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Review

Veterinary applications of induced pluripotent stem cells: Regenerative medicine and models for disease?

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ABSTRACT

Induced pluripotent stem cells (iPSCs) can now be derived from a tissue biopsy and represent a promising new platform for disease modelling, drug and toxicity testing, biomarker development and cell-based therapies for regenerative medicine. In regenerative medicine, large animals may represent the best models for man, and thereby provide invaluable systems in which to test the safety and the potential of iPSCs. Hence, testing iPSCs in veterinary species may serve a double function, namely, developing therapeutic products for regenerative medicine in veterinary patients while providing valuable background information for human clinical trials.

The production of iPSCs from livestock or wild species is attractive because it could improve efficiency and reduce costs in various fields, such as transgenic animal generation and drug development, preservation of biological diversity, and because it also offers an alternative to xenotransplantation for in vivo generation of organs. Although the technology of cellular reprogramming using the so-called 'Yamanaka factors' is in its peak expectation phase and many concerns still need to be addressed, the rapid technical progress suggests that iPSCs could contribute significantly to novel therapies in veterinary and biomedical practice in the near future. This review provides an overview of the potential applications of iPSCs in veterinary medicine.

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Introduction

The generation of induced pluripotent stem cells (iPSCs) by the enforced expression of a small number of embryonic transcription factors in adult mammalian cells launched a new field of stem cell research. From the outset, iPSCs have generated enormous interest. In particular, it was anticipated that iPSCs would share most of the advantages of embryonic stem cells (ESCs), while overcoming some of their most important limitations (Robinton and Daley, 2012). From a veterinary perspective, the successful derivation of iPSC lines from many important domestic animal species in recent years (Fig. 1) represents a significant milestone. In particular, the reprogramming technology is expected to increase the accessibility of stem cells and their many potential uses in veterinary science and practice (Fig. 2). Moreover, domestic animals may help fill the considerable gaps between experiments in laboratory animals, especially mice, and clinical trials in humans; in fact, bridging this gap may become a major application for domestic animal iPSC research in the near future.

While there are great expectations for iPSC technology, sceptics have rightly warned that similarly high expectations for ESCs and somatic cell nuclear transfer (SCNT) are still largely unfulfilled despite years of basic research. On the other hand, the rapid rate of progress currently being made within the iPSC field is fundamentally different to the more laborious progress witnessed for ESCs and SCNT. This suggests that iPSC technology has a higher likelihood of becoming a clinical reality in the foreseeable future. Indeed, treatments based on iPSCs are already moving towards clinical practice; the RIKEN Centre for Developmental Biology in Kobe and the California Institute for Regenerative Medicine (CIRM) are awaiting administrative approval to launch human clinical trials using iPSCs to cure macular degeneration and dystrophic epidermolysis bullosa, respectively. As a spin-off these trials may generate techniques by which iPSC therapy can be used to treat some forms of blindness or skin disease in veterinary patients.

The aim of this review is to provide an overview of the potential applications of iPSCs in veterinary medicine, highlighting recently published articles and indicating connections between these publications and potential applications.

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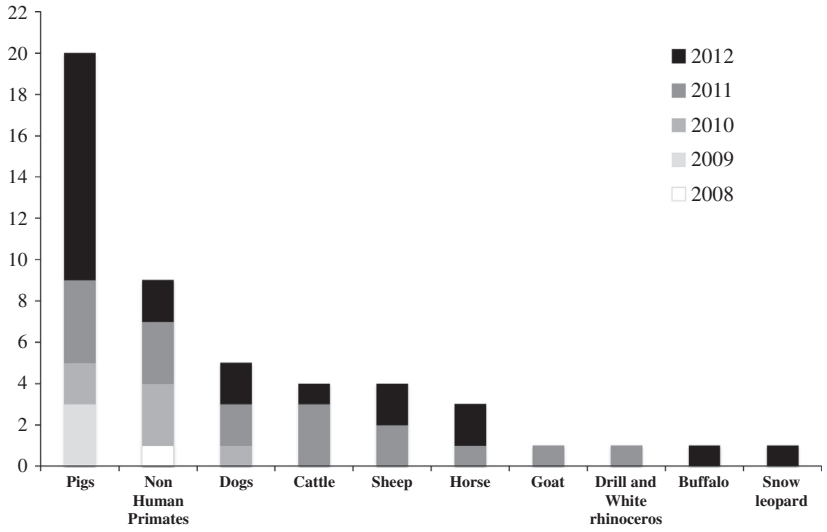

