CSE 701: Seminar

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Report

Induced Pluripotent Stem Cells - iPSCs
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1. Introduction

With the improvement in the field of bio-computing we are able to achieve milestone which were not achievable before. Induced Pluripotent Stem Cells or iPSCs is one such hot field which holds a lots of promises for the near future. Shinya Yamanaka pioneered iPSCs in 2006 and for which he received the Nobel Prize in 2012. The first human iPSCs was done by James Thomson in 2007. iPSCs holds great promises in the field of regenerative medicine. iPSCs, once perfected, would also have the ability to bring great changes in sexual reproduction. But the fact is that iPSC technology has not yet advanced to a stage where therapeutic transplant, clinical trials have been deemed safe and still there are multiple ongoing debate on the benefits of iPSCs.

This report tried to bring forward a holistic view of this technology. We start by understanding what iPSCs is, how they are made and other details associated with iPSCs. We then progress to understand these techniques by looking into two peer reviewed articles from Scientific America. This review would help us understand what to expect from iPSCs. The next approach is to understand the current research in this field and this helps to understand our current standing in iPSCs. To understand the practical aspect we look into two case studies conducted and in which iPSCs was a success on live species. This studies indeed act as promises for those days when iPSCs can become efficient and safe on human. We then move forward to understand the impact or implication that iPSCs can have in our daily lives. One of the main implication of impact of iPSC would be on sexual reproduction in human being. We focus on this topic to understand how iPSCs can bring a drastic change to human life or to human sexual reproduction. The final section is dedicated to the ethical issues that iPSCs would face in the long run. We try to illustrate the ethical, legal, economical question that iPSCs has to answer. The last section is the conclusion which summarizes this report. This conclusion also describe where we stand in the progress on iPSC and how long it would take for the humans to make this an established norm.

2. Induced Pluripotent Stem Cells - iPSCs

Induced Pluripotent Stem Cells or iPSCs are cells that are derived from the adult tissues, these adult cells are reprogrammed to behave as embryonic stem cell. Before understanding iPSCs we will look into Stem cell characteristics. Stem cells are undifferentiated biological cells that can differentiate into specialized cells and can divide to produce more stem cells. They are characterised by Self-renewal and Potency. Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell. Pluripotent SC are descendants of totipotent cells and can differentiate into nearly all cells. In Mammals two broad types, Embryonic stem (ESC) cells which contains the pluripotent stem cell and Adult stem cells which act as a repair system for the body, replenishing adult tissues. Adult stem

cells have limitations with their potency. They are deemed multipotent. Reprogramming allows for the creation of pluripotent cells i.e induced pluripotent stem cells from adult cells. The resultant cells are not adult stem cells, but adult cells (e.g. epithelial cells) reprogrammed to give rise to cells with pluripotent capabilities.

iPSCs are typically derived by introduction of a specific set of pluripotency associated gene or “reprogramming factor” into the given cell. The first demonstration was by Shinya Yamanaka at Kyoto University in 2006. The original reprogramming factor used by Yamanaka are the transcription factors Oct4, Sox2, c-Myc and Klf4 and it was done on mouse fibroblasts. These factors are conventionally used for iPSC, i.e reprogram mouse fibroblasts to undifferentiated, pluripotent stem cells, but each of them can be replace by another related transcription. miRNAs, small molecules or even unrelated genes. First Human iPSC was demonstrated by James Thomson at the University of Wisconsin–Madison in 2007. They were able to replicate Yamanaka's finding that inducing pluripotency in human cells was possible.

To understand more about iPSCs we will look into the paper **‘Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells’** [1] by James A. Thomson and his team, who was the first to derive the iPSCs in human. The creation of human iPSCs involved a different set of transcription factor unlike the one used by Yamanaka, it involves Oct4, Sox2, Nanog and Lin28. Studies by James A. Thomson and team showed that the use of c-Myc causes death and differentiation of human ES cells. The expression of NANOG also improves the cloning efficiency of human ES cells and thus could increase the survival rate of early reprogrammed cells. Multiple testing was done for the last transcription factor, and OCT4, SOX2, NANOG, and LIN28 resulted in colonies with a human ES cell morphology (iPS colonies) which were visible 12 days after transduction. After 20 days total of 198 iPS colonies were visible. This new transcription was sufficient to reprogram human somatic cells to pluripotent stem cells that exhibit the essential characteristics of embryonic stem (ES) cells. The cells derived after this transcription exhibited characteristics of human ES cells, and maintain the developmental potential to differentiate into advanced derivatives of all three primary germ layers. Such induced pluripotent human cell lines should be useful in the production of new disease models and in drug development, as well as for applications in transplantation medicine. However these application face a huge amount of technical limitations. It is also evident to notice that the transcription factor varies from species.

