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Chapter

Induced Pluripotent Stem Cells from Animal Models: Applications on Translational Research

Laís Vicari de Figueiredo Pessôa, Naira Caroline Godoy Pieri, Kaiana Recchia and Fabiana Fernandes Bressan

Abstract

Over the history of humankind, knowledge acquisition regarding the human body, health, and the development of new biomedical techniques have run through some animal model at some level. The mouse model has been primarily used as the role model for a long time; however, it is severely hampered regarding its feasibility for translational outcomes, in particular, to preclinical and clinical studies. Herein we aim to discuss how induced pluripotent stem cells generated from non-human primates, pigs and dogs, all well-known as adequate large biomedical models, associated or not with gene editing tools, can be used as models on *in vivo* or *in vitro* translational research, specifically on regenerative medicine, drug screening, and stem cell therapy.

Keywords: pluripotency, regenerative medicine, stem cell, therapy, domestic animals, non-human primates

1. Introduction

For centuries, animal models have been used to aid on the quest for knowledge regarding human anatomy, physiology, and health, at first by simple observation, progressing to a proper investigation, selection of adequate models for given conditions and resuming on the development of specific transgenic animal models [1]. A recent concern regarding welfare and animal rights [2] has highlighted the relevance of in vitro models, such as pluripotent and adult stem cells. Here we describe the recent advances of biomedical research using induced pluripotent stem cell (iPSCs) models isolated from non-human primates, pigs, and dogs. Due to anatomical, physiologic, genetic, environmental, and other similarities to humans and conditions, those animals are considered highly relevant models for translational studies, each presenting specific advantages and drawbacks. Herein we discuss the advantages of using iPSCs, associated or not with gene editing tools, to enlarge the value and possible applications for pharmaceutical development and therapeutic approaches in these models.

2. Stem cells from animal models: applications on translational research

2.1 Non-human primates: most promising although challenging model?

Although non-human primates (NH-primates) represent only a small share of the animals used in medical research, the significance of those studies for human health, especially pharmaceuticals and new therapeutic approaches, is prominent [3, 4]. NH-primates are often the most suitable model for assessing the safety and efficiency of said drugs prior to human trials [5] and supply information to connect data from other relevant clinical models, such as rodents, to humans [6].

As study models, NH-primates are highly attractive due to longevity, behavioral, anatomical, genetic, physiological, and immunological similarities with humans [5, 7–10]. Over the past decades, NH-primates have been used on studies and research to prevent or cure human conditions, through the development of vaccines and drugs or treatment for cancer, diabetes, obesity, Parkinson's and other neurodegenerative, respiratory and cardiovascular diseases [4, 5, 11, 12], as well as methods to prevent mother-fetus transmission of diseases such as HIV [13], amongst other conditions and illnesses. Moreover, it has recently been shown that some NH-primates present a working memory capacity similar to that of human children [14], which highlights their importance for cognitive and neurological studies.

Stem cells are also considered an excellent tool for disease modeling and drug screening [15]. Although pluripotent cells derived from embryos, also called embryonic stem cells (ESCs), and multipotent adult stem cells (ASCs) are relevant and have been widely used on stem cell research and therapy purposes [16–23], ESCs limited sources and ASCs limited proliferation, and differentiation potentials have hampered their use. The advent of inducing pluripotency in vitro on virtually any somatic cell from any species reported since 2006, led to an entire flock of biotechnological and therapeutic applications. Thus, since the debut of induced pluripotent stem cells (iPSCs) [24], it is possible to produce patient-specific pluripotent stem cells that are highly valuable as models [15]. Furthermore, supported by age-related changes on the immune system of both humans and NH-primates [25], the use of said animals modeling human diseases associated with stem cell research might provide remarkable insight on translational stem cell-based therapy and transplantation [6].

Since iPSCs were first reported, these cells are now available for a variety of wild and domestic animal species (reviewed by [26]). Amongst NH-primates, they include but are not limited to the rhesus [27]; drill [28]; cynomolgus monkey [29, 30]; marmoset [31]; baboon [32]; orangutans [33]; Japanese macaque [34]. These cells were mainly generated from fibroblasts and integrative methods, but more recently, they were produced through non-integrative methods, such as Sendai-virus and episomal vectors [10, 35–37]. NH-primate-derived iPSCs have been used in research related to or as models for neurological [38–41], cardiac [36, 42, 43], reproductive [44], hematopoietic conditions [37, 45], transplantation and grafting [30, 46] and others.

