Induced pluripotent stem cells throughout the animal kingdom: Availability and applications

Laís Vicari de Figueiredo Pessôa, Fabiana Fernandes Bressan, Kristine Karla Freude

ORCID number: Laís Vicari de Figueiredo Pessôa (0000-0002-3780-6046); Fabiana Fernandes Bressan (0000-0001-9862-5874); Kristine Karla Freude (0000-0001-9480-2386).

Laís Vicari de Figueiredo Pessôa, Kristine Karla Freude, Group of Stem Cell Models for Studies of Neurodegenerative Diseases, Section for Pathobiological Sciences, Department of Veterinary and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg 1870, Denmark

Fabiana Fernandes Bressan, Department of Veterinary Medicine, Faculty of Animal Science and Food Engineering, University of São Paulo, Pirassununga 13635-000, São Paulo, Brazil

Corresponding author: Kristine Karla Freude, BSc, DPhil, MSc, PhD, Associate Professor, Group of Stem Cell Models for Studies of Neurodegenerative Diseases, Section for Pathobiological Sciences, Department of Veterinary and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Grønnegårdsvej 7, Frederiksberg 1870, Denmark. kkf@sund.ku.dk
Telephone: +45-25572261

Abstract

Up until the mid 2000s, the capacity to generate every cell of an organism was exclusive to embryonic stem cells. In 2006, researchers Takahashi and Yamanaka developed an alternative method of generating embryonic-like stem cells from adult cells, which they coined induced pluripotent stem cells (iPSCs). Such iPSCs possess most of the advantages of embryonic stem cells without the ethical stigma associated with derivation of the latter. The possibility of generating "custom-made" pluripotent cells, ideal for patient-specific disease models, alongside their possible applications in regenerative medicine and reproduction, has drawn a lot of attention to the field with numbers of iPSC studies published growing exponentially. IPSCs have now been generated for a wide variety of species, including but not limited to, mouse, human, primate, wild felines, bovines, equines, birds and rodents, some of which still lack well-established embryonic stem cell lines. The paucity of robust characterization of some of these iPSC lines as well as the residual expression of transgenes involved in the reprogramming process still hampers the use of such cells in species preservation or medical research, underscoring the requirement for further investigations. Here, we provide an extensive overview of iPSC generated from a broad range of animal species including their potential applications and limitations.

Key words: Pluripotency; Embryonic; Stem cell; Reprogramming; Animal; Wild; Induced pluripotency

Core tip: Induced pluripotent stem cells (iPSC) have opened up the possibility of converting literally any mature cell type into an embryonic like pluripotent state. This procedure has had a large impact on biomedical sciences for patient specific disease modeling, cell-type specific differentiation and regenerative medicine with or without gene editing. These advances are clearly not restricted to human iPSCs, and indeed it was mouse iPSCs that were derived first. In this review we will provide a comprehensive overview of iPSC generated throughout the animal kingdom as well as an elaboration on their possible applications and limitations.

INTRODUCTION

The ability to differentiate into any given cell type within an organism was limited solely to embryonic stem cells (ESC) until 2006. ESCs possess the capacity to proliferate indefinitely without differentiation, form chimeras and display germline transmission. Currently, ESCs with these characteristics have only been confirmed in mice and rats[1]. In regard to culturing ESC of other species, besides human, mice and rats, undefined culture conditions already present the first hurdle.

In 2006, an alternative means was developed to generate embryonic-like stem cells whereby differentiated adult cells are reprogrammed into induced pluripotent stem cells (iPSC)[2]. This reprogramming process entails the delivery of so-called pluripotency factors to mature cells to induce their conversion into ESC-like cells, which subsequently triggers the transcriptional and translational activation of endogenous pluripotency factors. These pluripotency factors are all regulators of ESC proliferation, renewal and pluripotency.

