Induced Pluripotent Stem Cells: An Innovative Patient-Specific Neurodegenerative Disease Modeling

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Received Date: April 04, 2017, Accepted Date: June 14, 2017, Published Date: June 20, 2017.

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Abstract
Recent Progress in pluripotent stem cell biology has nourished the hope to use for brain repair stem cell based therapy. Cell reprogramming diseases models seems particularly hopeful in the field of human neurological disorders including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, for which animal models could be not enough inclusive for describing all aspects of disease pathology. In addition, to improve specific subtype neural differentiation developments aimed at reprogramming technology have been made.

Brain repair issue, recognized the induced pluripotent stem cells as the most significant space of intervention because of the high rate expansion, as a cell source in transplantation and cellular therapy. It possess attractive features, including the capacity for large-scale expansion as a cell source for neural transplantation, procedures and potential for differentiation into a range of potentially therapeutic cell types relevant for specific neurological conditions.

While collecting iPSC we obtain a unique and well characterized source to clarify disease mechanisms. Such a procedure represents a human stem cell platform for discovering potential drugs as well as new opportunities for mechanistic studies. In this review, we introduce iPSC-based disease modeling to be applied in neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

Keywords: Induced pluripotent stem cells; Neurodegenerative disease; Disease modeling; Drug screening

Introduction
History and Perspective of Human Embryonic and Somatic Stem Cells

The physiological processes where tissues reconstitute their missing or damaged parts are called “regeneration”. The abilities of mammals to regenerate cells, tissues or organs have attracted the attention of many researchers from all over the world. In some tissues, such as in liver; after partial hepatectomy regeneration occurs; thanks to pre-existing progenitors and does not require differentiation [1–7]. This evidence raised the expectation that some debilitating human diseases can be treated with cell-based therapy. Although the development of a stem cell therapy is still initial and implies ethical and technical difficulties, the first successful achievements are beginning to be reached as in the case of bone marrow transplants in patients suffering by blood disorders [1,8–11].

Regeneration of tissues originates from “stem cells”, a term originally coined by botanical researchers observing the regenerative abilities of plant meristems, and then it has been extended to the animal world. In the next section, we will provide a brief overview about stem cells.

The human body is made by four categories of cells: embryonic-, primordial germ-, fetal- and somatic stem cells, also classified according to their developmental ability as multipotent, pluripotent and totipotent. As germ cells give rise to gametes (i.e. eggs and sperm), somatic cells give origin to differentiated cells with its own copy of the genome. Stem cells, as that, have the capability to replicates indefinitely and to acquire specialized phenotype in culture. The stem cell dividing process (characteristically asymmetric) leads to daughter cells with a possible double fate: one goes towards a mature somatic cell and/or generating a new stem cell. This second path ensures a constant replenishment of stem cells pool in adult organs [8,12]. The capability to give rise to all cell types of the body, including the entire fetus and placenta, is referred as totipotency. This characteristic endows cells the possibility to form the whole organism. After fertilization, human totipotent cells become approximately 16 and lose their totipotency, forming the blastocyst. This cluster of cells contains a smaller group of pluripotent cells, known as the inner cell mass (ICM), which will give rise to tissues of the three germ layers generating the complete soma of the adult organism. For this reason, they are often termed “true” stem cells.

Embryonic Stem Cells (ESCs) are generated in the Inner Cell Masses (ICM) of mammalian blastocysts and expands in vitro to express the telomerase gene, preventing cells from undergoing senescence. These cells also preserve a normal karyotype after continuous passage in vitro, thus making them truly immortal.

A pluripotent stem cell class that has been well characterized is represented by Primordial Germ Cells (PGCs), which migrate to the developing gonads where the close association with their somatic cells gives rise to the ovaries and testes in females and in males, respectively. After a period of mitotic proliferation, the PGCs undergo meiosis and differentiate into mature gametes, either eggs or spermatozoon.

Another particular type of pluripotent stem cell isolated from the developing gonadal ridge of 5–9 week-old fetuses of elective abortions are the human embryonic germ cells [13,14]. These cells are pluripotent and capable to generate all three germ layers.