As previously stated, similarities between humans and NH-primates make them essential models to assess the safety of drugs and therapeutic methodologies before human trials [5]. Immunologic similarities were considered when multiple NH-primate species were chosen as models to establish an iPSCs-derived multipotential hematopoietic progenitor cell differentiation protocol [37] and baboon enucleated red blood cells derived from iPSCs [45], aiming at blood disease and others preclinical testing. Cell transplantation is a relevant therapeutic methodology for some cardiac conditions leading to heart failure [42]. NH-primates iPSCs-derived

cardiomyocytes were generated from rhesus monkeys [36, 43] and cynomolgus monkeys [42, 47] to assess drug screening, regenerative therapy, grafting viability, and immune rejection potential.

Aside from immunologic, physiologic, and genetic similarities, NH-primates cognitive capacity and longevity drag special attention for these animals as models for mental illness, age-related or not. Huntington's disease transgenic animals iPSCs have been used for generating neural progenitor cells that may be addressed for drug screening [48] pathogenesis modeling [40] and epigenetic and transcriptional profile analyses [49]. iPSCs and iPSCs-derived neural stem cells have also been generated from other NH-primate species aiming to develop regenerative therapy methods and modeling other neurological conditions, such as Alzheimer's and Parkinson's Disease [10, 36, 50–52].

Nevertheless, another possibility is the generation of custom-made specific transgenic disease models, by injecting retroviruses expressing target genes or gene editing techniques. The most known gene editing tools are zinc finger nuclease (ZFN), transcription activator-like effectors nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPR). More recently, ZFNs and TALENs have been superseded by CRISPR/Cas9, which is equally, if not more efficient in inducing double-strand breaks (DSBs) and in stimulating homology-directed repair (HDR) [53, 54], also offering improved target specificity, prediction of off-target effects and activity [53, 55, 56]. Those approaches have been successfully applied to generate various NH-primate models (Reviewed by [57, 58]), including the above mentioned Huntington's disease transgenic monkey [59], Parkinson's [41, 60], neurodevelopmental disorders [61], Duchenne muscular dystrophy [62], severe combined immunodeficiency [63], and others.

Those models represent a significant scientific advance, allowing more faithful models than rodents previously used [58]. Although the use of NH-primate as research models is notable, some issues still need to be addressed. The greatly developed social skills of those animals implicate in environmental and social requirements to be met to keep NH-primates in an ethical and healthy environment ([64] art. 17), which implicates in high costs. Furthermore, results obtained from NH-primates studies are often not translatable to human research [65], highlighting the need for other research models, such as porcine and canine.

2.2 Swine: a large model in an already optimized production system

The domestication of swine (*Sus scrofa domesticus*) as a farm animal in established and controlled housing conditions, including specific conditions free of pathogens, has led to an important wide public acceptance that requires only minor adaptations for research [66]. The swine reproductive maturity is relatively fast compared to other large species (6–8 months), and they present a short gestation period (115 days) associated with the capability to produce large litters, with around 8–16 piglets per litter. Also, the swine body size, anatomy, physiology, and genetic homology are compatible with humans [66–69]. Hence, they are one of the most exciting species as a translational model for regenerative medicine research, and probably the most similar physiological model for humans apart from NH-primates.

The swine has already been explored as a biomedical model to develop diagnostic methods, studies, and treatment for several different conditions and diseases. For example, immunology studies and allergy models [70], and respiratory and cardiovascular conditions, such as pulmonary surfactant function, reperfusion injury, pulmonary hypertension, and asthma [71–73]. Similar to humans, swine are omnivores, reassuring its adequacy in studies examining the gastrointestinal system: transit time of pharmaceuticals [74], inflammatory bowel disease [75],

gastric dilation [76] and metabolic disorders that influence of endocrine system [77–79]. The swine model has also been used to study neurological and neurodegenerative human disorders, such as amyotrophic lateral sclerosis, Alzheimer's Disease [80, 81], and Huntington's Disease [82].