The most commonly used genes for achieving such conversion are: *Homeobox protein* (*NANOG*); *octamer-binding transcription factor 4* (*OCT4/POU5F1*); *SRY-Box 2* (*SOX2*); *Kruppel Like Factor 4* (*KLF4*); *proto-oncogene MYC* (*c-MYC*) and *Lin-28 Homolog A* (*LIN28*). NANOG is a key transcription factor inhibiting differentiation towards extraembryonic endoderm and trophectoderm lineages. Moreover, by directly inhibiting SMAD Family Member 1, NANOG prevents bone morphogenetic protein-induced mesoderm differentiation[3]. NANOG also plays an important role in binding and activating the OCT4 promoter and is consequently a transcriptional activator of OCT4[4]. OCT4 is required for naïve epiblast formation, and *OCT4*-null embryos lack pluripotent characteristics within their inner cell mass[5]. Furthermore, abrogation of OCT4 expression in ESCs results in trophoblast differentiation of the inner cell mass[6]. OCT4 therefore plays prominent roles in pluripotency maintenance in ESCs and during the reprogramming of mature cells to iPSC. SOX2 forms a complex with OCT4 to bind DNA and govern the expression of several genes required for embryonic development[7].

Consequently, it has been claimed that NANOG, OCT4 and SOX2 act as master regulators of ESC pluripotency[8] at least for the generation of mouse, human and rat iPSC. However, less is known about gene expression requirements for achieving pluripotency in other species. Therefore, several additional genes have been tested for their ability to generate iPSC. These include KLF4, which regulates the expression of key transcription factors during embryonic development, including NANOG[9]. MYC has been shown to play a role in maintaining the glycolytic energy metabolism in stem cells[10]. Additionally, while not essential, MYC has been shown to promote the generation of iPSC from human and mouse skin fibroblasts[11]. Finally, LIN28 is an RNA-binding protein and regulates gene expression at a post-transcriptional level. The products of genes regulated by LIN28 function in developmental timing and self-renewal in ESCs[12].

Other less commonly used genes involved in achieving and/or maintaining the undifferentiated state will be discussed directly in the following description of the various iPSCs generated from various species. In addition to the plethora of pluripotency factors applied for reprogramming, several methods exist with which to deliver them into adult cells. Both early protocols and reprogramming efforts in notoriously challenging species use viral approaches, such as retrovirus and

lentivirus[13,14]. Whilst the human and mouse fields have progressed to employing non-integrative methods such as Sendai-viral[15], episomal[16] and mRNA transfection[17], very few attempts have been made to apply these to other species. In the following sections we will provide a comprehensive overview of the iPSCs available from various species, their method of generation, their pluripotent characteristics and their applications in science.

DOMESTIC RUMINANTS

The establishment of iPSC from domestic ruminants was reported for human[13], mouse[2], monkey[18], rat[19,20], pig[21-24], dog[25] and rabbit[26]. These species, from which iPSCs have already been generated, unsurprisingly comprise commonly used animal models in the field of regenerative medicine. However, ruminants, especially small ruminants, are equally attractive for biomedical research. For example, sheep are often employed as the preferred model for human pregnancy and perinatal-related studies[27], as models for rare or degenerative diseases[28,29], for several chirurgic procedures[30,31] and cancer[32]. This is predominantly based on the fact that ruminants share more phylogenetic characteristics, similar size and longevity with humans than do rodents[33].

Aside from being explored as biomedical models, small ruminants, cattle and buffalo present significant commercial value and agricultural importance, being raised for meat or milk production and for wool and other animal-derived products. In this context, the generation of genetically modified animals for the production of therapeutic proteins in milk (bioreactors), with increased resistance to diseases or selection for other valuable traits is highly desirable. To date, robust pluripotent stem cells derived from these species are still lacking[34-36] despite very recent encouraging efforts[37]. The production of genetically modified livestock is usually accomplished through somatic cell nuclear transfer (SCNT) after genetic modification of donor cells[38-40].