Fetal stem cells have been isolated in the fetus which is responsible for the production of different tissue-specific cellular precursors as neural stem cells, abundant in the fetal brain differentiating into both neurons and glial cells, fetal hematopoietic stem cells, fetal mesenchymal stem cells and pancreatic islet progenitors.

Somatic stem cells are present in all tissues and are considered multipotent because their differentiation potential is restricted to a limited range of cells and tissues confined in their location, e.g. blood stem cells give rise to red blood cells, white blood cells and platelets.

Within this vast class, the Hematopoietic Stem Cell (HSC) has
been the best-studied and widely applied for over 40 years in clinical practice creating the background for the bone marrow transplantation success [15]. Unfortunately, HSCs, are difficult to isolate in large numbers because of their in vivo niche. However, somatic stem cells have been also derived from many organs such as brain (neuronal stem cells), skin (epidermal stem cells), eye (retinal stem cells) and gut (intestinal crypt stem cells) [11,16–18]. In the presence of a local injury, they start to divide generating daughter cells able to differentiate into that specific tissue.

In vitro, somatic stem cells, such as HSCs or MSCs can undergo the phenomenon "trans-differentiation", subverting the previous conviction that attributed a rigorous commitment during embryonic development.

Pluripotency Controlling Pathways: Role of Transcription Factors

Human Embryonic Stem Cells (hESCs), owned by self-renewal capacity, represent a powerful model to investigate early human development by pursuing new strategies in the regenerative medicine field [19]. For the achievement of this goal it is not enough to develop new in vitro culture techniques indeed, we should know intrinsic and extrinsic regulatory factors of stem cell proliferation knowledge which is still limited.

Although hundreds of genes tightly correlated with hESCs, differentiation have been identified, by using whole genome investigation only several transcription factors as OCT4, SOX2 and NANOG are known to be necessary for the maintenance of self-renewal and pluripotent state of hESCs. In fact, it has been demonstrated by gene knockout studies that hESCs lose the capacity to conserve pluripotency, upon knockdown expression of these proteins. To date, many scientific studies have focused on the molecular mechanisms subtended hESCs pluripotency and differentiation, and it is now clear that both transcriptional and post-transcriptional levels of regulation have decisive roles.

It is known that OCT4, SOX2 and NANOG constitute a core regulatory circuitry [20–22]. In fact, the three transcription factors co-occupy an extensive subset of their target loci, by activating either genes involved in the maintenance of the undifferentiated pluripotent state or in the repression of genes involved in tissue specific differentiation co-operating with Polycomb group proteins [22]. Finally, OCT4, SOX2 and NANOG also sustain each other’s transcription in auto-regulatory and feed forward loops [23]. The maintenance of such transcriptional regulatory circuitry is crucial to preserve the pluripotency of hESCs, as even slight variations in the levels of the core factors is sufficient to trigger differentiation [22].

It is known that Oct4 plays a key role in the maintenance of pluripotency, as demonstrated by the failure of pluripotent ICM in embryos defecting for Pou5f1 gene. As reported for embryo defecting for Pou5f1 gene, the lack of Sox2 genes in mutant embryo results in the loose of the pluripotent character. This result confirms the essential role of Sox2 plays in early embryo precursor cells and their in vitro stem cell equivalents [24,25].

Nanog is a homeodomain (HD) protein that seems to be crucial for mammalian development and it is required for the growth and differentiation of the ICM in the preimplantation embryo [26,27]. For this reason, it has been shown that the successful derivation of ESCs from the mouse blastocyst is tightly correlated with the expression of Nanog [28].

The Opportunity of iPscs: Reprogramming Adult Somatic Cells to Become Pluripotent Stem Cells

In 2007, Kyoto University researchers identified experimental conditions useful to induce adult somatic cells to become a pluripotent stem-like cell trough genetically "reprogramming" technique [29]. The introduction of genes that regulate the pluripotent developmental stage to maintain the properties of embryonic stem cells (ESCs) is the key to reprogram adult cells to embryonic stem-like state obtaining the so called induced pluripotent stem cells (iPSCs).

