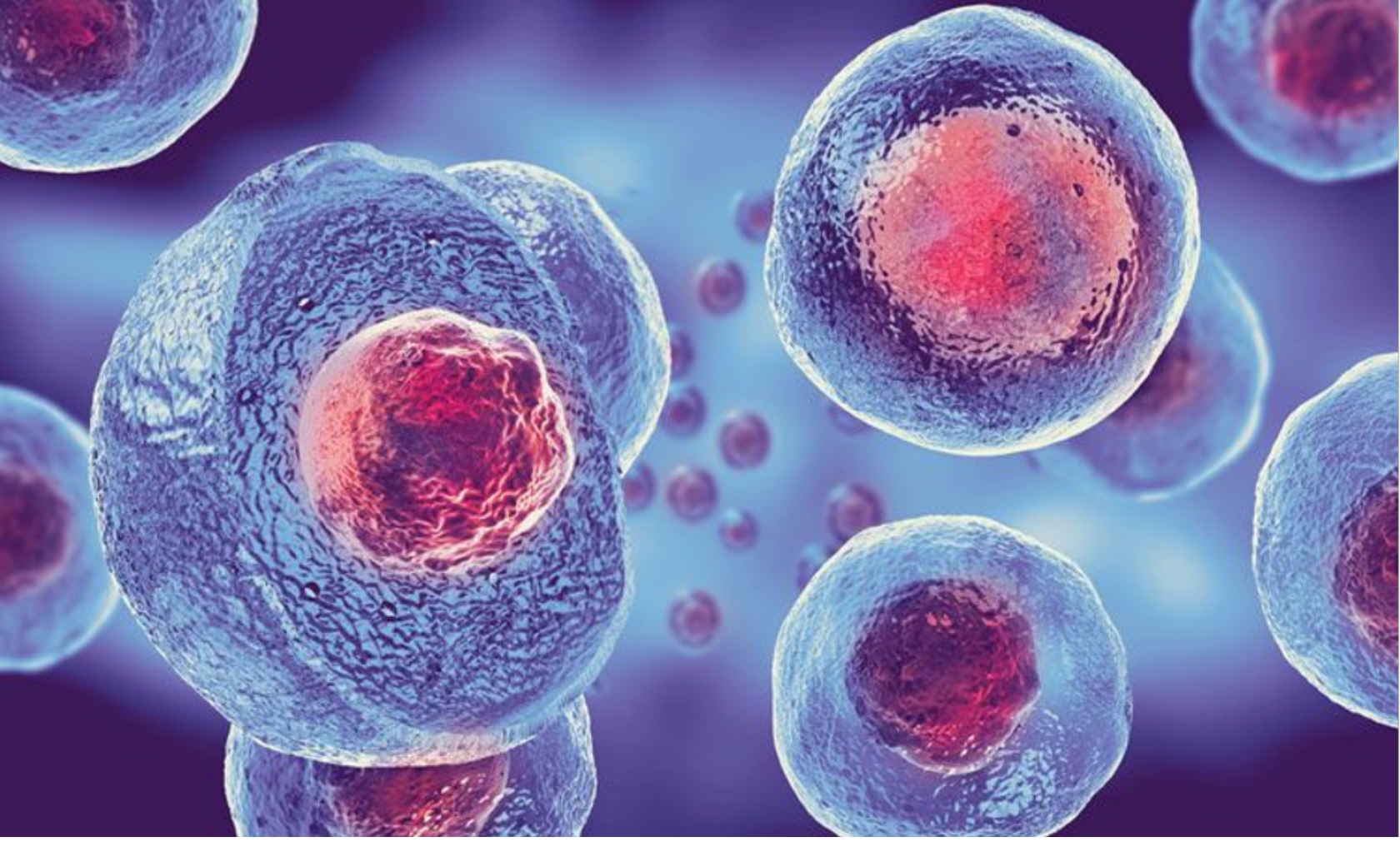

Stem Cell Research: A Brief History and Implications

BY AASHI PARIKH

Introduction

"To be, or not to be, that is the question."

Unlike any other cell in our body, stem cells maintain the dual properties of differentiation and self-renewal. They are the unspecialized precursor for all other cells in an organism, possessing the potential to differentiate into specialized cells in the body—be it a blood cell, nerve cell, or skin cell—depending on the signals they receive.1 Unlike differentiated cells such as muscle or nerve cells, which cannot replicate and have a limited life span, stem cells have the ability to perpetuate for life. Each stem cell division can result in either two daughter stem cells, two differentiated cells, or one of each.