The generation of iPSCs from these species presents a major objective to facilitate the application of advanced reproductive technologies[41] including allowing easier genetic manipulation (knock-ins or knock-outs) in pluripotent cells used for chimera generation, improving SCNT efficiency by using iPSCs as nuclei donors[42,43] or producing functional gametes *in vitro*[44-46]. The first studies in cattle reported that the four Yamanaka factors were insufficient for inducing pluripotency, and that NANOG or NANOG plus LIN28 were additionally required[47,48]. In 2012, Cao *et al*[49] reported bovine iPSCs derived from buffalo defined factors [OCT4, SOX2, KLF4, and MYC (OSKM)] and fetal fibroblasts that could be differentiated into putative female germ cells, a first step towards future use in reproductive sciences. Subsequently, Kawaguchi *et al*[50] contributed to chimera production (90 d of gestation) (Supplemental material 1).

In cattle, different cell types such as adult or fetal fibroblasts, amniotic, mammary and retina-derived cells have been used in conjunction with integrative vectors[47-54]. Testicular cells were induced into pluripotency after electroporation of OCT4 alone[55]. However, silencing of exogenous factors when integrated was not reported, and some studies were unable to characterize bovine iPSCs (biPSCs) after culture due to characteristics related to quiescence *in vitro*[56,57]. It has been shown that buffalo fetal fibroblasts can be retrovirally reprogrammed into iPSC by buffalo OSKM, and that the generation efficiency of biPSCs can be increased by inhibiting p53 expression[58] (Supplemental material 1).

In small ruminants, both ovine and caprine iPSCs were reported only from fibroblasts, either embryonic, fetal or adult[59-69]. Although integrative methodologies (retro- and lentiviral) are still most commonly used, silencing of exogenous factors has already been reported[63,64] (Supplemental material 2). This is a significant achievement considering the objective of producing new organisms from pluripotent cells. Recently, induction of pluripotency using an mRNA approach with OSKM transcription factors was achieved in goats[69]. Regarding generation of animals from iPSCs, ovine iPSCs were already reported contributing to the inner cell mass of blastocysts[63] and live born chimeras[62]. BiPSCs were used as donor cells in SCNT, and cloned embryos were generated in cattle. Despite initial beliefs that the use of pluripotent cells might enhance cloning success, low rates of embryonic development were observed. No live-born animals have yet been reported probably due to persistent expression of transgenes and increased numbers of aneuploidies in iPSC donor cells[67,68].

SWINE

The generation of pluripotent cell lines from swine has very clear and common objectives even between different research groups, being either the use of these cells for regenerative medicine or to preserve and/or augment agriculturally important traits in this species. The pig is considered the most attractive non-primate animal model for biomedical purposes due to its similarities to human immunology, genome organization, aging and whole animal physiology[70-72]. The use of this large domestic animal (or also its miniature version-the minipig) enables long-term studies on tissue or organ transplantation or for modeling specific diseases[73-75] in a more ethically acceptable environment when compared to the use of non-human primates or domestic pet animals (dogs and cats). It is envisaged that pluripotent cells will facilitate the generation of transgenic animals for use as preclinical models and production of animals with valuable traits through the use of chimeric or nuclear transfer technologies.

The swine, however, is considered one of the "non-permissive" species meaning that bona fide robust pluripotent stem cells derived from blastocysts-ESCs have not yet been successfully generated[41,76,77]. The generation of iPSCs is of great importance. The pig was the first domesticated species from which iPSCs were derived, which was after ESCs had already been established for mouse, human, rat and monkey[78-82].

At least 25 studies have already described porcine iPSC (piPSC) production *via* various reprogramming and characterization protocols in the last decade (Supplemental material 3). The first three reports date from 2009 and describe human ESC-like cells dependent or not on basic fibroblast growth factor (bFGF) supplementation[21-23]. Most of the subsequent studies focused upon dissecting the differences between naïve or primed cell generation, especially attempting to obtain naïve cells in order to produce chimeric offspring through the use of leukemia inhibitory factor (LIF) supplementation with or without other inhibitors such as CHIR99021, PD0325901, 5-AZA and others[83-92].