Starting from the discovery of the reprogramming technique, the experimental protocols to generate iPSCs have been rapidly improved by interfering with the developmental fate of the adult cells. The utility of iPSCs has revealed its masterpiece application in the field of disease modeling, drug development and transplantation medicine considering that ethical and moral issues correlated with the derivation of ESCs do not involve iPSCs preparation by offering no controversial approach.

Another advantage in the use of iPSC technique is overcoming the difficulty in obtaining (for large-scale production), isolating, culturing, purifying, and differentiating pure stem cell lines directly derived from embryonic tissues. Therefore, it is understandable that clinicians and researchers have been attracted by the possibility to obtain an immune-matched supply of pluripotent cells coming from patient’s tissues.

The iPSC strategy initially set up by Yamanaka et al. in 2006 [30], regarding the reprogramming of mouse fibroblasts, using a retroviral expression vector reported only four transcription factors (Oct4, Sox2, Klf4, and c-Myc) to switch on the expression of genes involved in the maintenance of the embryonic pluripotent stem cells state (Figure 1).

In fact, DNA encoding transcription factors must be introduced and integrated into the somatic cells genome. One possible delivering approach system, selected by Yamanaka, has been performed by using retroviral vectors.

The initial acquisitions on iPSCs obtained by using reprogrammed mouse fibroblast injected into an early mouse blastocyst opened the application of a similar technique in the human field allowing the de-differentiation of human dermal fibroblasts into human iPSCs [29,31,32].

These iPSCs similar to human ES for differentiative potential, self-renewal, surface antigens, and morphology were capable to generate all of the three germ layers cells sharing the same gene expression. Since then, many other research teams worldwide have improved this technique. Several reprogramming conditions to improve the efficiency rate of the technique (still around of the 2% of the adult cells) and to decrease potentially detrimental side effects.

Although these technical upgrades in the reprogramming procedures, a major problem remained the retrieval DNA expression in the host cell’s slightly controlled. So it is necessary to look elsewhere toward other types of viruses and even to increase the reprogramming efficiency [33]. To achieve this goal, high precaution for minimizing DNA alterations is needed; the introduction of a cocktail of transcription factors in a single viral cassette into an identified genetic location was considered the best way for reprogramming.

In addition, the developmental stage of the initial cell seems to influence directly the reprogramming efficiency rate; in fact several researchers in order to increase efficiency [34] are investigating the reprogramming of stem cells or adult progenitor cells from mice [32] and humans comparing to that observed with mature cells [19,35].
Although the safety of reprogramming protocols is a priority, the use of retroviruses known to be potential mutagen does not accomplish in exhaustive way this goal. The mutagenic potential of retroviral vectors has induced researchers to explore new strategies to reprogram cells without their use in order to make reprogramming protocols more safely and at the same time more efficient [32].

Therefore, the refinement of current viral vectors together with the development of novel vectors represents the new goal of the reprogramming technique.

On this route it comes to help a single negative strand RNA virus, Sendai Virus (SeV), isolated for the first time from mouse in Japan in 1953 [36]. SeV has been widely used as a research tool in cell biology and in industry, but the application of SeV as a recombinant viral vector has been investigated only recently. Recombinant SeV vectors show exclusive advantageous features for various purposes: for example to avoid exogenous genes nuclear integration in iPSC reprogramming protocols with low pathogenicity and a wide host range.

Wild-type SeV vectors installed with Oct4, Sox2, Klf4 and c-Myc cDNAs were reported to generate external-gene-free iPSCs, dependent on passive elimination of the genome through cell passage.

Our preliminary results support the use of SeV protocol in reprogramming peripheral blood mononuclear cells in pluripotent stem cells. The SeV genes expression is sufficient for activation and expression of endogenous genes that can be used as stem markers, such as Tumor Reagent Antigen 1-60 (TRA1-60) (Figure 2).

Neurodegenerative Disease Modeling by iPSC

Neurodegenerative diseases have been the subject of intensive efforts in order to find effective treatments but our knowledge in this clinical field is only at the beginning probably because of the absence of fitting disease models of human neurons. Patient-specific neuronal cells obtained from adult somatic cells, through the iPSC technique, offered a unique opportunity as an unlimited source of patient-specific stem cells, by opening the way to the so called disease modeling.