Fig. 1. Number of articles on large animal induced pluripotent stem cells published in a recent period (2008–2012). *Pig*: Esteban et al. (2009), Ezashi et al. (2009, 2011), Wu et al. (2009), Telugu et al. (2010), West et al. (2010), Montserrat et al. (2011, 2012), Nowak-Imialek et al. (2011), Zhou et al. (2011), Aravalli et al. (2012), Cheng et al. (2012), Fujishiro et al. (2013), Gu et al. (2012), Hall et al. (2012), Kues et al. (2013), Liu et al. (2012b), Tang et al. (2012), Templin et al. (2012), Yang et al. (2012). *Non human primates*: Liu et al. (2008), Tomioka et al. (2010), Wu et al. (2010), Zhong et al. (2011a,b), Chan et al. (2010), Deleidi et al. (2011), Zhu et al. (2011), Gori et al. (2012), and Torrez et al. (2012). *Dog*: Shimada et al. (2010), Lee et al. (2011), Luo et al. (2011), Koh et al. (2012), and Whitworth et al. (2012). *Cattle*: Han et al. (2011), Huang et al. (2011), Sumer et al. (2011), and Cao et al. (2012). *Sheep*: Bao et al. (2011), Li et al. (2011), Liu et al. (2012a), and Sartori et al. (2012). *Horse*: Nagy et al. (2011), Breton et al. (2013), and Hackett et al., 2012. *Goat*: Ren et al. (2011). *Drill and white rhinoceros*: Ben-Nun et al. (2011). *Buffalo*: Deng et al. (2012). *Snow leopard*: Verma et al. (2012).

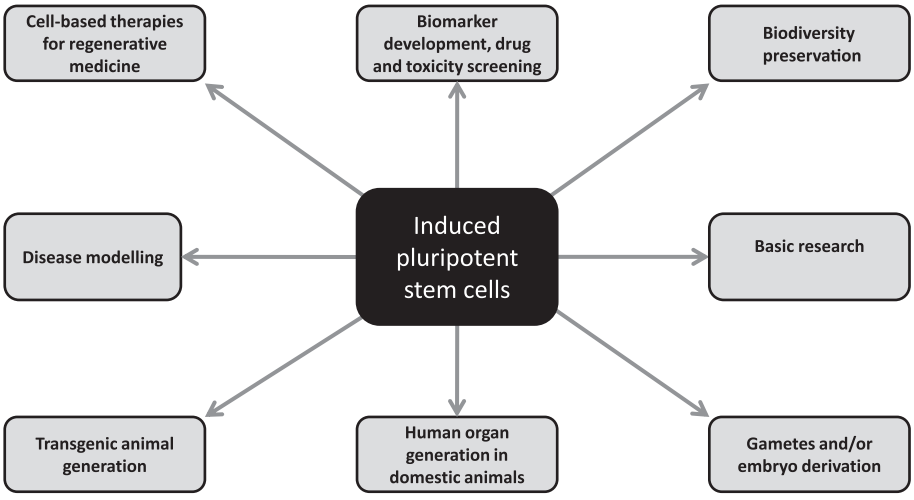

Fig. 2. Potential veterinary applications of induced pluripotent stem cell technology.

Historical background

Two milestones paved the way for the recent breakthroughs in iPSC technology in mammals. First, the isolation over 30 years ago of pluripotent stem cells from the inner cell mass of a mouse blastocyst, and their maintenance in the pluripotent state during in vitro culture (Evans and Kaufman, 1981). These cells, which are generally referred to as ESCs, showed two unique and invaluable characteristics, namely, the ability for unlimited self-renewal and the capacity to differentiate into tissues of all three major lineages (endoderm, ectoderm and mesoderm).

The second major milestone in the development of mammalian genetic reprogramming methods was the discovery that terminally differentiated mammalian somatic cells could be reprogrammed to the totipotent state by an oocyte, and subsequently used to create 'cloned' embryos capable of generating grossly normal live offspring. The production of 'Dolly the sheep' by SNCT was undoubtedly the most famous example of this breakthrough (Wilmut et al., 1997).

Induced pluripotent stem cell discovery

In an attempt to identify the major transcriptional regulators capable of reprogramming adult cells to the pluripotent state, Takahashi and Yamanaka (2006) examined the effect of transfecting cells with various combinations of 24 genes associated with the induction of pluripotency in somatic cells. To their surprise, the reprogramming of adult cells to pluripotency could be achieved by the transfection and co-overexpression of only four of these genes (*OCT4*, *SOX2*, *cMYC* and *KLF4*; the 'Yamanaka factors'). Soon after this breakthrough, similar cells, termed iPSCs, were derived in other laboratories (Fig. 3). Most significantly, their pluripotency was confirmed when it was shown that they could be used to

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