Contribution to embryo development at short term (embryos and/or fetuses) was reported by several groups, even though the status of exogenous gene silencing was not described and/or teratoma formation was not robust in some lineages[24,85,87,90-93]. In contrast, contribution to live chimeric offspring and germline contribution has been proven by only one group thus far[24,94], with piPSCs resembling primed, human ES-like cells. The study reports[24] contribution of piPSCs to both embryo and placenta during gestation and 85.3% efficiency of chimerism in live-born piglets. As only naïve, but not primed pluripotent cells are believed to support chimerism, this suggests that the classical definitions differentiating between the two types of pluripotent cells may be a lot more complex and still poorly-defined in other species compared to mouse and human.

PiPSCs have also been tested for specific *in vitro* differentiation potential; for example, they were able to differentiate into beating cardiomyocyte-like cells[95,96] and neuronal lineage[97]. PiPSCs have also been used as donor cells for nuclear transfer experiments. Although blastocysts were produced, the efficiency rate did not significantly increase when compared to blastocyst developmental rate achieved using embryonic fibroblasts as nuclei donors, and no born piglets were reported[85].

In summary, the production of piPSCs until now has predominantly relied upon the use of integrative vectors, lenti- or retrovirus-carrying human or mouse OSKM, including some variations such as NANOG, LIN-28 or the absence of OCT4 or SOX2 and KLF4. Few studies have described the use of porcine or monkey factors. Even when episomal non-integrative approaches have been used, persistence or integration of plasmids, and therefore silencing of the transgenes, was reported (please refer to Supplemental material 3 for details). Failure to inactivate the exogenous factors is considered a major flaw in the generation of bona fide iPSCs. Defining proper culture conditions and reprogramming protocols is still the major objective of most of the reported studies, even though differentiation is possible in this sub-optimal condition. Ji *et al*[89] reported that two cell lines transduced with lentivirus containing monkey OSKM and cultured with LIF, bFGF and inhibitors presented silencing of exogenous factors. Using episomal vectors, Li *et al*[93] were the first to report the generation of cell lines able to maintain pluripotent characteristics for 20 passages and absence of integration at this time. This represents a great advance in the generation of pluripotent cells from pig, which arguably remains the most desirable model for both human and veterinary medicine.

HORSES

According to the latest report from The American Horse Council Foundation, the United States horse industry has an economic impact of United States $122 billion with 74% of horses participating in the sports sector (racing and competition). Sports horses are constantly exposed to risks of career-ending or even life-threatening musculoskeletal injuries[98]. Besides the magnitude of the horse industry, the possibility of using these animals as models for human musculoskeletal injuries or diseases[99] has contributed to intensify the stem cell and regenerative research in the last few years.

During the past decade, equine iPSCs (eiPSCs) have been produced using both integrative and non-integrative systems carrying mouse or human reprogramming factors in conjunction with multiple cell sources, including adult or fetal fibroblasts, adipose tissue mesenchymal cells, keratinocytes, myogenic mangioblast, peripheral mesenchymal stem cells and umbilical cord cells (Supplemental material 4)[100-108]. Although subsequent attempts were made using episomal vectors[107], only the initial eiPSCs report succeeded in producing equine pluripotent stem cells with a non-integrative PiggyBac transposon system, which is considered safer for clinical uses but allegedly with lower reprogramming efficiency[100,109]. Of the eiPSCs generated *via* integrative systems, only one group has reported transgene silencing[106] with others reporting partial silencing[102,104] and others conversely showing transgenes to still be activated[101,103,108]. Other studies do not mention the state of transgene expression[105,107]. Regarding further characterization procedures, eiPSCs generated in the above studies show *in vitro* or *in vivo* potential to generate cells of all three germ layers as well as expression of multiple pluripotency markers (Supplemental material 4).

