It's not magic, it's stem cells!

By Judith Anderson

With the wave of their pipettes, what scientists can do with stem cells almost seems like magic. Stem cells are a group of cells characterized by their ability to produce different cell types and unlimitedly self-renew (Figure 1). Think of it as though stem cells are the magician's hat, and anything can be pulled out of their hat. Anything can come from that hat based on the tricks, wands used, and the magician. In this scenario, all the tricks and factors influencing what the hat produces are equivalent to the stem cells' micro-environment. Their micro-environment is often referred to as the stem cell niche. In different stem cell niches, surrounding cell groups and molecules influence what the stem cells will produce. The niche will also instruct the stem cells on when and how they'll divide.

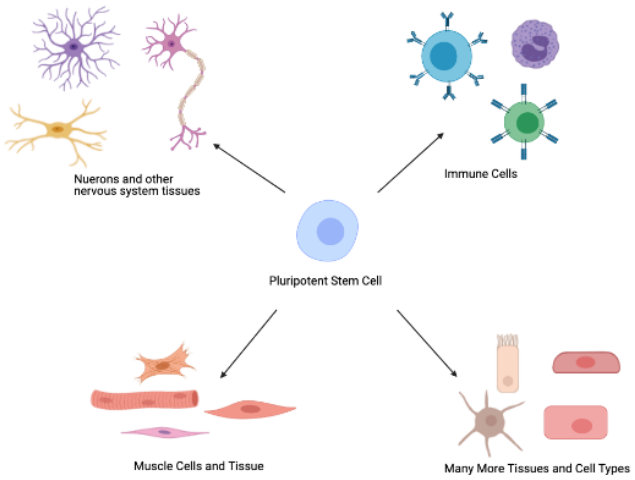

Figure 1: The Stem Cell Maintenance

Stem cells are often divided into different groups based on their "potency". The "potency" of stem cells refers to the range of cell types they can give rise to[1]. The three types of stem cell potencies are: (1) totipotent—can develop into any cell type, including placenta, (2)

pluripotent—can develop into any cell type, except placenta, and (3) multipotent—can develop into a more limited set of cells.

The most common type of stem cells used in laboratories are pluripotent stem cells. Pluripotent stem cells are the most common because they can give rise to any cell type and aren't restricted to specific tissues[2]. Figure 2 shows a couple of examples of the wide variety of cells that pluripotent stem cells can give rise to. There are two common types of pluripotent stem cells, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs).

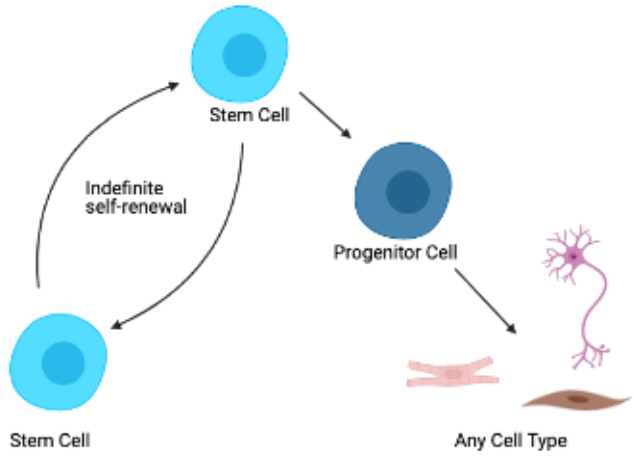

Figure 2: The Magic of Pluripotent Stem Cells

ESCs are derived from a very early stage of the human embryo termed a blastocyst, which develops 7-10 days post-fertilization. Before the blastocyst implants into the uterus, it contains a group of pluripotent cells called the inner cell mass. Human ESCs derived from the inner cell mass are typically from blastocysts formed at in vitro fertilization clinics.

Due to their origin, ESCs present a unique ethical dilemma. The dilemma revolves around the cells being derived from a human embryo. It is true that if the blastocyst was left intact and was also able to successfully implant into a uterus, it could develop into a baby. A common misconception regarding ESCs is that that they come from an already

implanted fetus. This is not true. In fact, early embryos from IVF clinics have never even been inside a human. Another misconception is that these cells are viable outside the uterus and can still produce a baby. That is also not true. Without the human body, the early embryo is unable to form fetal structures.[3,4,5]

Given that there will likely always be controversy surrounding ESCs, iPSCs are a great alternative. iPSCs come from taking cells already restricted to a certain tissue type and reverting them back to their stem cell state. This is referred to as de-differentiating, which is like an adult being magically turned back into a baby. De-differentiating is accomplished by using specific signaling factors that tell the cell to go back to an unrestricted state. So, instead of taking cells from an early embryo, scientists are taking cells like fibroblasts—a cell found in connective tissues throughout the body, including the easily accessed dermal layer of skin—and reprogramming them back into pluripotent stem cells. The discovery of how to de-differentiate any cell into a pluripotent stem cell was first published in 2006 and it has revolutionized regenerative medicine[6].

iPSCs have three main "magic tricks" they can perform: (1) disease modeling, (2) therapeutics, and (3) drug discovery and toxicity studies. Figure 3 shows a graphical depiction the three iPSCs "magic tricks."