For the advancement of regenerative medicine, specifically regarding cellular therapies, it is of great importance to study swine stem cells aiming to prove its efficacy and safety. Researchers have already demonstrated the effectiveness of treatment in the swine model using ASCs such as bone marrow mesenchymal stem cells (BM-MSCs) for the repair of myocardial infarction [83] and also for autologous therapy for disc degeneration [84].

However, cellular therapies using multipotent stem cells are restricted to specific diseases due to the limited capacity for differentiation to specific types of cells. Pluripotent stem cells, nevertheless, circumvents such drawback by presenting the ability to differentiate into several cells from the endoderm, mesoderm, or ectoderm origin, thus expanding the possibility translational studies for regenerative medicine [67].

ESCs are often studied and divided into two pluripotency states: naïve or primed. Naïve ESCs are found in the pre-implantation embryo, in the inner cell mass (ICM), and primed ESCs are found in the post-implantation stage in the epiblast [85, 86]. It is known that the mice ESCs cultured and maintained in vitro are considered "naïve", are collected from ICM and supplemented in culture with LIF, although human ECSs are collected from the epiblast and maintained in vitro with bFGF supplementation (for more details, refer to [87, 88]). For animal models including swine, the establishment of robust pluripotent ESCs using a straightforward and conventional approach has not yet been reported, and protocols regarding naive or primed pluripotency state characterization have not been consistent in the last decades [89].

Hence, the generation of iPSCs has shown to provide critical advantages over ESCs, particularly, when animal models are used. The iPSCs were already derived in the swine model (pig iPSCs or piPSCs) and reported in over 25 studies. The majority of those studies have used integrative methodologies to reprogram cells derived from embryonic, fetal, or adult fibroblasts. Although more efficient then non-integrative methods, integration of reprogramming factors onto the cell's genome might lead to the persistent expression of said factors, which can generate tumors and become unfavorable for cell therapy [90, 91]. Pluripotency induction using non-integrative vectors would greatly assist their use in cellular therapy [92]; however, piPSCs produced by episomal non-integrative methodology were until now only considered iPSCs-like [93].

piPSCs have already been induced to differentiate into several lineages: cardiomyocytes [94], hepatocytes [95], and even neuronal precursors cells [80, 96]. Kim et al. [96] for example, reported the derivation of piPSCs using porcine embryonic fibroblasts (PEFs) with four doxycycline-inducible human factors inserted into the cell by lentivirus, and the iPSCs generated were induced into neuronal progenitor cells (NPCs), positive for neuronal cells markers (PLAG1, NESTIN, and VIMENTIN). The differentiation protocol of iPSCs into NPCs can assist in future studies on animal models for neurodegenerative diseases, and the transplantation of these cells may provide details regarding the regenerative potency in vivo.

In particular, the swine is an attractive model to study human genetic diseases due to the genetic homology found between the species [97–99]. The extension of genetic editing tools to the piPSCs could significantly increase their value as a biomedical model, motivating efforts to develop safe and efficient genome editing technologies in this model, aiming to replicate human disease and develop therapeutic approaches [100].

In swine, gene editing tools are more prone to be effective and accepted once reproductive biotechnologies (such as embryo manipulation and microinjection and somatic cell nuclear cloning – SCNT) are far more studied than other models such as NH-primates and dogs [101]. The use of CRISPR/Cas9 injection into swine zygotes, for example, has been reported as an exciting model for human disease based on gene knock-out [102–104], in special, presenting high efficiency and without detection of off-targets [105].

Gene editing is highly explored in human iPSCs for cardiovascular, neurodegenerative diseases like Alzheimer's and Parkinson's, and degenerative muscular dystrophy (DMD), however, its applicability in autologous therapies is still restricted. Thus, gene editing in piPSCs to study diseases and their treatments [106] and transplant these cells or even to generate new entire edited organisms is a game-changer in the regenerative medicine field. Yu [104] edited swine zygotes using CRISPR/Cas9 for DMD the piglets born had the disease in skeletal muscle, heart and decreased smooth muscle thickness in the stomach and intestine. These models would enable, trough gene editing on piPSCs, to test autologous therapies for DMD.