The human iPSCs described in this paper meet the qualities to qualify as a ES cells except the fact that they are not derived from the embryos. Similar to the human ES cells, human iPS cells should prove useful for studying the development and function of human tissues, for discovering and testing new drugs, and for transplantation medicine. The later part of the paper describes the uses of iPSCs. iPSCs can be used as a substitute for the ES which are obtained from human embryos thus this can end ethical issues associated with it. For transplantation therapies based on these cells, with the patient-specific iPS cell lines should largely eliminate the concern of immune rejection. However It is important to understand that before the cells can be used in the clinic, additional work is required to avoid vectors that integrate into the genome, potentially introducing mutations at the insertion site. For drug development, human iPS cells should make it easier to generate panels of cell lines that

more closely reflect the genetic diversity of a population and should make it possible to generate cell lines from individuals predisposed to specific diseases.

Even though iPSCs sounds attractive, there are many challenges that iPSCs face which would limit the use of iPSCs in clinical trials in the near future. iPSCs has a very low efficiency. Reprogramming into iPS cells has a success rate of 0.01–0.1%. This reflects the need for precise timing, balance, and absolute levels of expression of the reprogramming genes. It is also a reflection on the lack of technological advancement. One of the major concern is the Tumorigenicity associated with iPSCs and this is considered as a significant risks that limits their use in humans. Many experiments have shown that iPSCs readily form teratoma. Teratoma is a tumor with tissue or organ components resembling normal derivative of more than one germ layer. Another common issue with iPSCs is Incomplete reprogramming, iPSCs faces the challenge of completeness. In United States iPSCs have not yet been approved for clinical trial and iPSCs has not yet yielded any clinical benefits as of present.

In the face of all the challenges and limitation associated with iPSCs one of the greatest advantage of iPSCs would be an ethical one. The human ES cells used for studies has always been a controversial subject as it involves destruction of human preimplantation embryos, and iPS cells remove this concern. Further work is needed to determine whether human iPS cells differ in clinically important ways from ES cells. But we need to go a long way before iPSCs can be safe and perfect for clinical trials on human.

3. Scientific American Articles

To understand more about iPSCs we look into two articles that are published in Scientific America. The first article is "**Fat cells can be used as efficient iPSC**" [2]. This article explains now Fat cells are used to create iPSC team of cardiologists and plastic surgeons, explains the advantages of this.

The normal norm to make a iPSCs is from the skin cell and reprogramming the cells to form the iPSCs. This team from Stanford University School of Medicine, which consist of cardiologists and plastic surgeons found adipose fat cells to be much more efficient than skin cells at turning back into stem cells. When the skin cell is used to create the iPSCs it takes few weeks to be cultured into pluripotency. This team of researcher has come up with the conclusion that fat cell, adipose cells which are readily available as they would have ample fat to harvest the iPSC culturing. They have estimated each liter of fat promises hundreds of millions of potential cells, this is however can be considered as an ideal assumption because iPSCs has a success rate of 0.01%. Other cells were also tested for this, like the stomach cell, liver cell but it turn out that the Fat cell was the prime cells to culturing the stem cell. It was also studied that adipose cell can turn into iPSCs twice as fast as fibroblast skin cells and with 20 times the efficiency. The efficiency has always been a concern with iPSCs as described in the previous chapter. When using the skin cell for iPSCs there is an intermediate step where a mouse feeder cell is used to impart the pluripotency. Being able to

skip the mouse feeder cell step necessary with skin cells, along with the shortened culturing period, may make the new method more palatable to the U.S. Food and Drug Administration (FDA), which must approve such treatments for human use and prefers methods that reduce opportunities for contamination. And at present FDA has not given a thumbs up for clinical trials involving iPSCs on human.

But unfortunately we would need to have an intensive studies/research before iPSCs can be open for clinical trials. The potential of iPSC to spark cancer is also a major concern to this. This study was by Wu and Longaker, from Stanford University School of Medicine in the year 2009. After investigating on further research/studies or papers published, on how creating iPSCs from adipose can be made efficient, I would conclude that there has not been significant progress in this specific topic in the later years.