The use of iPSC becomes a tool in human neurodegenerative diseases etiology studies since it provides unique opportunities to interrogate specific human neural cell types of patients with familial and sporadic forms of complex multifactorial disorders as amyotrophic lateral sclerosis (ALS), Alzheimer’s disease (AD), or Parkinson’s disease (PD).

Although the innovative opening work performed by Yamanaka et al. on the idea that iPSC generated from patient tissues can be a suitable approach to the personalized medicine, it is now widely accepted that only few diseases can be really investigated trough the iPSC strategy.

Figure 1: Overview of cellular reprogramming into iPSCs using non-transmissible Sendai Virus (SeV) vectors. (Adult cells, such as skin fibroblast, peripheral blood mononuclear cells (PBMC) or odontoblast, can be transfected with non-integrating SeV vectors and genetically reprogrammed into iPSCs. After the fusion between viral envelope and cell membrane, the single chain RNA in minus sense is released into cytoplasm allowing its replication and the transcription of the four Yamanaka factors Oct4, Sox2 (KOS), Klf4 and c-Myc can occur. These factors are sufficient to suppress the differentiation and to induce efficiently self-renewal and pluripotency. So generated iPSCs can be switching lineages and converted into induced neuronal cells in order to create a patient specific in vitro model of neurodegenerative disease and validate novel and encouraging drug target.)
The reason of such a limitation resides on the consideration that reprogramming is influenced by many different factors such as DNA mutation load, gene expression, time-culture conditions and epigenetic signature together with the difficulty to choose the suitable controls. Such a wide amount of influencing factors would require a huge patient-specific iPSC cohort, to be clinically applicable, that is unrealistic. One possibility to minimize this requirement could be represented by the genome editing technologies e.g. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) or Transcription Activator-Like Effector Nucleases (TALENs). Pursuing this stratagem the potential of iPSC to treat patient with neurodegenerative disease becomes enormous. Combining the differentiative potential of iPSCs with the recent discovery of CRISPR/Cas9 endonucleases in bacteria and their adaptation for use in biomedical research, it is possible to generate in vitro models that more closely resemble the in vivo system than ever before [37,38].

An examination of iPSC use in clinical applications provided the optimization of reprogramming and differentiation protocols are reached, as following:

**Parkinson’s disease**

PD is the most common progressive neurodegenerative disorders with a frequency rate of about 100–300 per 100,000. Characterized by the prevalent loss of dopaminergic neurons (DAn) from the substantia nigra, PD is described as debilitating and progressive condition [39–41]. This disease is rapidly becoming a public health issue since the population’s aging is the major risk factor for developing PD.

The iPSCs technology allowed a new approach for modeling PD. Early studies using iPSC-induced dopaminergic neurons were performed to investigate molecular abnormalities in PD, but unfortunately only after significant symptoms were evident [42]. Successive studies in the first decade of 2000 demonstrated that early onset PD (age < 50) phenotype was closely related with the expression of Leucine-Rich Repeat Kinase-2 (LRRK2) gene, causing an enhanced susceptibility to oxidative stress (OS). Nowadays, LRRK2 protein mutations is the most common PD-related mutation and it has been considered a principal cause of familial PD [43,44]. Patient-specific iPSC-derived LRRK2 mutant
dopaminergic neurons have permitted to show their role in the disease’s development associated with the accumulations of α-synuclein, a major component of Lewy bodies that characterize other neurodegenerative disorders such as Alzheimer’s disease [45,46]. How this mutation can lead to the α-synuclein accumulation? The answer is tentatively given in the Sanchez et al. work [46] and Nguyen’s work [45] in which they have derived iPSCs lines coming from idiopathic PD (ID-PD) patients and with familial PD correlated to the G2019S mutation in the LRRK2 gene and age- and sex-matched healthy individuals as controls. In these works, it has been demonstrated the presence of an accumulation of autophagic vacuoles in both ID-PD and LRRK2-mutant-PD iPSCs, that were not evident in DAn obtained from Ctrl-iPSC indicating that dysregulated autophagy may be a pathogenic mechanism in PD. The increase of α-synuclein is due to the lack of chaperone-mediated autophagy (CMA) at lysosome sub-particle level that is the physiological pathway in the α-synuclein degradation [47]. However Sanchez et al. [46] have demonstrated that in LRRK2 mutant neurons after the inhibition of CMA, α-synuclein levels are higher than in the controls making evident that CMA is more active in the mutant neurons. Therefore, the elevated α-synuclein mRNA expression rate reported in the mutant neurons cannot be ascribed to defective CMA. In conclusion, major studies demonstrate that in iPSC-derived dopaminergic neurons, the mutation of LRRK2 is tightly correlated with α-synuclein accumulation but the molecular mechanism at the base of this process remains unclear. Nguyen et al. [45] have showed a relation between LRRK2 mutations and OS-related genes, e.g., Mono-Amine Oxidase-B (MAO-B) was highly increased in LRRK2-mutant neurons respect to controls. Since the proportion of apoptotic LRRK2-mutant DAn was found to be higher than control, it has been suggested that the LRRK2 mutations increase OS in neurons [43].