Apart from the use of edited cells for cellular therapy, the technology would also be useful to the production of human organs by interspecies blastocyst-iPSCs complementation [68, 107]. Wu [108, 109] described the chimeras' production through the complementation of hiPSCs in swine zygotes genetically edited via CRISPR/Cas9. Researchers also reported to efficiently disable pancreatogenesis in pig embryos via zygotic co-delivery of Cas9 mRNA and dual sgRNAs targeting the PDX1 gene. When combined with chimeric-competent human pluripotent stem cells, the authors inferred that these results would provide a suitable platform for the xeno-generation of human tissues and organs in pigs [108, 109].

Bypassing the ethical problems of possible humanization of the swine during the embryo complementation process, another option for producing patient-specific organs is to recellularize swine organ scaffolds with hiPSCs. The selected organ goes through the decellularization process that completely removes cells and organic components of tissue, such as lipids, DNA, and antigenic proteins, but maintains the extracellular matrix (ECM). Recently, Goldfracht [110] combined hiPSCS-cardiomyocytes (hiPSC-CMs) with extracellular-matrix (ECM) derived from decellularized swine hearts, developing an ECM-derived engineered heart tissues (ECM-EHTs) model. Ohata and Ott [111] decellularized the lungs of human, swine, and NH-primates, the structure kept the original bronchial tree, vascular network, and most of the ECM composition and bioreactors were used to recellularize the lungs, and successful cell growth was achieved with perfusion culture.

Organ engineering based on recellularization with patient-derived iPSCs offers the unique potential to promote autologous treatment, and are also promising as tools for animal production, once piPSCs differentiated into germinative cells could be used to re-colonize depleted ovaries or testicles in order to spread the desired genetics in other animals [112]. Also, the use of muscle differentiation from iPSCs in scaffolds would benefit not only the cellular therapy for injured muscles in general, but opens new possibilities regarding in vitro meat production. The production of "animal-free" meat offers a reduction in environmental pollution and allows disease-free meat production due to its controllable and manipulative production system. However, technical challenges and intense research are still needed to establish such "animal-free" meat culture system [68, 113].

Although the complete reprogramming of iPSCs in the swine model is not yet fully elucidated as it is for human and murine reprogramming, the technology has the clear benefit of improving animal production and reproduction, opening new perspectives to study genetic diseases or develop cellular transplantation therapies.

Studies are still needed to optimize the production of non-transgenic piPSCs and their association with other biotechnologies in the swine model, and the interspecies difference regarding pluripotency acquisition is important in order to define proper culture conditions to maintain the pluripotency and the reprogramming protocols in this model.

2.3 Canines: closer to humans than ever

The dog (*Canis lupus familiaris*) is considered a well-suited animal model for many diseases, drug development, and regenerative therapies. Like humans, dogs present a great phenotypic diversity and a well-mixed gene pool because of centuries of random breeding [114], and they also exhibit metabolic, physiological, and anatomical similarities to humans [115]. More than 200 known hereditary canine diseases have an equivalent human disease, including cardiomyopathies, muscular dystrophy, and cancer. Moreover, the dog was the most prevalently used species in early transplantation research, including bone marrow transplantation and gene therapy [116], due to their similarities to humans concerning stem cell kinetics, hematopoietic demand, and responsiveness to cytokines [117, 118].

Because of the many similar cancer characteristics in dogs and humans, including histological features, genetics, behavior, and response to conventional therapies [119], dogs are amongst the leading models for human cancer studies. Notably, the number of dogs that are diagnosed and managed with cancer is estimated to be over 6 million per year in the United States [119]. Such conditions triggered researchers' interest and efforts to identify cancer-associated genes, study the environmental risk factors, understand tumor biology and progression, and develop of novel cancer therapeutics [120]. Different researchers described similar types of cancer in dogs and humans that include prostate, skin, mammary, lymphoid neoplasia, and others [121–124]. Nonetheless, it should be recognized that just as in other models, both similarities and dissimilarities exist [119], including disparities concerning genomic factors, clinical behavior, and prevalence. For example, the BRAF gene's somatic mutation occurs in nearly 60% of melanoma from humans, but only in approximately 6% of dogs [125]. Also, while osteosarcoma most typically affects the appendicular skeleton and metastasizes to lungs in humans and dogs, peak onset occurs at a young age in humans, but more often at an advanced age in dogs [126].