The second article is "**Cell-Off: Induced Pluripotent Stem Cells Fall Short of Potential Found in Embryonic Version."**[3] from Scientific America. This article unlike the others looks into the darker side of iPSCs research - problems associated with iPSCs. This article is about the effects and uncertainty surrounding iPSC, It explains the high cell death rate for the iPSC. The initial advances in the studies and research conducted on iPSCs sounded promising but the reality appeared to been filled with uncertainty. It was believed that would be a non-controversial alternative to embryonic stem cell but the low replication rates and early senescences (loss of a cell's power of division and growth.) have impeded their efficacy in generating differentiated cell. There were multiple issues related to iPSCs, which has limited their use on human or clinical testing.

This study was done by Robert Lanza, chief scientific officer at Advanced Cell Technology in Worcester, Mass[3] in the year 2010. Lanza and his colleagues investigated a range of cell types derived from eight human iPS cell lines and 25 embryonic stem cell lines. At first they found that human iPS cells could indeed generate blood vessel, blood precursor and retinal cells with similar characteristics to those derived from embryonic stem cells. Studies also showed that iPSCs have higher rates of cell death, than ones from embryonic stem cells. Moreover, whereas the blood vessel cells that resulted could also form capillary like structures, they and the retinal cells aged prematurely, losing their ability to divide. In addition, iPSCs lacked potential for proliferating when compared to ES cells. And it was noted that there is a significant reduction in the rate, up to 1,000- to 5,000-fold less activity. The abnormality in the iPSCs may be related to the viruses uses to create them. Some of the studies shows that these anomalies are lower in those iPSCs which are created by virus-free reprogramming strategies. But still we lack solid evidence to conclude this claim.

4. Current Researches - Peer Reviewed Articles

This section deals with the current research in the field of iPSCs. Two of the recent and more latest paper/studies in the field of iPSCs are discussed in this section. The first study is

on the paper **"Bioinformatic analysis of the four transcription factors used to induce pluripotent stem cells."** [4] published in the year 2014.

As discussed iPSCs are type of pluripotent Stem cell artificially derived from normal cell, non-pluripotent cells by overexpressing the transcription factors Oct4, Sox2, Klf4 and Nanog. These factor plays a crucial role in these cells but however the function of these factors are not fully characterized. This study analyzed Oct4, Sox2, Klf4 and Nanog in ten different species using bioinformatics. Nanog does not exist in the invertebrates, which can be responsible for the developmental differences between vertebrates and invertebrates. Expression of Klf4 reduced to the least during differentiation, and Klf4 was found to be specifically expressed in several normal tissues, especially the salivary gland. This paper performs an in-depth analysis of different transcription factor and how there variation affected the organism. Multiple bioinformatics technique were used to study and analysis these factors.

The conclusion that can be drawn from this study is that Oct4, Sox2, Klf4 and Nanog play important roles in stem cells and the early stages of development and they need to be well characterized. The four transcription factors used to induce pluripotent stem cells were not found to be similar for the species. For example Nanog is functionally conserved from fish to mammals. This indeed was a fact which was already evident from the experiment of mouse iPSCs created by Yamanaka and human iPSCs created by James Thomson uses different set of transcription factors. The use of transcription factor that Yamanaka used to create the mouse iPSCs did not give expected result when used to create Human iPSCs by James Thomson. The human cell deaded out and had abnormal behaviours. The exact mechanisms regulating the reprogramming of somatic cells back to a pluripotent state are not fully characterized. Systematic analysis done in this study of the transcription factors used to induce stem cells has provided further information. But however, some details of the function of Nanog, Oct4, Sox2 and Klf4 remain unclear. The paper conclude by stating that further research is required to investigate why some of these stem-cell related factors are present in various species and absent from others.

The second study is on "**MicroRNA-199a induces differentiation of induced pluripotent stem cells into endothelial cells by targeting sirtuin 1**" [5]. It is a study on how miR-199a is involved in EC differentiation from iPS cells. miR-199a inhibited the differentiation of iPS cells into smooth muscle cells. Notably, sirtuin 1 was identified as a target of miR-199a.

