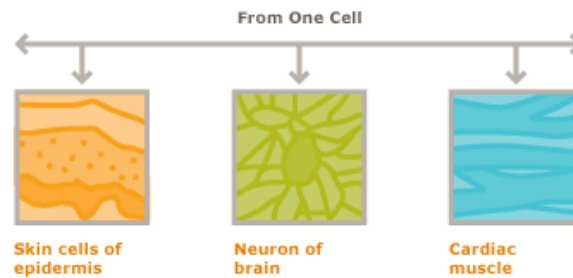


## STEM CELL PRIMER

### Embryonic Stem Cells:

In 1998, the first human embryonic stem cell (hESC) line was created from a fertilized egg. This was a significant milestone in regenerative medicine because hESCs are pluripotent, meaning they can become any cell in the body, and stem cells could conceivably be grown and differentiated into replacement cells for any applicable therapeutic need (Figure 1).



*All the Cells in the Body to Restore Health*

Figure 1: The promise of regenerative medicine

However, the seemingly unlimited therapeutic potential associated with hESCs were tempered with the sobering safety issues that hESCs presented. Specifically, because of the limited population source from which hESCs are derived, potential patients would be exposed to similar immune rejection risks as those of organ transplant recipients when receiving organs from donors of not identical genetic matches. Moreover, hESC recipients would face increased risks to potentially unknown genetic diseases of the donor. Accordingly, the ability to generate patient-specific replacement cells with pluripotent capabilities became the next sought after milestone to fully realize the therapeutic potential of regenerative medicine.

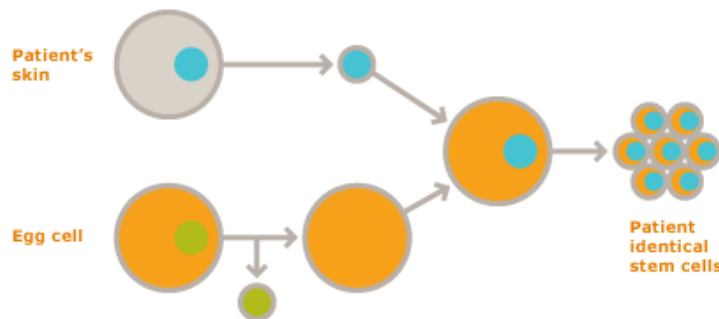


Figure 2: Schematic of nuclear transfer, a previously explored method to generate genetically-matched stem cells.

Scientists tried to address this hurdle with a technique that replaces an egg cell's nucleus with the nucleus from a patient's skin cell (Figure 2). Since the nucleus of an adult skin cell has a full set of chromosomes, the egg cell would in a sense be fertilized with an exact copy of the patient's DNA. The embryonic stem cell line derived from this "fertilized" egg cell would be a genetic match to the patient and likely to not be rejected. However, this technique was highly inefficient and relied on donated egg cells, which are from a limited population source and difficult to obtain.

### Induced Pluripotent Stem Cells (iPS cells or iPSCs):

In 2007, in separate publications Drs. Yamanaka and Jaenisch, the later a scientific founder of Fate Therapeutics, reported that fully differentiated adult cells, such as a skin cell, could be “reprogrammed” to become embryonic-like stem cells by forcing expression of four transcription factors (Figure 3). Called induced pluripotent stem cells (iPS cells or iPSCs), as iPS cells were derived from the potential patient’s own cells, the issue of creating patient specific cells was addressed. Furthermore, ethical issues involving the use of embryos or eggs had been avoided.

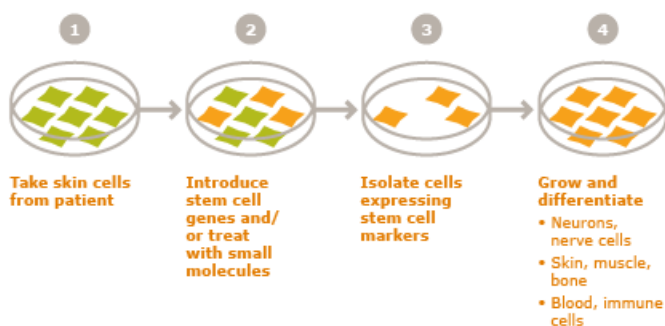


Figure 3: A schematic of creating iPS cells, a more efficient and reproducible process for generating personalized cell replacement therapies.

iPS cells were first created by genetic manipulation using viruses, which carry risks from insertion and makes the cells unsuitable for clinical use. Fate Therapeutics and the company’s scientific founders have found safer and more efficient ways to create iPS cells using non-genetic methods, such as small molecules and biologics. As iPS cells can potentially be made from any adult cell and differentiate into any cell type, iPS cells have the greatest potential for drug discovery and patient therapies. In addition, Fate Therapeutics believes iPS cells are of essential importance to research how to control cell fate with small molecules to develop conventional therapeutics.<sup>1</sup> These small molecules could potentially be applied to modulating adult stem cells to stimulate the body’s own healing process to repair and regenerate tissues.

### Adult Stem Cells Are Naturally Found in the Body:

ESCs and iPS cells are types of stem cells made in the lab, while adult stem cells naturally occur in the human body. Adult stem cells are found in tissues or organs and primarily maintain and repair the tissue in which they are found. Some populations of adult stem cells are also thought to remain quiescent (non-dividing) in areas of the body called “niches” until they are activated by disease or tissue injury. Adult stem cells can renew themselves and can differentiate to yield the major specialized cell types of the tissue or organ. Some researchers are trying to grow adult stem cells in the laboratory for cell replacement therapy; however Fate Therapeutics is taking a different approach. Fate is using conventional drug discovery<sup>2</sup> and iPSC technology to identify small molecules that can specifically activate these adult stem cells in the body to repair and regenerate tissue.

<sup>1</sup> All drugs in pill form, like aspirin, are composed of small molecules. Small molecules are easier to turn into drugs because they can be tested for safety and efficacy. Thus, they follow a conventional pharmaceutical drug development approach with a well-defined regulatory and commercialization path

<sup>2</sup> Conventional drug discovery relies on a deep understanding of the biological pathways and mechanisms which control a specific cell or cellular process. Small molecules and biologics are developed into drugs based on their selectivity to modulate these cellular processes in a way that has therapeutic benefit.