicine products has been accompanied by an increase in the number of steps required for manufacturing the cells. It has become increasingly clear that unless certain roadblocks are eased, the time and cost of introducing a new product will make it prohibitively expensive to deliver regenerative medicine products [4]. This is particularly true for autologous therapy products, for which the costs cannot be amortized over a large number of units. The cost burden and the time period of development also make it likely that the number of companies willing to shoulder the risk and cost burden will be small. Reducing the cost is a challenge, however, because one cannot simply eliminate the regulations or requirements intended to ensure the safety of any proposed treatment. Thus, the challenge is to examine the BLA process carefully, to understand what can be modified and what needs to remain unchanged, and to discover innovative ways to meet those unchanged requirements more efficiently. In the following sections, we provide a personal perspective on how this might be achieved and suggest that a combined effort by the various stakeholders in this domain will be necessary to make induced pluripotent stem cell (iPSC)-based therapy cost-effective (Fig. 1).

Any cellular therapy approved via the BLA process requires that one manufacture the cells, develop an appropriate release assay, perform the required preclinical studies, plan a series of safety- and efficacy-based human studies, and submit that application for review and approval [3]. Approval is granted for the use of that particular product for a specific indication in a particular class of patients as defined in the label requirements. A change in the dose or the use for a different indication or a different class of patients requires additional studies for approval. In addition, if the manufacturing process used to make the product is significantly altered, it will also be considered a new product. Any change in input material, culture conditions, or the facility used will constitute a significant change and require additional studies, possibly including human studies. Furthermore, if two manufacturers are manufacturing the same product, it is likely that each product will be made slightly differently or that the release criteria or potency tests will be different. As such, the products will not be equivalent in the eyes of the regulators, and additional studies will be required to demonstrate equivalence. Although this will mean added expense and time for approval of a new product, such costs should not be a significant concern, because these manufacturing, testing, preclinical, and clinical study costs can be amortized over a large number of treatments and, as such, represent a small proportion of the total cost of therapy.
As one extends this model of one product for many individuals to an autologous therapy model using iPSCs as a starting material, several problems begin to emerge. The starting material will be different for each individual. Also, if different groups manufacture the differentiated cells, the processes, suppliers, and sites will also be different. It is also likely that the release criteria used by each group and the tests performed in the preclinical models will be different, and, no doubt, the clinical studies will not be identical. Each “new product” under current law requires testing or approval for a new indication and requires a new BLA application and, as such, results in additional costs. These costs will be applied to a single dose or, at best, a few doses, making this prohibitive as an option for therapy. Indeed, Dr. Takahashi, who performed the first autologous transplant with iPSC-derived retinal pigment epithelium, stopped the process and turned to developing allogeneic cell-based therapy, because the costs were so prohibitive [5].

Examining the process, we have identified possible ways in which the costs could be reduced (Table 1). Perhaps the simplest and easiest to implement is to recognize that iPSCs are not the final end product used in therapy. They are input material in a manufacturing process and as such should be regulated the same as any other input material, albeit with the recognition that the genetic components of this input material will be included in some of the final products. This would enable multiple manufacturers to produce iPSCs and then develop a certificate of analysis, permitting use as input material such as is done with other materials used in a manufacturing process. The FDA could regulate the manufacture of such input material and even set standards for use. Therapeutic product manufacturers would then choose which line they would use for their product and would have a straightforward change process for replacing one “input” line with another, much as is done today when one changes suppliers for any other material. Suppliers would compete to develop the best quality line or to customize a line for different therapeutic products. Equally importantly, one could choose to manufacture the line in a Current Good Manufacturing Processes (CGMP) environment, because this is not necessary for all input material.

This definition of iPSCs as input material would be particularly apt for the haplobanking effort that has been proposed by the Global Alliance for iPSC-based therapy (GAIT) and others. In this model, multiple banks of cell lines that carry a specific widely distributed human leukocyte antigen (HLA) type would be generated. Each of these lines could provide donor material for multiple individuals. Banks could be licensed for the production of this input material, just as tissue banks are currently, and they could distribute the input material globally. This would reduce the numbers of cell lines needed to be generated and reduce the manufacturing costs enormously.

Additional cost reduction could be obtained in manufacturing a final product if common manufacturing processes were used. Thus, the drug master file (DMF) could be referenced, and repeat testing and validation of material suppliers, assays, and processes would not be needed. This would require sharing data or, at the very least, allowing reference to a DMF, which has historically not happened because large companies have believed that not allowing a DMF has offered them a competitive advantage. In an autologous market, however, we suggest that the savings that would accrue to all parties and the industry as a whole provides a compelling imperative.