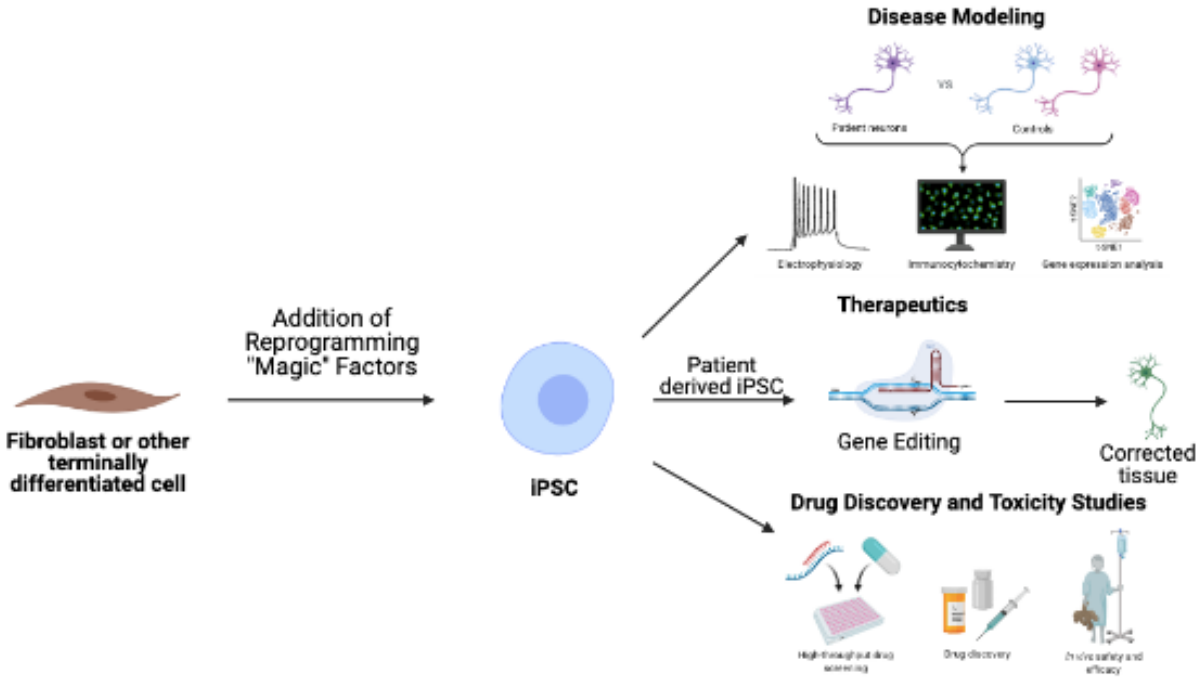

Figure 3: The Magic Tricks of iPSCs

Using iPSCs for disease modeling has helped further characterize diseases in humans. This works by taking diseased tissue from a patient's cells and inducing the cells from that tissue to form iPSCs. Once the cells are reverted into stem cells, they can be induced to form any tissue type. Observing how the cells develop into the target ell type or how they function once they form that cell type can help us better understand how diseases manifest. For example, to better understand the underlying mechanisms of Parkinson's disease, researchers were able to use fibroblast cells from Parkinson's patients. The patient fibroblasts were induced to form iPSCs and — because Parkinson's disease is a neurological disorder— the iPSCs were then differentiated into neurons.

Many scientists have used the approach to determine specific genes, like LRRK2, involved in disease manifestation[7,8,9].

iPSCs have clinical applications in the treatment of injured and degenerative tissues. Therapeutic applications can range from treatment of diseases like Duchhene muscular dystrophy to spinal cord injuries[11,12]. These iPSCs can be used for both autologous and allogeneic processes. Autologous means the cells used to make iPSCs must come from the same patient that the iPSCs will be used to treat. Allogeneic means the cells used to make iPSCs come from a donor who is different than the patient the cells will ultimately be used to treat[13]. Figure 4 shows an example of a therapeutic approach for correcting a mutation that affects neurons, using gene editing and iPSCs. There are many other areas of clinical application, which truly shows how dynamic these cells are.

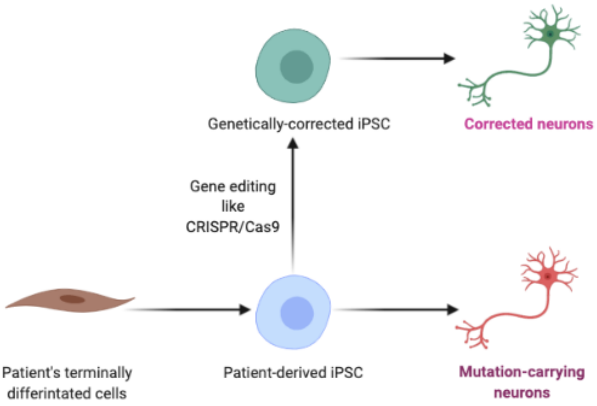

Figure 4: Therapeutic Example of Correcting a Mutation in Neurons

iPSCs can also be used for drug discovery and to study the toxicity of drugs. A primary reason for using iPSCs is that a scientist can take any human cell type, reprogram them into iPSCs, induce the iPSCs to form any tissue, and then test the impact of a drug or treatment on those specific cells. This allows for a more precise and accurate model for understanding the effects of drug treatments in human diseases; for example, in

understanding testing of cardioactive drugs[14]. One study examined how cardioactive drugs impact cardiac rhythm in cardiac arrhythmic diseases[15]. To do this work, scientists tested the drugs on cardiac cells derived from iPSCs. To expand their work, the authors discussed the utility of using iPSCs developed from fibroblasts taken from patients with cardiac arrhythmic diseases[15]. Another benefit of using patient-derived iPSCs is the ability to develop patient-specific drugs.

These are just a few examples of how iPSCs have impacted the field of disease modeling, regenerative medicine, and drug screening. There are many more things iPSCs can be used for, and that we have yet to discover. But stem cells already represent the magic and wonder of science.

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