In the same way OS susceptibility has been used as indicator of PARK2 (responsible for autosomal recessive juvenile Parkinson disease) and P-(phosphatase 2 of homologue) TEN-induced putative kinase 1 (PINK1) genes mutations in the onset of the disease [48]. PARK2 and PINK1 genes mutation are responsible in the altered mitochondrial function [42,49]. Recent studies demonstrated that mitochondrial function is influenced by both Parkin and PINK1 [50]. Infact Parkin localized in the cytosol, works as an E3 ubiquitin ligase, whereas the mitochondrial kinase PINK1 is confined on the external mitochondrial membrane. Furthermore, Parkin is translocated to damaged mitochondria in a PINK1 dependent mode, demonstrating that PINK1 functions upstream from Parkin in a common pathway [51]. Starting with this consideration, it has been investigated that the quality-control system at mitochondrial level performed by PARK2/Parkin seems to be activated by PINK1 in response of damage for the activation of mitophagy. In addition, the release and the reuptake of dopamine (DA) by PARK2 mutant neurons are involved in the OS susceptibility. PARK2-mutant neurons exhibit increased spontaneous DA release and diminished DA uptake, suggesting that these neurons present elevated extracellular DA levels in vivo. What seems clear is that these neurons display increased susceptibility to oxidative stress following treatment with DA [48,52]. In fact, it has been demonstrated the role of PARK2 as predisposing agent for the OS. This result has been validated by the ROS analysis showing significantly higher levels in PARK2-mutant neurons than in controls, even if this mechanism it has proved to be not univocal [50,51]. Although ‘idiopathic’ PD is more common, about 2-3% of PD cases can currently be linked to a single genetic factor and the recently discovery of the PARK2 and PINK1 genes has provided insights into the cellular and molecular pathogenesis of PD [49]. A clinical syndrome closely resembling ‘idiopathic’ PD has been reported for recessively inherited Parkin mutations, suggesting that pathways uncovered in these monogenic forms of PD may play a direct role in the etiology of the more common sporadic disorder:

Zeng’s research group developed an example of the use of iPSCs for drug screening. In order to generate a platform of DAn for drug screening, hNSCs were obtained from hESCs and hiPSCs. To validate this system, a set of several candidate neuroprotective agents were tested in a model of cell neurotoxicity by MPP+, a specific neurotoxin for DAn. The results of this study showed that from 44 compounds tested only a third were neuroprotective. Interestingly, molecules which were reported previously as cytoprotective in vitro but failed in clinical trials, did not have neuroprotective action in this model, suggesting that DA neurons derived from PSCs may represent an accurate system for drug testing [44-46,48].