The safety of clinical and reproductive applications of iPSCs remains a concern, especially regarding tumorigenesis, epigenetic abnormalities and eventual immune rejection[110-112]. Fittingly, some reports do address these issues. Aguiar *et al*[113] analyzed the immunogenicity of allogenic eiPSCs intradermally transplanted into immunosuppressant-free horses and observed moderate cellular response but not acute rejection. This suggests that allogenic eiPSC banking might serve as a future possibility for cell therapy. In the reproductive field, eiPSCs have been used as donor cells in an attempt to improve SCNT efficiency, but blastocysts were not successfully produced[114].

The possibilities of applying eiPSCs in tissue engineering and regenerative medicine are also being actively explored. While some have reported failure of eiPSCs to generate artificial tendons after induced differentiation[115], others have demonstrated eiPSCs to be capable of inducing muscle regeneration in immunodeficient mice with dystrophin deficiency[105]. Furthermore, Aguiar *et al*[116] showed that eiPSCs could be differentiated into keratinocytes focusing on skin trauma and wound management. Other research groups have studied eventual uses for mesenchymal-like progenitors capable of chondrogenesis and adipogenesis[117] or even induction into functional osteoblasts[118] and transgenic induced myocytes[119], thus providing extra cell sources for regenerative veterinary medicine. Although some studies have already tested the potential and applicability of eiPSCs as seen above, there is still a long road ahead until eiPSCs and their derivatives are completely understood and deemed safe to use in disease models and regenerative veterinary medicine.

DOGS

Dogs play multiple roles in modern society, ranging from livestock management, rescue and security services and emotional and disability assistance besides their major role as companion and best friend[120]. Every year, the number of households with pets increases, having reached 68% in the United States during 2017-2018 with the majority of people owning dogs , and secondly cats. This represented an expenditure of around United States $70 billion during that period of which a little over United States $17 billion was spent on veterinary services. If that alone was not ample reason to increase dog-related research on innovative therapies like regenerative medicine and stem cells, dogs are also considered physiologically relevant model of human diseases. In addition to hundreds of canine hereditary diseases having equivalent human disorders, humans also share a similar physiology and environment with their canine companions[121]. The first canine iPSC (ciPSC) report was published in 2010[25], and since then around ten reports on new ciPSCs lineages have been published. The main cell source used for reprogramming was adult fibroblasts[122-126] followed by fetal or embryonic fibroblasts[25,127-129] and adipose tissue mesenchymal cells[123,130].

As seen in Supplemental material 5, with the exception of studies using non-

integrative Sendai viruses[126,129] the majority of the ciPSCs reported were generated using retroviral or lentiviral systems. Although they are considered more efficient than non-integrative systems, their use in research with clinical applications raises concerns, specifically through potentially dangerous viral integration in the cell genome, transgene reactivation and epigenetic changes[131]. Transgene expression on these ciPSC was reported in variable levels from silenced[128,130] to low levels of expression[124,125] to expression in different states[122,127,128] and not reported[25]. These ciPSCs also vary widely on the pluripotency markers used for characterization purposes (Supplemental material 5).

Further studies on ciPSC applications have been performed by few research groups. Lee *et al*[123] generated endothelial cells from ciPSCs and tested their therapeutic potential in mouse models of myocardial infarction and hindlimb ischemia, besides transplanting labeled ciPSCs autologously into dogs' hearts to monitor cell fate in large animal models of cardiac delivery. Others derived mesenchymal stem cells from ciPSCs that exhibited high proliferative potential, capacity to differentiate into mesodermal-derived tissues and both mesenchymal and pluripotent markers but did not form teratoma-like tissues, a desired characteristic for stem cell therapy[132]. Chow *et al*[126] compared ciPSC-derived mesenchymal cells with adipose tissue and bone marrow mesenchymal cells with regard to their surface markers, gene expression profiles and immune modulation potency. The results showed ciPSCs-derived mesenchymal cells to present a slightly different surface phenotype than regular mesenchymal cells but to be capable of inducing suppression of *in vitro* immune function much like the other analyzed cells. Taken together, these studies demonstrate the continued efforts of the veterinary and research fields, not only in order to pursue longer and healthier lives for our pets, but also to develop disease and therapeutic models for human disorders.

