Review

A Review on Induced Pluripotent Stem Cells in Livestock Conservation: Advances, Applications and Future Perspectives

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ABSTRACT

Conservation of threatened and endangered species requires maintaining viable populations with sufficient genetic diversity. Recent advances in reproductive biotechnology, particularly the generation of induced pluripotent stem cells (iPSCs) from cryopreserved somatic cells offer transformative opportunities for conservation. Global biobanking efforts have created extensive repositories of tissues and cells that can be reprogrammed into iPSCs and expanded indefinitely, providing a renewable platform for multi-omics research, genetic resource preservation, and potential production of live offspring. Emerging technologies such as *in vitro* gametogenesis (IVG) and stem cell derived embryo models (SCBEM) promise routes to functional gamete and embryo generation entirely *in vitro*, enabling scalable assisted reproduction, embryo transfer, and enhanced cryobanking strategies. Major challenges remain, including preserving genomic integrity across generations, developing species-specific reprogramming and culture protocols (including optimized growth factor regimens), and achieving robust germline competency. This review evaluates the current state of iPSC-based approaches for livestock conservation, discusses technical and ethical hurdles, and highlights critical research priorities to translate stem cell technologies into practical tools for preserving genetic diversity in endangered and threatened livestock species.

Keywords: Biobank, Embryo, Germ cells, iPSC

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Received: July 31, 2026
Accepted: August 14, 2026

INTRODUCTION

The planet is approaching a critical phase of Holocene-scale biodiversity loss, marked by accelerating environmental pressures and sharp declines in both wildlife and livestock populations (Ceballos *et al.,* 2015). Livestock genetic resources underpin food security, rural livelihoods, and resilient agricultural systems in which indigenous breeds contribute milk and meat, provide draught power, and offer disease resistance, heat tolerance, and local adaptation. Yet climate change, habitat degradation, disease outbreaks, uncontrolled crossbreeding, and falling effective population sizes are rapidly eroding this diversity, creating an urgent need for more effective conservation strategies. Conservation must therefore preserve not only population numbers but also the biological and reproductive potential encoded in valuable genomes.

Traditional approaches such as semen and oocyte cryopreservation, embryo banking, and somatic cell repositories remain essential but have limitations (Saini *et al.,* 2025, Prasad *et al.,* 2024) as shown in Fig. 1. Semen and oocyte banks preserve only haploid paternal or maternal genomes, respectively, while embryo banking stores a diploid genome but is highly dependent on donor availability and reproductive performance. Somatic cell repositories maintain differentiated material that cannot directly generate offspring without reprogramming or cloning (Sharma *et al.,* 2018a). Although these methods have preserved valuable genetic resources, they remain limited in their ability to reconstruct fully competent and developmentally intact livestock genomes through assisted reproduction technologies (Sharma *et al.,* 2018, Sharma *et al.,* 2018b). Embryo, iPSC and somatic cell biobanks conserve the diploid genome, capturing both genetic and epigenetic information. Together, these platforms enable long-term germplasm preservation and support assisted reproduction, genetic rescue and advanced regenerative strategies for sustainable livestock conservation.

Pluripotent stem cell (PSC) technology offers a promising extension to existing conservation frameworks and are of two types-Embryonic Stem cells (ESCs) and Induce pluripotent cells (iPSCs). ESCs are derived from the inner cell mass of blastocysts and possess the capacity for indefinite self-renewal and differentiation into all primary germ layers. In contrast, iPSCs can be generated from a wide range of adult somatic cells, independent of donor age or sex, without the need for embryo destruction, thereby providing an ethically acceptable, accessible, and virtually unlimited source of pluripotent cells and like ESCs,