**Alzheimer’s Disease**

AD is a chronic neurodegenerative disease affecting roughly 36 million of people worldwide and characterized by a gradual loss of memory and consequently a decreased learning ability. The analysis of post-mortem tissues shows β-amyloid plaques (Aβ) in the extracellular matrix, and an hyper-phosphorylation microtubule associated protein Tau (MAPT), producing neurofibrillary tangles aggregates [53]; however, there is a great debate on the mechanism(s) generating this histopathological evidences. Alzheimer’s disease can be classified into familial or sporadic form characterized by early- or late-onset. In order to investigate genetic contributions in developing this pathology, familial type represents the best disease model even if the sporadic form is the most diffused.

Mutations in amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes are considered the primary responsible for the familial form disease’s development as also the risk to evolve familial AD is increased when apolipoprotein E4 (APOE4) and/or receptors are expressed on myeloid cells 2 (Triggering receptor on myeloid cells 2-TREM2).

Initial AD modeling efforts were focused on reproducing well-known characteristics of the disease in order to validate the iPSCs approach since AD mouse models did not seem to be able to completely emulate all the complex aspects of the disease [54,55].

AD patient-derived neurons trough iPSCs technology have been recently used to modeling AD and some studies have confirmed efficacious generation of iPSC-derived neurons from patients with familial AD. Both familial and sporadic AD patients iPSC-derived neurons, respect to non-demented controls, showed an higher presence of App and glycogen synthase kinase 3β (GSK3), two proteins considered common markers of the two histopathological hallmarks of Alzheimer’s disease, i.e. the extracellular senile plaques of beta-amyloid and the intracellular neurofibrillary tangles formed by hyper-phosphorylated tau [56,57].

In the AD iPSCs model reported by Israel et al. [58], iPSCs were generated from: two familial AD (fAD) subjects, presenting APP triplication, two sporadic AD (sAD) patients, and two healthy, age-matched control subjects. Relevant findings of this study showed in both fAD cases and sAD patient lines an increased level of Aβ1-40 in the conditioned media, with no effect on Aβ42/40 ratios, augmented basal phospho-tau (pThr231), increased GSK3β activity (lower pSer9), and enlarged Rab5-positive early endosomes as has been seen in AD patient brains [59].

Initial studies by Israel et al. [58] in 2014 related to fAD iPSC-derived neurons mutant for PSEN1, PSEN2 and APP showed an increase of the ratio between Aβ42 and Aβ40, a hallmark feature of fAD with presenilin mutations. Numerous subsequent iPSCs studies have focused on increased APP copy number and mutations. In this context a trisomy 21 Down syndrome (DS) model using both...
of cytoplasmic localization of protein aggregates although they presented an elevated sensibility to PI3K signaling inhibition and mild elevated cell death in iPSC-derived motor neurons from ALS patients. In the same year, Egawa et al. [67] showed in ALS patient iPSC-derived motor neurons the presence of TDP43 cytoplasmic aggregates and reduced neurites length.

Conclusions

In this review, we addressed our attention toward neurological model disease-derived iPSCs and we described the state of art on this theme. Recent stem cell research progress suggests that patient-specific iPSC technology can accurately report pathological condition rising up before the beginning of clinical symptoms. In this optics, the molecular investigation of pathogenic mechanisms is possible by combining disease-specific iPSC technology with whole-genome analysis and non-invasive imaging technology.

iPSC technology allows potential opportunities for cell replacement therapy by regeneration of specific neuronal populations or by differentiating and genetically modifying a large number of immune cells that can be used exerting therapeutically an immunomodulatory effect as previously reported [76,77].

Combining the differentiative potential of iPSCs with the recent discovery of CRISPR/Cas9 endonucleases in bacteria and their use in biomedical research, it is possible to generate in vitro models that more closely resemble the in vivo system than ever before. In addition, iPSC generation can be used as the technology of genome-wide epigenetic resetting in the cancer research field.

In this context, the possibility to test patient-specific drug treatment protocols makes this reprogramming technology unique by providing a cell-based assay to identify the molecular correlation of individual patient drug response variations in accordance with the new trend of personalized drug therapy.