MicroRNAs (miRNAs) are involved in a number of core biological processes, including cardiogenesis, hematopoietic lineage differentiation and oncogenesis. The **miR-199 microRNA precursor** is a short non-coding RNA gene involved in gene regulation. miR-199 genes have now been predicted or experimentally confirmed in mouse, human and a further 21 other species. An improved understanding of the complex molecular signals that are required for the differentiation of iPS cells into endothelial cells (ECs) may allow specific targeting of their activity in order to enhance cell differentiation and promote tissue regeneration. **Endothelium** is a type of epithelium that lines the interior surface of blood vessels and lymphatic vessels, forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall. It is a thin layer of simple squamous cells called

endothelial cells. They line the blood vessels of the circulatory system, and from the barrier between the circulating blood and the rest of the vessel wall. The present study reports that miR-199a is involved in EC differentiation from iPS cells. Augmented expression of miR-199a was detected during EC differentiation, and reached higher levels during the later stages of this process. miR-199a inhibited the differentiation of iPS cells into smooth muscle cells. Sirtuin 1 was identified as a target of miR-199a. Finally, the ability of miR-199a to induce angiogenesis was evaluated in vitro. The present study provides support to understanding of the molecular mechanisms underlying vascular cell differentiation, stem cell regenerative therapy may ultimately be developed as an effective treatment for cardiovascular disease.

The endothelium is a dynamic and heterogeneous organ with secretory, metabolic, synthetic and immunological functions. Impaired EC function may result in hypertension, thrombosis, inflammation and atherosclerosis. Repair and regeneration of vascular cells, in particular of ECs, has been a research focus for a number of years. However, in the context of human disease, the use of adult progenitor or vascular stem cells has certain limitations, such as the identification and availability of appropriate, and effective cell-types. The ability to derive ECs from pluripotent stem cells has extended the scope of regenerative medicine.

The paper describes the in-depth steps and procedure that the team has followed to provide evidence to their arguments on the effect of miR-199a on EC differentiation. This experiment provides insight into how iPSCs can be used for **regenerative medicine**. Most of the treatment for serious illness which needs a matching of donor are difficult because it's always not possible to find the perfect donor to proceed further. In this matter iPSCs can be a life changer as the required cell (in this experiment the ECs) are derived from the patient and there would not be much of a issues with compatibility with the patient . iPSCs have greater promises in the field of regenerative medicine. The current progress are worth crediting, but however it would take a couple more of year for iPSCs to be perfected and used on human. The tendency to cause tumor associated with the cells derived from iPSCs and the low life expectancy of these cell have always been a concern. In the long run it would take a couple of years for iPSCs to be perfected for clinical trial.

5. Case Studies

In this section the discussion is on iPSCs experiments conducted on live animals, this provided solid evidence that life can be created with iPSCs. This section discuss two experiments done on mice to produce mouse embryo with the aid of iPSCs. The first case study is the "**Eggs Created in Dish Produce Mouse Pups**"[6], published in Sciencemag done, by a group of researcher led by stem cell biologist Mitinori Saitou, at Kyoto University, Japan in 2012.

The stem cell used are embryonic stem (ES) cells and induced pluripotent stem (iPS) cells. embryonic stem (ES) cells are taken from embryos and the induced pluripotent stem (iPS) cells are adult tissue cells that are reprogrammed to act like stem cells. In the case of sperm, the group started with ES and iPS cells and cultured them in a cocktail of proteins to produce primordial germ cell-like cells. To get the egg cells they mixed the primordial cells with fetal ovarian cells, forming reconstituted ovaries that they then grafted onto natural ovaries in living mice. Four weeks and 4 days later, the primordial germ cell-like cells had developed into oocytes. The team removed the ovaries, harvested the oocytes. This was followed by fertilization in vitro. The fertilizer eggs is implanted into surrogate mothers. About 3 weeks later, normal mouse pups were born. This was one of the experiments that proved it's possible to produce oocytes capable of sustaining complete development starting with embryonic stem cells.