RABBITS

Rabbits have long been used as animal models in research. They are considered highly physiologically relevant even for some human pathology such as heart diseases[133]. Their larger size compared with mice and rats enables their use in surgical procedures, they possess a longer life span and rabbits are phylogenetically more similar to humans. When compared to other suitable larger animal models such as pigs and dogs, rabbits are easier to handle and maintain, are more economical to keep and have shorter reproductive cycles, which facilitates breeding and long-term research analyses[26,134]. It has been reported that rabbit ESCs are very similar to human ESCs in regard to their morphology as well as biochemical and pluripotency features[26].

Rabbit iPSCs (rbiPSCs) have been described in few reports. Honda *et al*[26] generated rbiPSCs from adult liver and stomach cells using lentivirus and human OSKM. These rbiPSCs were silenced after about 18 passages. Interestingly, the authors were not successful in reprogramming fibroblasts using the same methodology. The rbiPSCs produced in this report were LIF- and bFGF-dependent and expressed the same pluripotency markers as rabbit ESCs (Supplemental material 6). In a follow-up study, the rbiPSCs generated were converted to a naïve-like state *via* forced expression of human OCT3/4 increasing these cells' potential for *in vitro* neural differentiation[135].

Using a retroviral system also containing human OSKM, Osteil *et al*[136] compared adult fibroblast-derived rbiPSCs with ESCs. Theses rbiPSCs showed transgene silencing at passage 25 and expressed the pluripotency markers OCT4 and NANOG. Later, the same group showed that *via* expression of KLF2 and KLF4, rbiPSCs could be converted into epiblast-like cells, capable of colonizing pre-implantation rabbit embryos[137].

Finally, the most recently published study on rbiPSCs also employed human OSKM in a retroviral system to reprogram embryonic fibroblasts. The cells generated were dependent upon LIF and bFGF, expressed key pluripotency markers and showed no transgene expression. Focusing on the use of rabbits as heart models, the authors showed these cells to be capable of successful differentiation into cardiac cells, underscoring a possible future application as a disease model[133].

AVIAN

According to the United States Department of Agricultureâs Production and Value Summary, the combined value of avian products reached United States $42.7 billion in 2017, besides the over 20 million birds kept as pets currently in the United States

(APPA, 2018), denoting the significance of these animals to modern society. In research, avian models are considered extremely important because they permit easy monitoring of embryonic development[138] and can also be used as disease models[139].

Avian iPSCs (aiPSCs) were the first non-mammalian iPSCs to be derived[140] and were reported for quail, chicken and zebra finch (Supplemental material 7). The majority of the reports published used embryonic fibroblasts[140-145], but they were also isolated from adult feather follicles[146]. Although non-viral approaches have been applied[142,144], retroviral and lentiviral methodologies have mostly been used and transgene expression was either detected[140,145,146] or not discussed[142-144] with the exception of the chicken iPSCs reported by Rosselló *et al*[141] where transgenes were silenced after five passages.

Further characterization of aiPSCs was performed by Dai *et al*[138], who were able to produce aiPSCs-derived neurons. So far, perhaps the most exciting potential application of these cells is vaccine production and related research[147,148]. In those reports, it is shown that aiPSCs grown in modified conditions possess great potential as candidates for Newcastle disease virus production serving as a suitable replacement for the embryonating eggs currently used for vaccine generation[147]. It should be possible to generate aiPSCs more tolerant to the Newcastle disease virus, which might eventually also be employed in disease-resistant poultry studies[148]. These newly developed methodologies represent a great potential application of aiPSCs to future livestock, health and food security.