Stem cells are categorized by their levels of potency. Totipotent stem cells are, simply put, a fertilized egg that can develop into an entire organism as well as the extraembryonic tissue necessary for its development.2 From totipotent cells arise pluripotent stem cells, which can differentiate into nearly any kind of specialized cell. Finally, multipotent stem cells, also known as adult stem cells, have a limited scope of cells they can differentiate into.

Deriving Human Embryonic Stem Cells

Pluripotent stem cells are the most widely used stem cells for both research and clinical studies. The only naturally existing pluripotent stem cells are embryonic stem cells, the cells found in the earliest stages of embryonic development. In 1981, Martin Evans and his colleagues at Cambridge University were the first to successfully identify, isolate, and culture embryonic stem cells from mice. This key discovery propelled James Thompson's research at the University of Wisconsin-Madison. In 1998, he successfully modified Evans' method to extract human embryonic stem cells (hESC).[3] Thompson's method involved extracting stem cells from donated embryos no longer needed for in vitro

fertilization.

This seminal discovery opened the doors to modeling human diseases with human cells, thus circumventing the limitations of animal models. Thompson's method was widely used for nearly ten years; however, there were several issues with its sustainability, including the fact that donor embryos come in limited supply.[4] Furthermore, this method of hESC derivation has been shrouded in controversy, primarily due to the ethical implications of "destroying" an embryo to extract the embryonic stem cells. This considerably slowed the pace of research utilizing stem cells due to stringent scrutiny by review committees and funding restrictions.[5]

Induced Pluripotent Stem Cells

In 2006, Kyoto University researcher Shinya Yamanaka made a breakthrough discovery for which he won the Nobel Prize in 2012. Yamanaka and his team demonstrated that somatic cells from adult mice could be reverted back to a "stem cell state." By expressing just four key genes, an adult cell was re-programmed to what is termed as an induced pluripotent stem cell, or iPSC.[6] These cells behaved almost exactly like naturally occurring pluripotent stem cells, only, unlike hESCs, they did not require an embryo. In addition to averting the ethical dilemma, iPSCs provided a virtually unlimited supply of pluripotent stem cells, unconstrained by donor availability.[7] As such, iPSCs have truly been transformative to the industry. However, their wide applicability does not owe to Yamanaka's discovery alone, as this study utilized fibroblasts from the skin of mice, rather than humans. In 2007, Thompson once again made a valuable contribution to stem cell research when he successfully altered Yamanaka's method to develop iPSCs from human fibroblasts.[8]

Since then, the use of iPSCs in research has been booming. 2022 alone saw nearly 3000 papers about iPSC-involved research.9 And with each year, this number only increases. According to research scientist Rémi Magnan of Tecan Genomics, iPSCs are "ideal candidates for the development of human cell models for research and drug screening, as well as for use in regenerative medicine, to repair destroyed tissue or even grow into new functioning organs."[10]

Clinical Applications

The remarkable regenerative and differentiative characteristics of pluripotent stem cells make them attractive candidates for therapeutic use. Currently, both ESCs and iPSCs are being explored in various clinical trials for conditions ranging from heart failure and Parkinson's disease to spinal cord injury. In spite of the promise they hold, their use in the clinic is currently limited due to potential safety concerns such as tumor formation and unwanted immune responses.[11] However, this has not impeded the unfortunate upsurge of fraudulent clinics touting unproven stem cell therapies for a wide range of diseases, many of which have led to patient injury and death.[12] In June 2019, a judge ruled against the actions of U.S. Stem Cell, a private company which declared that they could treat a variety of diseases using adipose (fat) stem cells derived from patients. Not only was there a lack of scientific or clinical evidence to support their claim, but the procedure ultimately resulted in the loss of vision for three