### Table 1. A variety of different strategies can reduce the cost of a regenerative medicine product

| Cost reduction strategies |
|---------------------------|
| Define iPSC as input material |
| Manufacture in a GLP environment |
| Develop a DMF that is accessible to investigators |
| Provide kits to make iPSCs |
| Use a modular manufacturing protocol and manufacture multiple products from same MCB |
| Develop calibration material and comparability assays |
| Widen approved use based on function instead of treatment of a particular disease |
| Consider haplobanking |
| Simplify freedom to operate rules and patent licensing |
| Harmonize rules internationally and consider common approval |
| Simplify the process of approval of products already approved in another geography |
| De-risk development along the lines of the European Union, Japan, and U.S. efforts |

Most of these strategies can be combined to achieve additional synergistic savings; implementing such savings, however, will require coordination of effort among scientists, regulators, and clinicians.

Abbreviations: DMF, drug master file; GLP, good laboratory practice; iPSCs, induced pluripotent stem cells; MCB, master cell bank.

An alternative to sharing processes is to agree as an industry that the end product manufactured by different proprietary processes, which are not shared, would be functionally equivalent, as defined by an agreed-on functional assay. One can imagine developing comparability assays by consensus, such that a product could be defined, not by process, but by function. This has the prospect of enormously reducing costs because no retooling to a specific identical process would be required, and no exchange of competitive data would be required. One would simply agree that these tests, validated against a standard control, would provide the low bar of acceptance for safety and functional utility. Groups could still compete regarding why their product is better using criteria other than safety and minimal efficacy. This has been the case for serum albumin, for example, which can be manufactured, purified, synthesized, and developed in plants and supplied for the same use using release criteria for acceptance.

A similar “common” strategy for autologous cell-based therapy can be considered as a pooled trial by multiple manufacturers of autologous therapy. Samples that are functionally equivalent but manufactured by different groups in different facilities and at different sites are included in the same trial. Because the number of cases will be larger, it is likely that more specific and better information will be available. This will require redesigning trials and their interpretation slightly, but we would argue that this has already occurred for approval of products such as cord blood and no reason exists why this could not be applied to iPSC-derived products. It does, however, require groups to work together and consult with the regulatory authorities to ensure that no unanticipated complications or regulatory infractions will occur.

The inclusion of a calibration material or reference cell line that was widely available and well characterized would offer the flexibility of performing a trial independently with a product
Figure 1. Flow diagram highlighting a modified manufacturing protocol that accounts for the various cost reduction strategies we have outlined. Abbreviations: GLP, good laboratory practice; iPSC, induced pluripotent stem cell; MCB, master cell bank.

made by a unique process in which one showed that the product was functionally equivalent in vitro and in vivo. Furthermore, if the control was a therapeutic agent, it could even serve as a control in human studies. This is certainly possible, because large numbers of iPSCs have been generated and are well characterized [6, 7]. The NIH has commissioned two CGMP lines and has committed to characterizing them and distributing them widely; thus, in principle at least, such clinical grade controls will be available.

A final consideration in cost reduction is the approval, not for a specific indication such as for a particular disease or a subclass of that disease, but for the function that the cell is expected to perform in vivo. Thus, cord blood could be approved for hematopoietic stem cell replacement in any indication for which such replacement is required or astrocytes could be approved to provide trophic support in all indications in which such trophic support will provide functional benefit. This is not akin to what is done in the allogeneic world with product use extensions after approval and requiring limited studies. In an autologous or HLA-matched setting, this also would not seem to be an unreasonable process. It would reduce the number of trials needed and still provide the option that data would be collected for autologous products, and the use of such products could be reimbursed because the therapy would not be considered experimental.

All these options require developing clarity on which assays to use, which reference material is acceptable, and what is functional equivalence. It will require a concerted effort by all stakeholders to develop a formal, ultimately novel or modified, BLA process for autologous manufactured therapy. Models of this exist, just as does experience. In particular, we believe that the cord blood BLA process offers a good starting point and an example of what can be accomplished when all stakeholders work together to ensure approval [8, 9]. We remind readers of the consequences of a failure to make the effort, which has been exemplified by the mesenchymal stem cell (MSC) field. A lack of consensus has meant we are still unsure of whether the so-called MSCs used by different companies are the same or different. As such, developing autologous therapies has been difficult and quite expensive.

Although we have focused on how such costs reduction can be obtained in the United States under FDA guidelines, conceptually, a similar effort could also be initiated in other countries. Some aspects of this process will be different. For example, Europe does not have the same 510K, DMF model [10]. However, Europe has developed a new Advanced Therapy Medicinal Product classification system and a unified submission process [11], which likely will enable costs reductions. In other countries, such as Japan, additional costs reductions and acceleration can be obtained because of the legislative changes that have been implemented [12]. Perhaps GAIT [13], a recently formed non-profit organization to help develop iPSC-based therapy as an international harmonized effort, offers the best hope of making iPSC-based therapy globally viable.

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**AUTHOR CONTRIBUTIONS**

M.S.R. and A.A.: manuscript writing, figure preparation, development of viewpoints after discussion with various stakeholders.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicated no potential conflicts of interest.