Disease in the Dish: Transformation of HealthCare Continues

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After going through a lot of contention on various ethical concerns, stem cell research has grown up to become one of the most powerful biological tools which can potentially influence the treatment of almost every human disease. The Nobel Prize in Physiology or Medicine for the year 2012 was bestowed upon two stem cell researchers, Sir John Bertrand Gurdon, a developmental biologist from the United Kingdom, and Shinya Yamanaka, a Japanese clinician-scientist, for their discovery of methods which enable one to convert mature differentiated cells to pluripotent stem cells.

Sir John B. Gurdon is the pioneer who reached the biological start point beginning from the biological end point. He was the first to clone an animal from its intestinal cell in the early 1960's as a postgraduate student. There is a gulf of half century between the publishing of that path breaking paper, "The Developmental Capacity of Nuclei, taken from Intestinal Epithelium Cells of Feeding Tadpoles" in 1962 and the celebration of the work which has revolutionized the understanding of the science of cellular differentiation and laid down the foundation stone of regenerative medicine. Coincidently, in the same year of publication, Shinya Yamanaka was born who discovered, in 2006, the transcription factors, which are essential for initiating and maintaining the pluripotent state in a particular cell.

In 1952, Robert Briggs and Thomas J. King reported, "normal hatched tadpoles can be obtained by transplanting the nucleus of a blastula cell to the enucleated eggs of Rana pipiens" [1]. This fact led to the idea of transplanting nuclei from differentiated cells in the inquisitive mind of Sir John B. Gurdon at the time of his PhD in Oxford [2]. Every multicellular organism starts its life from a single cell but have different types of specialized cells in the adult stage to perform different functions. After fertilization of the egg, the zygote and subsequent initial cells have the potency to give rise to all types of specialized cells. However, as an embryo matures, cells start becoming more committed to a particular embryonic layer and then to an organ, a process of differentiation. However, all these cells contain the same DNA and should have the ability to form any type of cell. The question in front of Sir Gurdon was that whether these differentiated cells could be 'de-differentiated' to a stage where they are similar to early embryonic cells. Its answer lies in the revolutionizing study of Sir Gurdon which stated that free swimming tadpoles can be generated by replacing the egg nuclei with nuclei from fully differentiated intestinal epithelium [3]. Capability of conversion from a state of differentiation to a state of pluripotency of a somatic cell was conclusive from Gurdon's findings. The great insight provided by this experiment was that nucleus of a differentiated cell retains the ability to form all kinds of cells and that cytoplasm of an egg contain certain 'factors' that can control the de-differentiation of a nucleus from a differentiated cell. According to the Nobel Prize committee, "this discovery shattered the dogma that cellular differentiation could only be a unidirectional process" [4]. Gurdon's findings created the possibility of making animal clones using any nucleated differentiated cell. This possibility had turned into reality after 34 years of Gurdon's discovery in 1996 in the hand of Ian Wilmut by successful creation of Dolly, the sheep, thus silencing the critics who had looked upon Gurdon's discovery with skepticism.

After 44 years of Gurdon's discovery, Shinya Yamanaka identified 24 embryonic stem cell transcription factors. He planned to reprogram the differentiated cell into the pluripotent cell by adding these factors. His laboratory actualized a lucid recipe to reboot the differentiated cell nucleus and to turn the mouse skin fibroblasts into primitive stem cells in the duration of few weeks. Eventually, four transcription factors (Myc, Oct3/4, Sox2 and Klf4) were recognized to achieve the pluripotent-like state, designated as induced pluripotent stem cell (iPS cells) by Yamanaka and his colleagues [5, 6]. Later, germ line competent iPS cells were generated. He changed the history of science by developing the

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first human iPS cells in 2007. Basically Yamanaka's work has expanded this fundamental research arena beyond the ethical debate because his simple technique does not involve the nuclear transplantation in egg or embryo and does not involve the generation of an embryo.

In the 21st century when the world is facing a huge burden of communicable and non-communicable diseases, a novel strategy like iPS cell technology has tremendous prospects in the clinical setting. It has ignited a whole new arena in the field of regenerative medicine. The use of stem cell technology in the treatment of Parkinson's disease [7], thrombocytopenia [8], spinal cord injury [9], brain injury, macular degeneration [10], Alzheimer's disease [11] and schizophrenia [12] is already being studied in animals. It has also recast the therapeutic strategies to deal with type-1 diabetes mellitus. Damaged, degenerated tissue can potentially be replaced by this iPS cell technology. Pathology of the disease state can be better traced with the help of "disease in a dish" model which also helps to explore new drug targets. Beyond its potential clinical applications, iPS cell technology is now being explored by genetic engineers for the advancement of animal biotechnology. It has the potential to help wild life conservation projects by creating the possibility of generating clones of endangered species. This stem cell technology is also expected to have a profound impact in the science of organ transplantation because it is theoretically possible to generate human organs by this revolutionizing technology. Gurdon's work had given an impetus to the idea of therapeutic cloning. However, for that to happen, somatic cell nuclear transfer to an unfertilized egg was needed to generate the tissue required for transplantation. The main advantage is that there is less chance of graft rejection as the regenerated tissue carries the same genomic sequence. But this process involved generation of live embryos with severe ethical implications. Yamanaka's laboratory has alleviated this ethical concern by introducing just four transcription factors to the somatic cells and converting them to the iPS cell from which various specialized tissue can be generated as desired.

While the iPS cell technology has great potential to be helpful in clinical and biological arena, further research is needed before these benefits can be harnessed for the benefit of humanity.

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