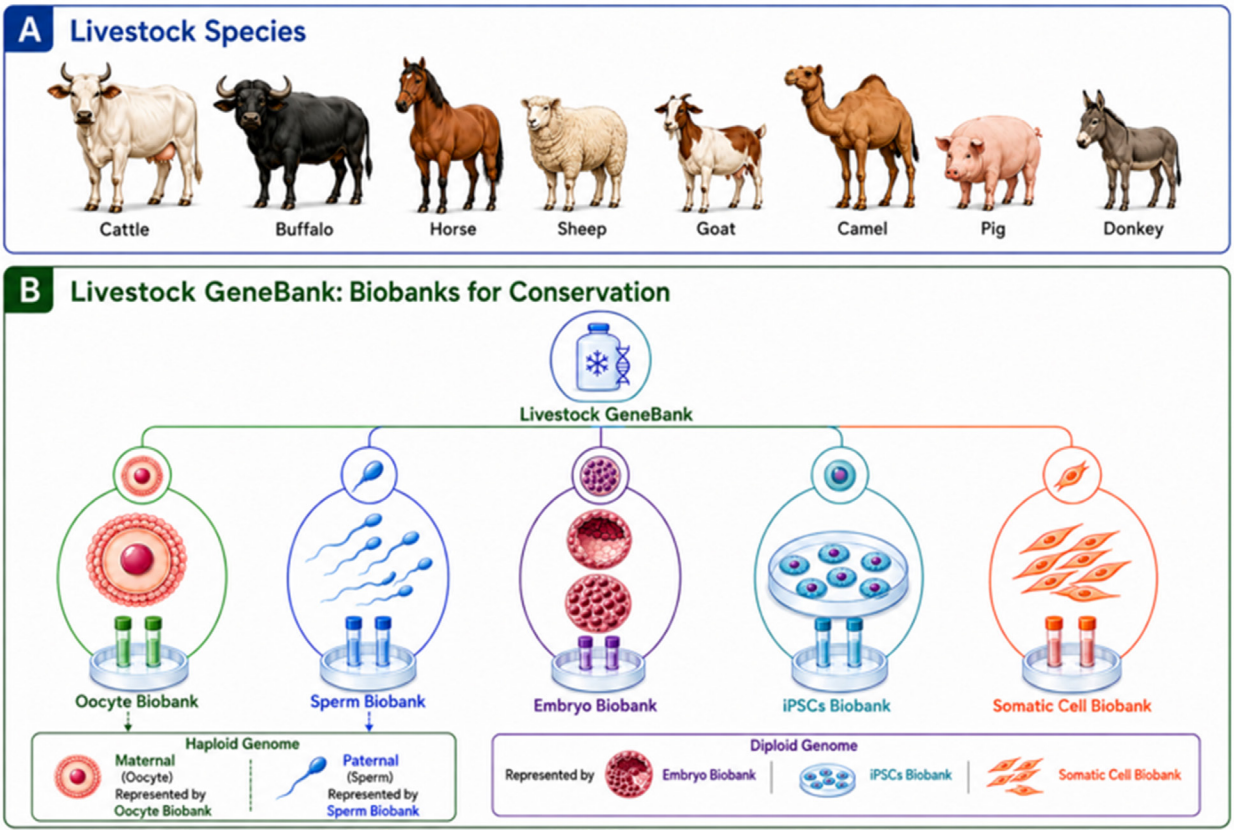

Fig. 1: *Livestock conservation strategies through biobanking (A) Schematic representation of diverse livestock species of conservation importance. (B) Schematic of a Livestock GeneBank comprising five complementary biobanks: oocyte, sperm, embryo, induced pluripotent stem cell (iPSC) and somatic cell repositories.*

these are capable of self renewal and differentiation into three germ layers. iPSCs can be generated through the molecular reprogramming of terminally differentiated somatic cells into a pluripotent state by over expressing four transcription factors generating renewable cell lines that can be expanded indefinitely and potentially differentiated into multiple cell types, including germ cells (Takahashi and Yamanaka, 2006). The initial establishment of iPSCs in murine systems, followed closely by successful derivation in humans, represented a major breakthrough in stem cell biology, enabling extensive advancements in both fundamental and translational research (Takahashi *et al.,* 2007). This property is particularly valuable for livestock conservation because a small tissue sample from a rare or endangered animal can, in principle, be converted into a living, expandable genetic resource for long-term storage, genomic characterization, and future reproductive use.

Reprogramming somatic cells into iPSCs creates a versatile platform for preserving genetic material from rare breeds and threatened taxa. iPSCs can be directed toward germline differentiation to produce functional gametes i.e. *in vitro*- oocytes and spermatozoa that can be used with ART technologies such as *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), and somatic cell nuclear transfer (SCNT) to generate viable offspring (Hildebrandt *et al.,* 2024). Importantly, iPSCs provide an ethically and logistically advantageous route to pluripotency without relying on embryos or donor oocytes, a critical benefit when access to embryos is extremely limited (Dejosez and Zwaka, 2012). iPSC lines have been derived from many livestock species such as sheep, goats, cattle, buffalo, pig, horse, camel, and others, demonstrating broad applicability for their conservation. Functional developmental potential of iPSCs has been first demonstrated by producing live offspring in murine using tetraploid complementation and intracytoplasmic nuclear injection in model systems (Boland *et al.,* 2009; Zhao *et al.,* 2009; Fan *et al.,* 2013), and followed by the generation of viable piglets using iPSCderived nuclei in SCNT (2013). These results indicate the potential for iPSC based routes to restore or augment endangered livestock genomes, while underscoring the need for species-specific optimization and rigorous assessment of genomic integrity.