To concern with, before the clinical application of iPSC treating human diseases, it is necessary to verify the safety of iPSC generation procedures. In fact, until now, one common procedure to generate iPSCs cells has been the application of a retro- or lentiviral transduction of cellular dysfunction or tumorigenesis caused by mutagenesis at the insertion site. To prevent this genome integrative methodologies, transfection with adenoviruses or plasmid vectors, episomal vectors and piggyback transposons were attempted with some success [78]. Another possibility has been offered by Kim’s et al. intuition. They used fusion proteins where each of the four Yamanaka’s reprogramming factors was fused to the cellular membrane. The protein-based iPSCs differentiated into dopaminergic neurons rescued motor deficits when transplanted into PD rat models [23]. However, these methods may require repeated rounds of treatment and is limited by reprogramming efficiencies ratio up to 1000-fold lower than with retroviral vectors.

In this review, we showed that SeV is an ideal vector for generating human iPSC that fulfills the safest criteria. Firstly, SeV vector allows expression of transgenes without risk of modification of host genome. The efficiency of iPSC generation by gene transduction with SeV vectors is significantly higher than that by other methods. Finally, it is easy to select iPSC-depleted viral genome. Hence, since resulting viral-free iPSCs are genetically intact and carries the same genome DNA as the original cells, SeV vectors have been considered useful for gene therapy clinical studies as for cystic fibrosis, critical limb ischemia or vaccines for AIDS [79].

In summary, respect to the different procedures used to generate iPSCs, the clinical application of reprogramming technologies trough the generation of simple human cell models of
adult neurological disorders is a true promising approach, without forgetting that the iPSCs generating protocols need to be improved. Even if nobody is expecting to recapitulate aging diseases “in a dish”, since molecular and cellular responsible factors for the hereditary neurological diseases may be presymptomatic long-life present, the molecular or event trigger is often unknown so it should be very fruitful to have cell models both for the identification of such event and/or for suppressing it.

Although in this review we restricted our attention only on this three neurological disorders due to their worldwide diffusion, the application of the reprogramming-based cell model is useful for studying other neurological disorders such as Autism, Fronto-Temporal Dementia (FTD), Herpes Simplex Virus-1, encephalopathies, X-fragle syndrome, Atypical Measles Syndrome (AMS), non-familial disease and sporadic risk associated variants. The acquisition of this emergent regenerative platform for personalized medicine applications needs the establishment of bioequivalence criteria trough derived pluripotent lines and lineage-specified derivatives. Moreover, a major difficulty to the interpretation of human reprogramming-based disease models is the inherent variation among patience samples, due both to genetic diversity as well as to the distinct personal histories that may lead to epigenetic diversity. The successful achievement of whole genome sequencing and microarray technologies should remove the major obstacle relative variation among patients due to the genetic and personal diversity. It is implied that large control cohorts have to be used for obtaining statistically meaningful analysis. Furthermore, studies that lack a genetic or biochemical complementation approach to link directly a given genetic variant (or mutation) to a disease model is useful for studying other neurological disorders such as Autism, FTD, Herpes Simplex Virus-1, encephalopathies, X-fragle syndrome, Atypical Measles Syndrome (AMS), non-familial disease and sporadic risk associated variants. The acquisition of this emergent regenerative platform for personalized medicine applications needs the establishment of bioequivalence criteria through derived pluripotent lines and lineage-specified derivatives. Moreover, a major difficulty to the interpretation of human reprogramming-based disease models is the inherent variation among patients due to the genetic and personal diversity. It is implied that large control cohorts have to be used for obtaining statistically meaningful analysis. Furthermore, studies that lack a genetic or biochemical complementation approach to link directly a given genetic variant (or mutation) to a phenotype must be treated with some skepticism.

Our fervent hope is that the achievements in the field of diseasespecific IPS cell research will be made available to all patients for whom no treatment of the cause underlying disease currently exists.

Acknowledgments

We gratefully acknowledge Cristina Calì, Alfaia Corsino, Maria Patrizia D’Angelo and Francesco Marino for their administrative and technical support.

Conflict of Interest

The authors declare no conflict of interest.

References


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Received Date: April 04, 2017, Accepted Date: June 14, 2017, Published Date: June 20, 2017.

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