EXOTIC ANIMALS

The most obvious reason for generating iPSC from exotic animals is species conservation. Genetic material can be stored and expanded on demand in the form of viable and proliferating iPSCs. Ideally, protocols would be developed to differentiate such iPSCs into primordial germ cells and subsequently generate egg and sperm cells to facilitate *in vitro* fertilization. Such efforts form the basis for the generation of iPSC from *Madrillus leucophaeus* (primate/drill) and *Ceratotherium simum cottoni* (northern white rhinoceros). Both species teeter on the brink of extinction, and the generation of iPSCs might be beneficial for species conservation. Drill iPSC lines were generated using retroviral vectors containing the human sequences for *OCT4*, *SOX2*, *KLF4* and *c-MYC*. The fibroblast source originated from a 15-year-old drill. All factors integrated successfully into the drill genome and the authors were able to show that exogenous transcription factors ceased to be expressed whilst the endogenous drill transcription factors became activated. Drill iPSC were karyotypically normal and exhibited the potential to form teratomas containing all three lineages (ectoderm, endoderm and mesoderm)[149].

The same report describes the generation of iPSC from northern white rhinoceros. Here, the same human genes for *OCT4*, *SOX2*, *KLF4* and *c-MYC* were delivered using the retro VSV-G virus system. These also integrated successfully with the exception of *KLF4*. Similar to the drill iPSC, exogenous gene expression was silenced and endogenous gene expression initiated. Northern white rhinoceros iPSCs were karyotypically normal and gave rise to teratomas[149] (Supplemental material 8). These are extremely promising results for species conservation, but it remains to be seen whether these iPSCs can be used for SCNT or for the generation of *in vitro* germ cells.

Most efforts have centered upon the generation of iPSC from monkeys. Again, species conservation forms one aspect of such efforts, but another facet is the possibility of applying these monkeys and their iPSCs in biomedical research. Monkeys share a high degree of genetic, anatomical, physiological and cardiological similarities with humans[150-152]. Consequently, monkey iPSCs and monkey models represent powerful models for drug development. To date, iPSCs have been generated from rhesus monkeys[18,153,154]. Whilst the first two of these studies[18,154] used retroviral approaches, the more recent report[153] generated rhesus monkey iPSCs using non-integrative episomal plasmids (Supplemental material 8). In a further notable study[155], the retroviral method was employed to derive iPSCs from rhesus monkeys with Huntington's disease (Supplemental material 8). These monkeys and their iPSCs were not only very valuable for testing potential drug candidates but could also be used to investigate autologous and allogenic cell transplantations and graft incorporations as well as safety assessment of CRISPR/Cas9 gene-edited transplants.

Further iPSCs have been generated from cynomolgus monkeys[156,157]. Cynomolgus monkeys are commonly used in biomedical research and the described iPSCs have been derived using both retroviral approaches[156] and non-integrative Sendai virus[157] approaches. Whilst in the retroviral approach pluripotency was confirmed *via*

teratoma assays, the Sendai virus reprogrammed cells were not subjected to pluripotency assays and were directly differentiated into the cell type of interest (Supplemental material 8). Marmoset iPSCs have been generated from fetal liver cells *via* retroviral-mediated transduction with the six human pluripotency factors *OCT4*, *SOX2*, *KLF4*, *c-MYC*, *NANOG* and *LIN28*. These cells displayed a normal karyotype and pluripotency capacity as tested by embryonic body formation and teratoma assays (Supplemental material 8).

Lastly, even iPSCs of great apes such as orangutans have been derived using the retroviral approach with the classical four human pluripotency factors *OCT4*, *SOX2*, *KLF4* and *c-MYC* and pluripotency potential confirmed *via* teratoma assays[158]. Common amongst all of these studies is the lack of *in vivo* chimeric analyses using monkey-derived iPSCs. Only upon demonstration of bona fide germline chimeras will we be able to confirm the pluripotent status of monkey-derived iPSCs.

With the ultimate goal of species conservation, efforts have been made to generate iPSCs from wild feline species such as snow leopards[159] and Bengal tigers, servals and jaguars[160]. For all of these feline species, iPSC retroviral reprogramming was applied using *OCT4*, *KLF4*, *SOX2*, *c-MYC* and *NANOG* (Supplemental material 8). Similar to the iPSCs from monkeys, only teratoma assays were performed. Thus it cannot be excluded that germline transmission for actual cloning of these animals may prove challenging.