iPSCs can serve as inexhaustible genetic stocks that complement conventional cryobanking and has their relevance is greatest for indigenous, rare, and endangered breeds that exist in small, fragmented populations, are under-represented in formal gene

banks, cannot be conserved through traditional ARTs and carry adaptive traits difficult to recover once lost. iPSC based biobanking can preserve these genotypes before demographic decline or genetic introgression renders recovery impossible, and unlike DNA only repositories can retain functional cellular diversity suitable for future gamete derivation, cloning, or embryo reconstruction when conventional reproductive material is unavailable. Biobanking iPSC lines create a durable resource for multiomics research, phylogeography, taxonomy, and genetic diversity analyses that directly inform ex situ and in situ management.

Beyond conservation, livestock iPSCs have applications in reproductive biotechnology and developmental biology, including studies of early embryogenesis, generation of embryo-like 3D models, and support for SCNT, and derivation of germ cell like cells for assisted reproduction (Saragusty *et al.,* 2016; Ben-Nun *et al.,* 2011) as shown in Fig. 2. These approaches are especially valuable in species where ESC derivation is difficult and recovery of elite or endangered genotypes may depend on advanced cell based technologies. The generated iPSCs can be applied in multiple areas of livestock conservation and biotechnology, including germline cell generation for the production of primordial germ cells, sperm, and oocytes to support fertility restoration and preservation of rare alleles; embryo production for generating blastocysts and supporting breed recovery through assisted reproductive technologies; genome editing using CRISPR/Cas systems for the introduction of desirable traits such as disease resistance, climate resilience, and improved productivity; disease modelling and functional genomics for investigating disease mechanisms and evaluating therapeutic interventions; long-term cryobanking of iPSC lines as renewable genetic resources for future regeneration; and cloning and regenerative applications through nuclear transfer for breed restoration and clonal propagation. Nevertheless, iPSC research in farm animal's remains technically challenging, and highly species dependent. Derivation and stable maintenance of pluripotent cells in livestock is generally less efficient than in mouse or human systems (Goszczynski *et al.,* 2019b). Long-term culture while preserving full pluripotency is difficult; many lines exhibit incomplete reprogramming, epigenetic instability, or limited developmental competence. Progress is uneven across taxa, with ruminants (cattle, sheep, goat, buffalo) posing particular reprogramming and culture challenges (Goszczynski *et al.,* 2019b). Given these limitations, a focused critical review is timely. This review examines the current status of livestock iPSC research with emphasis on conservation applications, synthesizes progress across major species, evaluates the promise of iPSCs as a renewable conservation resource, and identifies key methodological, biological, and translational barriers that must be overcome before routine use in genetic resource management.