Stem cell research is a recent and increasing field for canines, unraveling the development of novel cell-based disease models, drug discovery, and therapies. Some research with ASCs has been performed dogs due to their regeneration properties. Canine MSCs (cMSCs), for example, successfully recovered damaged spinal cord neurons [127], increased tubular epithelial cell proliferation in cisplatin-induced kidney damage [128], successfully treated osteonecrosis [129], repaired infarcted myocardial tissue [130], are capable of chondrogenic differentiation [131] and suppression of inflammation of ruptured crucial ligament [132].

As previously discussed, ASCs cells have limitations when considered for therapy or regenerative medicine, such as limited proliferation, expansion, and differentiation potentials. In contrast, pluripotent stem cells can fill a critical void in regenerative medicine by allowing autologous studies or gene editing for in vivo or in vitro disease modeling. Similar to pigs, but in particular in dogs, isolation of genuinely pluripotent cells has been challenging. According to [133] six studies from 2007 until 2009 derived ESCs from blastocysts that expressed the core pluripotency markers and were capable of differentiating into representative lineages of all three germ layers in vitro; however, a limited proliferative potential and differentiation in

germ cells layers were observed in all [134–139]. Moreover, a consensus regarding typical morphology and cell culture conditions are still unreported [136, 138].

iPSCs generation in canines has evolved quickly. Some studies have shown that the generation of canine induced pluripotency stem cells (ciPSCs) from fetal or adult cells through retroviral transduction of dog, human, or mouse factors [140–149]. The pluripotency state of the ciPSCs (naïve, primed, or other) has been discussed, and the proper characterization of these cells lacks consensus. These studies tested different medium and supplement combinations in culture and reported different pluripotency acquisition requirements and maintenance (different culture supplementation and different cell surface markers detection). Interestingly, [141] obtained ciPSCs derived from adipose multipotent stromal cells that showed similarity to human ESCs regarding morphology, pluripotency markers expression, and the ability to differentiate into all three derivatives germ layers in vitro (endoderm, ectoderm, and mesoderm).

Remarkably, dogs develop breed-associated genetic predispositions to particular disorders and suffer from many of the same maladies as humans. Many genetic diseases, such as Alzheimer's disease, retinal atrophy, muscular dystrophy, cancer, obesity, cardiovascular diseases, and diabetes mellitus, affect dogs and humans [121, 135, 150]. For instance, the neurobehavioral syndrome called canine cognitive dysfunction (CCD), which affects 14.2–22.5% of dogs over eight years old, shares many clinical and neuropathological similarities with human aging and early stages of Alzheimer's Disease [151–154]. Recently, Hyttel and collaborators [155] aimed to characterize the CCD condition in iPSC-derived neurons from aged demented and healthy dogs, allowing the comparison of CCD with human Alzheimer's at the cellular level. Canine iPSCs have also been tested in other studies, as researchers transplanted autologous iPSCs into the myocardial wall of dogs to examine the potential for myocardial infarct treatment, and the stem cell population were tracked regarding distribution, migration, engraftment, survival, proliferation, and differentiation [142].

Although biotechnological techniques and tools for the dog are less developed than for other species such as swine, the progress on gene editing technologies that can correct genetic defects, thereby offering potential treatment of some inherited diseases, is of great interest in canines due to the genetic proximity to humans described before [156, 157]. In 2015, [158] explored the feasibility of producing gene knockout (KO) dogs using gene editing by CRISPR/CAS9. The study focused to knock out the myostatin gene (MSTN), that is a negative regulator of skeletal muscle mass and demonstrated for the first time that a single injection of Cas9 mRNA and sgRNA corresponding to a particular gene into zygotes, combined with an embryo transfer strategy, efficiently generated site-specific genome-modified dogs [158, 159].

Recent studies also focused on using CRISPR/Cas9 edition for canine cancer models [160, 161]. Eun et al. [161], reported the attempt to optimize the CRISPR/Cas9 system to target canine tumor protein 53 (TP53), one of the most important tumor suppressor genes. The establishment of TP53 knockout canine cells could generate a useful platform to reveal novel oncogenic functions and effects of developing anti-cancer therapeutics [161].