The second case study is on "**Mouse egg cells made entirely in the lab give rise to healthy offspring**"[7], published in Sciencemag, performed by Hayashi and his colleague Mitinori Saitou, at Kyoto University, Japan in 2016. This article describe how researchers have used stem cells to grow fertile mouse egg cells for the first time entirely in a lab dish. The eggs gave rise to pups after being fertilized and implanted into rodent foster mothers. There was a success rate of 1%, so producing human egg cells would not happen in the near future. But the technique could help to identify key genes involved in egg development and maturation. This research was the part of decade of studies by this group of researcher to develop an efficient way to derive egg cell and sperm cell also called as germ cell by the technique of iPSCs. In the first case study they made fertile egg cells from both mouse embryonic stem (ES) cells, derived from early mouse embryos, and induced pluripotent stem (iPS) cells. The final steps of egg development, involve the implant of those stem cells into a living mouse. This final step is discussed as the second case study in this report. The scientists used ES and iPS cells to make immature egg precursor cells. Then they inserted those precursors into clusters of cells taken from fetal mouse ovaries. They carefully cultured those cell clusters for more than a month.

These experiments also showed a higher rates of chromosome abnormalities. Out of the 300 two cell embryo only 11 - 3% - of these grow into full term pups, compared to the 62% of the eggs taken from adult mice and fertilized in vitro. The pups that did survive grew into apparently healthy, fertile adults. However these experiments has successful result on mouse but human trial would not happen any time soon as there is a need to perfect this technique and make it more safer and reliable.

6. Forecasting the Revolution in Human Reproduction using iPSCs

iPSCs come with many promises for the future, also it's true to argue whether the future is a distant or a near one. One of the greatest implication would be in sexual reproduction. iPSCs

once perfected can create a world where human sexual reproduction could become an obsolete term (as well as an act) and most would stop practicing this act, as they become more reliable on iPSCs for creation of the next generation. Although it sounds like a science fiction it's not as fictitious as it sounds as the studies done so far do promises that this can be possible in future. The article **"Forecasting the Revolution in Human Reproduction using iPSCs**"[8] deals with this topic.

The forecast is that within 20 to 40 years most human reproduction will happen in the lab, rather than the reproduction that occurs as a result of sexual act. One of the main point to be stated is that end of sex does not mean that it refer to the end of human sexuality but the act of sex for the main purpose of bearing a child. This article explains some of the view by Hank Greely, a Stanford professor who teaches law and genetics. The iPSCs approach is different from the designer baby concepts. In iPSCs we would obtains multiple fertilized embryos and the parents sit down with the lab assistant and filter out the best embryo that fits the description given by the parents. This approach can be possible if iPSCs turn out to be a flawless approach and produce a huge number of eggs and sperm (if father cannot produce, normally there is no deficient of sperms) and has a higher success rate. Once these are fertilized then the selection can be done. As the sample has a huge number this allows a wide choice to the parents. At the end the parents can choose the most healthy, intelligent or whatsoever is there desired quality baby. The quality of the baby is estimated by the gene sequencing, as this gives a blueprint on all the quality, risk of diseases etc of the baby. On the other hand designer baby is about getting a few embryo and changing their genome sequence to obtain a baby that is designed by required features. Designer baby concept is on modification of embryo to create the best one, but iPSCs approach would be selection of the best embryo among a huge sample.

iPSC allows making eggs thus focused mainly on eliminating the need for egg harvesting, which is expensive, unpleasant and risky. iPSC can make eggs from skin cells, you could make hundreds of thousands, potentially millions. Greely also question the moral aspect of iPSC. Like he discussed the possibility of getting some skin cells from a celebrity or a movie star and making a baby from them. It can be as easy as just a shake hands and rubbing off some skin cells, and then turn them into an egg and have their baby. Which again raises question of un-owned babies. Misuse of this technology to create a bunch of people who can be used for meaniant work, slaves, sex worker, personal live sex toys, army of clone super humans or anything that the human mind has imagined and fascinated to create would be possible with iPSCs. I would even imagine a situation where iPSC is used by insurance company to insure people and get their skin cell & use iPSCs to create their clones. These clone can be used as a life insurance and dissected to take organs for use by the insured person [reference to the movie **"The Island", 2005**]. Use of iPSCs for Organ harvesting and surrogate motherhood for wealthy people in the world would also turn out to be a true in the near future. There are ethical issues about the life of these clones, the 'right to live' for them is a question to be answer. Who gets to decided to end the life of the clones when there is a need by the insured person? These are ethical moral question which obviously needs answer, even if the society approves, these are still a matter of concern. It's a reflection of a dissected society divided by gene and superiority of gene with a dangerous mix of wealthy, power and richness.

