WHY EXECUTIVES AND INVESTORS SHOULD UNDERSTAND LEVELS OF REPAIR INDUCIBLE WITH IPSCS

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### Levels of Repair Inducible with iPSCs

For stem cell company executives and  industry investors, understanding the levels at which induced pluripotent stem cells (iPSCs) can induce repair is extremely valuable. While technical in nature, this understanding can guide both future product development decisions and competitive strategies.

An understanding of levels of repair at which iPSCs can exert their effects can also clarify what industry participants may have aligned interests and which will be competitive, because a company developing iPSC products that target a different level of repair are unlikely to represent a direct competitor. In fact, a company of this nature may actually represent a good target for partnership.

### Levels of Repair Inducible with Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells can be strategically utilized at several biological levels, which are shown below, from smallest to largest.

#### Four Levels of Repair Inducible with iPSCs

|  |  |
| --- | --- |
| Level of Repair | Description |
| **1. Gene-Level Repair  (Gene Therapy)** | Repairing disease-causing mutations by gene targeting & correction technologies. |
| **2. Cellular-Level Repair  (Cell Replacement Therapy)** | Implantation or injection of differentiated cells derived from human induced pluripotent stem cells. |
| **3. iPSC-Derived Blood Products** | Production of iPS cell derived human platelets, red blood cells, T cells, and more. Has the potential to replace blood donation. |
| **4. Whole Tissue Repair (Organ Replacement Therapy)** | Seeding three-dimensional biological scaffolds, organ replacement, or whole tissue regeneration. |

Each of these levels of repair at which iPSCs can exert their effects are considered in greater detail below.

#### 1. Gene-Level Repair (Gene Therapy)

An advantage of induced pluripotent stem cells over other transplant approaches is the ability to repair disease-causing mutations using gene targeting and correction technologies.1   Proof of principle examples that iPSCs can be used to treat disease by correction of the underlying genetic defect are presented below:

##### Examples of Gene-Level Repair with iPSCs

|  |  |  |
| --- | --- | --- |
| Disease | Species | Description of Repair |
| **Sickle Cell Anemia** | **Mouse** | In a mouse model of sickle cell anemia, the wild-type β-globin gene was used to replace the defective gene by homologous recombination. Transplantation with genetically corrected iPSC-derived hematopoietic progenitors was successful in improving symptoms of anemia and physiological function.2 |
| **Fanconi Anemia** | **Human** | In humans with Fanconi anemia, a disease characterized by extreme genetic instability, the mutant gene was replaced using lentiviral vectors prior to epigenetic reprogramming of the patient’s fibroblasts and keratinocytes, because the genetic instability of the mutant fibroblasts made them non-permissive for iPSC generation. Interestingly, these iPSCs could be differentiated into hematopoietic progenitors as efficiently as wild-type iPSCs, stably maintaining the disease-free phenotype*in vitro.3* |

Theoretically, the approach of repairing disease-causing mutations by cell transplantation facilitated gene targeting, and correction can be applied to any human disease for which the underlying mutation is known.

#### ****2. Cellular-Level Repair: Cell Replacement Therapy****

Another approach for using iPSC in cellular therapy is to employ mature cell types differentiated from iPSCs.  To date, this approach has been most often explored with hepatocytes derived from human induced pluripotent stem cells.  Hepatocytes are the main functional cells of the liver and perform critical endocrine and exocrine functions, but research utilizing human hepatocytes for cellular transplantation has been limited by the difficulties in sourcing and maintaining viable hepatocytes.4

Nonetheless, a number of cell-based and animal-model studies of human liver disorders have revealed the extreme regenerative capacity of hepatocytes *in vivo*, indicating that hepatocyte transplantation may represent a viable strategy for replacing damaged or diseased hepatic tissue.5  Transplantation of hepatocytes derived from human induced pluripotent stem cells could therefore represent an alternative to liver transplantation, as well as a method for correcting genetic disorders of the liver.6

In theory, the approach of repairing damaged or diseased tissue with differentiated cells derived from human induced pluripotent stem cells could be applied to any cell type within the human body.

#### 3. iPSC-Derived Blood Products

Another approach for therapeutically applying iPSCs is to create iPSC-derived blood products.  A leader in this area is [Megakaryon Corporation](https://www.linkedin.com/vsearch/p?company=Megakaryon+Corporation&goback=%2Egde_4117443_member_5962105200280875009&trk=prof-exp-company-name), a venture company founded in September 2013 through the collaboration of individual and corporate members associated with Tokyo University and Kyoto University.7  The company produces technologies for the production of iPS cell derived human platelets, red blood cells and T cells and sells them globally. Platelets and the red blood cells derived from iPS cells have the potential to be used as the blood products, without requiring blood donations from donors, while Leukocyte T cells derived from iPSCs may be used in the management of diseases that may include AIDS, cancer, hepatitis, and more.

#### 4. Whole Tissue Repair (Organ Replacement Therapy)

Currently, the standard of care for terminal organ failure is orthotopic8 transplantation.  However, the demand for transplantation far exceeds the number of available donor organs, which has driven tissue-engineering/regenerative-medicine approaches for creating functional organ replacements to be developed.

A possible  use of iPSC to regenerate tissues and organs is in engineering a whole organ using decellularization of matrix bioscaffolds and recellularization with iPSCs.9Decellularization and recellularization of matrix bioscaffolds has been shown to be a promising approach for whole-organ tissue engineering in recent years with other stem cell types, although it has not yet been accomplished with iPSCs.10  To date, it has been shown that donor organs such as the lung11, liver12, heart13, kidney14, and bladder15 can be successfully decellularized to an acellular biologic scaffold material and then be recellularized with selected stem and progenitor cell populations.  Preliminary studies in animal models have provided encouraging results for the proof of concept that these three-dimensional scaffolds can be successfully re-populated.

Extrapolating these findings, it can be assumed that decellularization of donor organs to provide an acellular, naturally occurring three-dimensional biologic scaffold material would allow for it to be seeded with induced pluripotent stem cells to facilitate functional organ replacements.  This medical possibility is likely to be a near-term reality.

In addition, proof of principle examples have demonstrated that it is possible to generate fully functional organs from a single adult stem cell.16,17,18 While this has not yet been accomplished with induced pluripotent stem cells, it has been accomplished with other stem cell types.   For instance, it has been elegantly demonstrated by independent research teams that the mammary gland and the prostate can be generated in vivo from a single adult tissue stem cell. The ability to perform this technique with iPSCs is similarly possible.

Finally, other methods of stem cell-derived full organ generation exist as well, such as generation of organs using a blastocyst complementation system.  Specifically, embryonic stem cells (ESCs) have been shown to be able to produce specific organs by using a strategy of injection of embryonic stem cells from one species into the blastocyst of another species.   Again, it is likely that this approach will be replicated with iPSCs.

#### ****Implications for Stem Cell Executives and Investors****

Understanding levels of repair at which iPSCs can exert their effects can help clarify what industry participants may have aligned interests, and which will be competitive. A company developing iPSC products that target a different level of repair is unlikely to represent a direct competitor when in fact, a company of this nature may actually represent a good target for partnership.

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