Whereas one of the key benefits of using ciPSCs in disease modeling is the already discussed advantage over murine models, mostly due to the higher similarity between dogs to humans, another important perspective about ciPSCs is its potential use in clinical applications to improve the health and welfare of dogs themselves, an important aspect to be considered, in particular, due to the increasing inclusion of pets inside families and their overall importance to the One Health concept.

3. Future perspectives and final considerations

Herein advantages and hurdles of using of induced pluripotent stem cells were discussed concerning ongoing and future applications in large animal models, summarized in **Figure 1**. While true ESCs have only been described in mouse and rat models, it is widely accepted that these models are not the most adequate for studies on cellular therapies in regenerative medicine. Therefore, progress on translational medicine relies on the development of pluripotent-based technologies in suitable environments such as NH-primates, swine, or canine organisms. The alliance between in vitro induced pluripotency and gene editing tools opens a new road to suitable and experimental preclinical protocols. Besides the in vivo or in vitro disease modeling, the validation of pluripotency in domestic and wild animals holds great promise to contribute to animal production, preservation, and health by enabling, for example, the generation of gene editing and improved gametes, embryos, and animals.

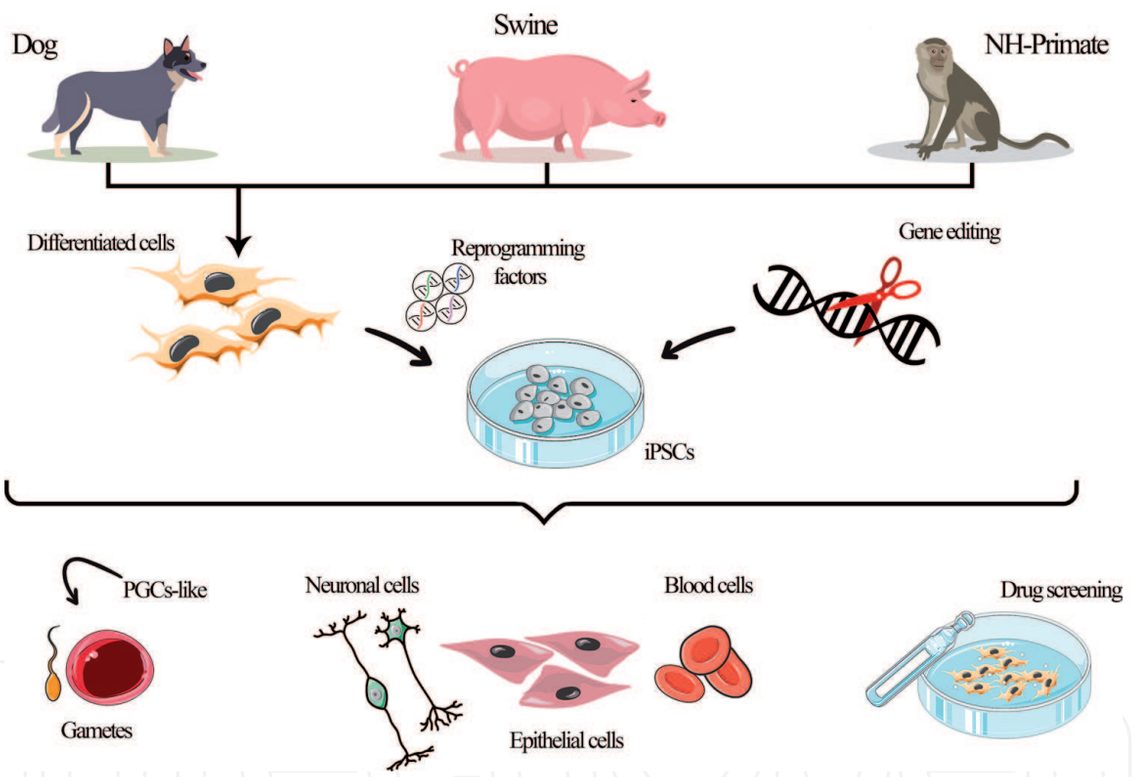

Figure 1.
Biomedical and regenerative possibilities for translational use of induced pluripotent stem cells derived from large animal models.

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