7. Ethical issues to iPSCs

To understand the ethical issues associated with iPSC the following article was referred - "**A Triumph for Ethical Stem-Cell Research"** - from a website StayCatholic (http://www.staycatholic.com)[9]. Even though it can be argued that the website or the source of information is not authentic but the points discussed are sensible and are sure to become ethical issues related to IPSC. It also explains the exploitation that iPSC can cause in society. It also illustrate how some scientific invention are praised by the science community but are considered as threat by another community of people.

One of the greater moral, ethical supporting factor to iPSCs is that is can be defined as an alternative to the embryo derived stem cell research. And iPSCs is one of the best experimented alternative for this. The result were so promising to say that iPSCs can be spelled the demise of embryonic stem-cell research. But the current advancement in iPSCs are not so promising as we still need both the embryonic stem cell as well as the iPSCs for the experiments. Hence the embryonic stem-cell is still in demand.

The next major question is will iPSCs be misused in the future. The greatest benefits of iPSCs when miss used, can in turn be the greatest ethical concern to iPSCs. If the researchers tried to use direct cellular reprogramming to produce human embryos, that is, if, rather than create pluripotent cells, they tried to create "totipotent" cells (e.g., cells such as the human zygote with a complete capacity for organismic development), then it would be just another type of unethical embryo-exploitative research. Reprogramming would also be unethical if it were used to create female or male gametes (eggs or sperm cells) with the intent of using them for assisted reproduction in humans. All the major points stated in the above section also holds true for this section as well as they can also be ethical issues related to iPSCs. Issues related to 'parentless' human embryos and the biological, ethical, and legal issues they will raise are of concern to iPSCs.

Once iPSCs is fully perfected, then it would be a social norm to have kids by this method, and the society/government would force people to take this approach, which itself would be a threat for the people's right, freedom, choice. This would create a society which has people with superior genes thrive and those with a lesser quality gene would have to struggle to keep up. Its can lead to development of a society which is governed by the superiority of gene and those with the best gene survive and get more benefits. I would like to explain this by an example, the selection to a job at present is based on, lets say background checks, but our future will be a Dystopian society that does a genetic test for jobs, marriage or all other activity (even driving, so as to reduce accident rates. The lesser human being are prone to more mistake and fatigue compared to their superior genetic counterparts). And I believe that this is exactly what is depicted in the movie "***Gattaca"***, 1997. A movie that is a science fiction in the year 1997, an inspiration in the present year - 2017 and probably & eventually a reality in the year 2047, 30 years from now.

8. Conclusion

iPSCs is indeed a promising field, but with the current technology and advances it would take a longer time to see things happen that are discussed in this report. Human ES cells remain controversial because their derivation involves the destruction of human preimplantation embryos, and iPSCS technique would be a solution for this. Further in the future, the technique could lead to a new tool for treating infertility. However, further work is needed to determine whether human iPS cells differ in clinically important ways from ES cells. iPSCs have not yet yielded any clinical benefits is of concern when discussing how beneficial iPSCs would be in future. Cancer causation and tumor formation is also a greater concern for use of iPSCs to treat human diseases.

iPSCs research/studies has many benefits to offer but this require time, resource, technology and international efforts. One idea I would believe is to develop a project like the **Human Genome Project (HGP)** (as discussed in class) which would be an efficient model to progress in this field of study. The Human Genome Project which was an international scientific research project which involved a large efforts and resources by multiple countries was [eventually] a success. A collaborative research project on iPSC would be one of the efficient approach to study this subject and to make progress as individual progresses are time consuming and not correlated well. If there is a community of internationally recognized team that focus on iPSCs research then we would be able to progress faster. It helps for resource sharing and aid other researcher, and help them to catch up and stay ahead. My search for such a community led me to this paper "**International Coordination of Large-Scale Human Induced Pluripotent Stem Cell Initiatives: Wellcome Trust and ISSCR Workshops White Paper**"[10], 2009, which clearly illustrates that there are global efforts going on to share the resources for iPSCs, especially human induced pluripotent stem cells (hiPSC). It is also a sign of growing recognition for the potentials for this technique. And I believe that an international project with combined efforts of many institutes and one with a well defined timeline would be required in near future to bring rapid progress in the field of iPSCs.

In short our knowledge of iPSCs is limited and we needs decades of studies, research, experiments on this field, and as suggested a universal efforts, to come up with a perfected iPSCs technique. I believe that it would take 2-4 decades and a wholehearted Universal Collaborations and Commitments, to achieve this state of perfection, until then iPSCs would be a matter of debate and concern.

9. References

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