Likewise, it is hoped that iPSC generation will safeguard the future of Tasmanian devils, which are currently precariously close to extinction. For their generation, *OCT4*, *KLF4*, *SOX2*, *c-MYC, LIN28* and *NANOG* were transduced *via* lentiviral approaches into dermal skin fibroblasts[161]. It is to be hoped that these iPSCs will provide excellent tools with which to develop strategies to treat Tasmanian devil facial tumor disease, which is desperately needed to halt the extinction of devils.

Other exotic animals from which iPSCs have been generated include the prairie vole using PiggyBac delivery of mouse *Oct4*, *Klf4*, *Sox2*, *c-Myc*, *Lin28* and *Nanog*[162]. The authors proposed that studying oxytocin and vasopressin effects on neurons derived from these iPSCs might be of benefit in dissecting the functional roles and effects (including on gene expression) of these factors in social animals. Another intriguing application would be bat iPSCs. Bats are considered long-lived animals in relation to their body size and thus might hold some interesting answers on how to extend lifespan in other species including humans. Moreover, bats possess an immune system, which allows them to carry viruses in high titers without deleterious effects. Studying specific immune cells *in vitro* might prove a possibility with successfully derived iPSCs. Bat iPSCs have been generated using the PiggyBac system delivering human *OCT4*, *SOX2*, *KLF4*, *c-MYC*, *NANOG*, *LIN28*, *NR5A2* and bat *MIR302/367*[163].

Additional exotic animals for which iPSCs have been generated include platypus[164] and mink[165] (Supplemental material 8). In contrast, it has proven challenging to generate iPSCs from more common but non-mammals model species such as drosophila and zebrafish. These attempts used mouse *Oct4*, *Sox2*, *Klf4* and *c-Myc* lentiviral delivery and resulted in only partially reprogrammed iPSCs[141].

CONCLUSION AND FUTURE DIRECTIONS

Taken together, the data reviewed here highlights some interesting and conflicting aspects of iPSC research throughout the animal kingdom. Although there exist a reasonable number of well-established animal iPSCs, the lack of description for some species, for example the domestic cat, draws attention to the fact that a global mechanism of cellular reprogramming has certainly not yet been unraveled. The non-standardized reports in most species hamper the comparison of some features, such as reprogramming efficiency. This information was estimated in some of the studies as the ratio between emerging colonies and seeded cells, and in others as the ratio between Alkaline Phosphatase (AP)-positive colonies and seeded cells. In some cases, reprogramming efficiency was not reported at all or was even reported as transduction efficiency through evaluation of fluorochrome-labeled reprogramming vectors. Another important matter is the lack of proper and robust characterization of some of the generated cell lines. Regarding *in vitro* characterization, perhaps the lack of criteria, based on the fact that no ES-derived cell lines exist, makes it difficult to define whether a given cell line is truly pluripotent or not.

Furthermore, residual expression of transgenes, even in high passage cells, is still observed in most of the cell lines derived, a flawed hallmark of true reprogramming. Alongside this, many of the animal iPSC lines established were not tested or even failed to produce viable chimeras, the golden standard validation *in vivo* of these cells'

ability to give rise to cells from all three germ layers. This introduces a veil of doubt regarding the actual reprogramming state of those cells.

Regardless, even if the generated cells lines are incompletely reprogrammed, there is no doubt that the production of iPSCs is a major breakthrough, especially for those "non-permissive" species. However, more comprehensive studies are still very much required to elucidate pluripotency acquisition mechanisms for each of them, once it is already known that they differ from human and mouse. Perhaps a deep dive into genomics or proteomics can enlighten us regarding the roles of specific pathways involved in those reprogramming processes and bring us closer to the practical application of iPSCs in such fields as stem cell research, regenerative medicine and reproduction.

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