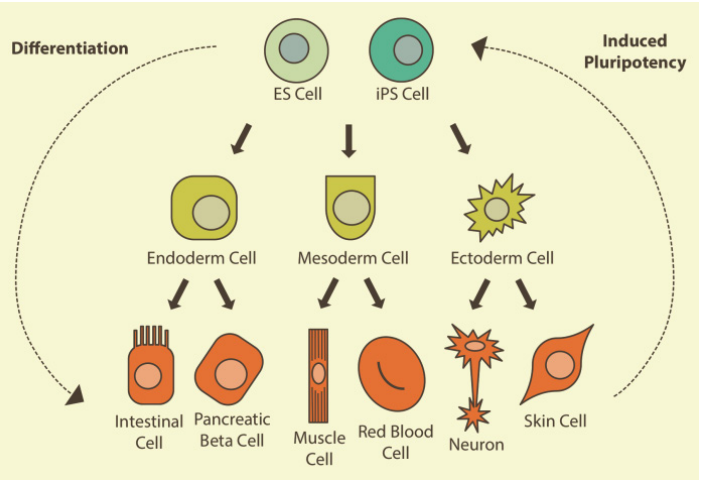

Figure 1: This diagram demonstrates two transformations: that of an embryonic stem cell (labeled ES Cell) into a specialized cell and that of a specialized cell into an induced pluripotent stem cell (labeled iPS Cell). *The ES cell can transform into one of 3 kinds of multipotent stem cells (endoderm, mesoderm or ectoderm), which then becomes a specialized cell (represented as the red cells). Induced pluripotency is the reversed processes, as demonstrated by the upward arrow to the left. It should be noted that this diagram is simply a representation; not all specialized cell types are shown.*[2]

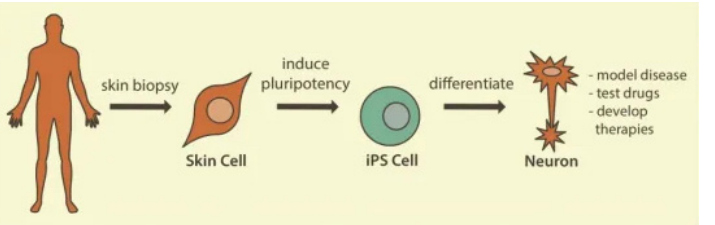

Figure 2: This diagram demonstrates the application of iPS Cells. *Adult cells are removed from the patient and then pluripotency is induced. The iPS cells are then differentiated again, into the kind of cell that is to be studied. In this case, a neuron is developed and can be used for the various purposes listed.*[2]

patients.[13] However, despite these unfortunate consequences, stem cell therapies are not a lost cause. With extensive research and improvements to our disease modeling methods, stem cell therapies have the potential to become a standard and widely used form of medical treatment.

Laboratory Applications

In regards to improving disease modeling, stem cells, more specifically iPSCs, are at the forefront of current research. Until recently, cell cultures (2D, single layer) were the most common method of modeling disease with stem cells. This method, however, does not faithfully replicate the cellular interactions of three-dimensional organ systems that may be critical to disease pathogenesis. The advent of using iPSCs to assemble miniature 3D organ models, called organoids, has opened up numerous possibilities in the field of medical research.[14] These remarkable structures have the ability to mimic the various functions of the organs they model, allowing the investigation of the disease at the

Figure 3: This image shows brain organoids developed from iPSCs in a University of California, San Diego laboratory. *They replace natural brain tissue in various studies with remarkable accuracy in their behavior.*[3]

whole organ level. Already, scientists are onto the next phase of adding a "4th dimension" to this modeling by designing multi-organ systems that are yet another step closer to building models that can more precisely mimic the complexity of the human body.[15]

Recent Research and Future Implications

One of the most groundbreaking developments occurred recently in August 2022. Two independent research teams, led by Magdalena Zernicka-Goetz[16] at the University of Cambridge, and Jacob Hanna17 at the Weizmann Institute of Science, published papers demonstrating the possibility of developing entire mouse embryos solely from stem cells: no sperm, egg, or womb required.

Although similar investigations have been long ongoing, the game changer in this study was the use of two kinds of multipotent stem cells. These, in conjunction with iPSCs, led to the formation of the yolk sac and placenta, two structures that are critical to embryonic development.[18] This would not have been possible with iPSCs alone. The scientists soon observed a remarkable phenomenon: akin to a natural embryo, the cells began to self-organize into embryo-like structures without requiring external triggers. Several of the expected features began to develop, including somites, which are the precursor for structures like skeletal muscle and vertebrae, a primitive heart that expressed genes necessary for cardiac development, and primordial germ cells (sperm and egg cells). But most significantly, the researchers found evidence that all of the regions of the brain had begun to develop, something that had never occurred in previous experiments.[19]

Models like this one reiterate how the field of stem cell research continues to expand. While Zernicka-Goetz hopes to use her research to better understand embryonic development and pregnancy failures, the implications of this breakthrough are truly staggering. For instance, there is interest in developing similar models of human embryos, which may provide researchers with the most complex, precise, and accurate human anatomical model to date. This might also lead to full-scale organ models, which would significantly expand disease research and treatment development. Although serious ethical ramifications are foreseen, the future remains very promising.

"To be or not to be." Perhaps it is no longer a question. As the research continues to advance, it has become increasingly clear that stem cells have endless potential, as they continuously break through the toughest biological barriers.

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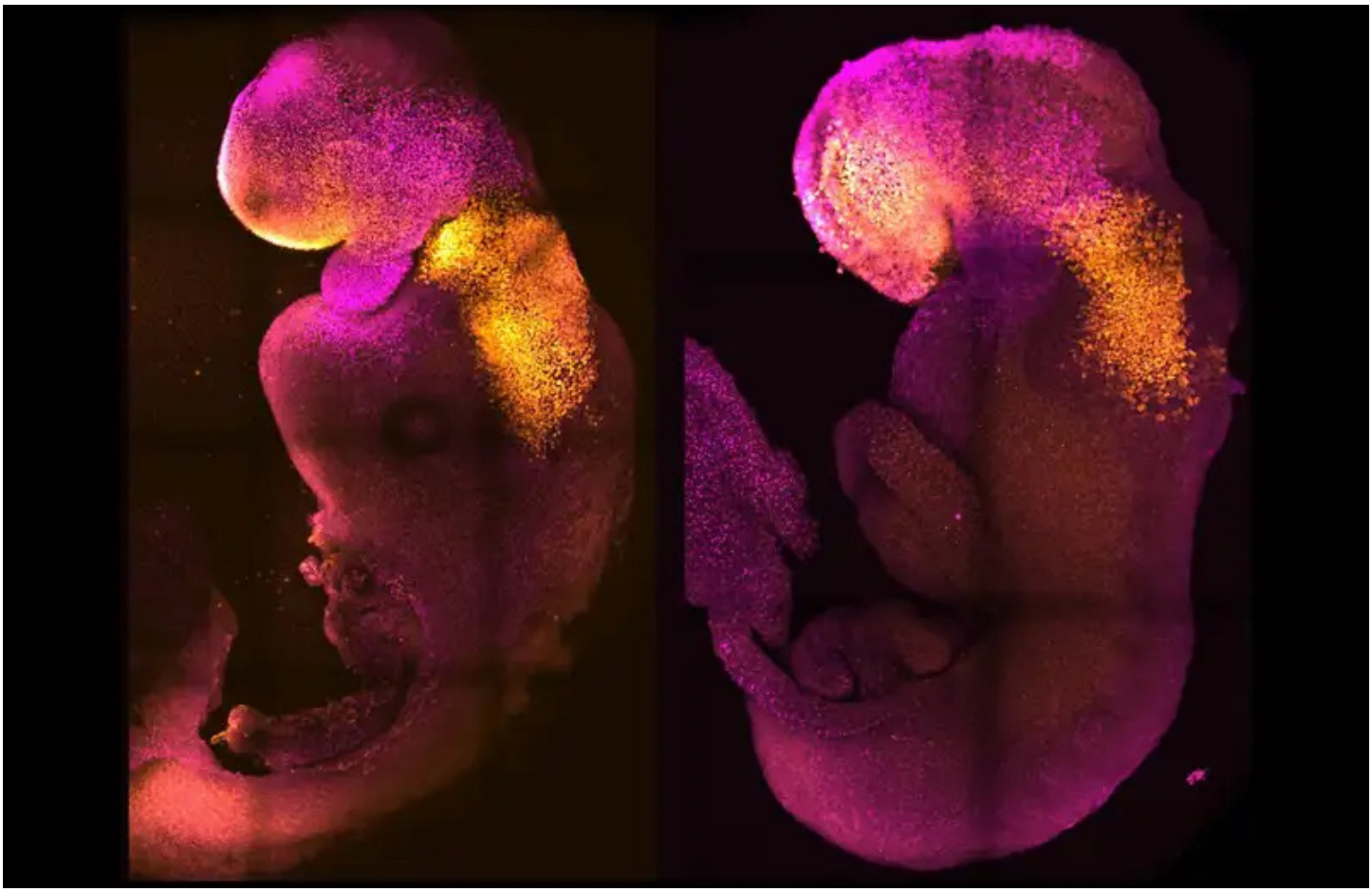

Figure 4: This image shows a side-by-side comparison of a synthetic (left) and natural (right) mouse embryos. *While there are some noticeable differences, it is evident that Zernicka-Goetz developed a rather realistic model.*[4]

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