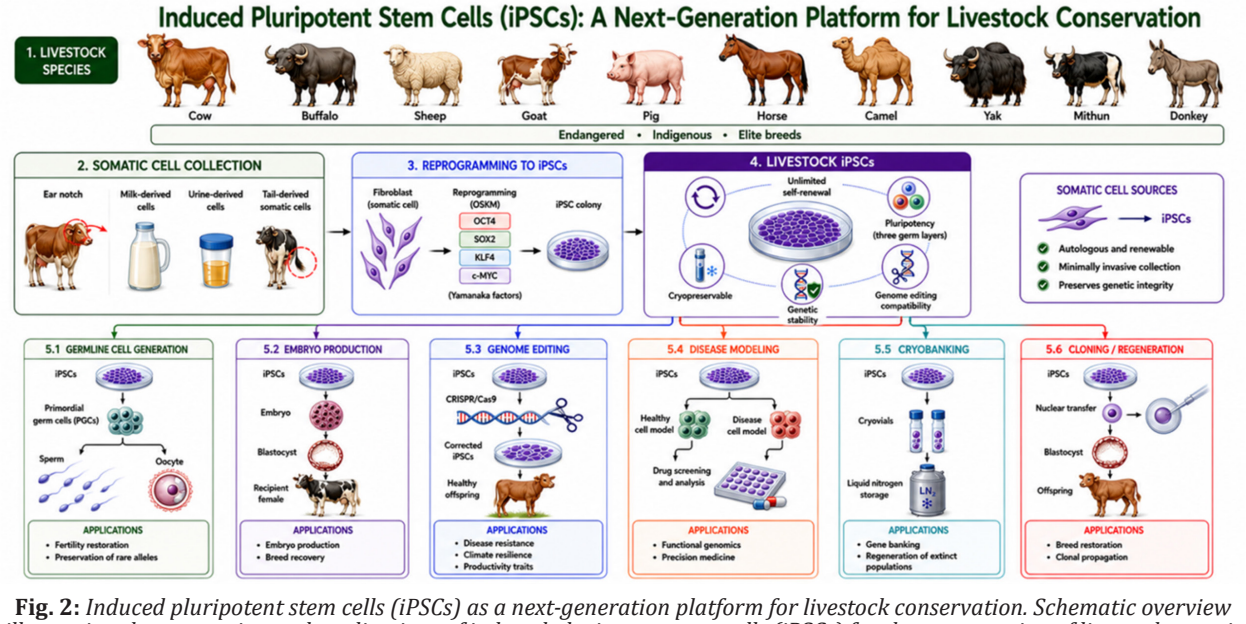

Fig. 2: *Induced pluripotent stem cells (iPSCs) as a next-generation platform for livestock conservation. Schematic overview illustrating the generation and applications of induced pluripotent stem cells (iPSCs) for the conservation of livestock genetic resources. 1) Diverse Indigenous livestock species, including cow, buffalo, sheep, goat, pig, horse, camel, yak, mithun, and donkey, serve as potential sources of somatic cells. 2) Somatic cells can be isolated through minimally invasive sampling methods such as ear notch, milk-derived cells, urine-derived cells, and tail-derived cells, followed by 3-cellular reprogramming using the Yamanaka factors (OCT4, SOX2, KLF4, and c-MYC) to generate iPSCs. 4) Livestock iPSCs possess the defining characteristics of pluripotency, unlimited self-renewal, cryopreservability, genetic stability, and compatibility with genome editing technologies. 5) The generated iPSCs can be applied in multiple areas of livestock conservation and biotechnology.*

Applications of iPSCs in conservation biology

Rapid progress in stem cell biology and ARTs has facilitated the successful generation of iPSC lines across a wide spectrum of species, including humans (Guan *et al.,* 2022, Takahashi *et al.,* 2007), non-human primates such as monkeys (Wu *et al.,* 2010), and several agriculturally important livestock species, including cattle (Bai *et al.,* 2016; Cao *et al.,* 2012; Sumer *et al.,* 2011; Pillai *et al.,* 2021), buffalo (Deng *et al.,* 2012), pigs (Ezashi *et al.,* 2009; Wu *et al.,* 2009), sheep (Bao *et al.,* 2011; Liu *et al.,* 2014; Sartori *et al.,* 2012), goats (Chen *et al.,* 2017; Ren *et al.,* 2011; Song *et al.,* 2013), equines (Nagy *et al.,* 2011, Breton *et al.,* 2013; Pessôa *et al.,* 2019b), rabbit (Honda *et al.,* 2010), dogs (Shimada *et al.,* 2010), avian species such as chickens (Lu *et al.,* 2014; Yu *et al.,* 2014) and recently in camels (Zhang *et al.,* 2024). A recent multinational initiative has focused on conserving tropical indigenous Suidae genetic resources through iPSC-based biobanking (Tiambo *et al.,* 2023).

Beyond livestock species, pioneering studies have extended iPSC technology to endangered and rare species, including the northern white rhinoceros (Ben-Nun *et al.,* 2011), drill (Ben-Nun *et al.,* 2011), snow leopard (Verma *et al.,* 2012), Bengal tiger (Verma *et al.,* 2013), primates (Bao Q *et al.*, 2024) and bats (Déjosez *et al.,* 2023). Accumulating evidence underscores the considerable potential of iPSC-based approaches for the conservation of threatened biodiversity, as these systems enable long-term preservation of genetic material, facilitate the *in vitro* derivation of germ cells or functional gametes without ethical constraints, and provide a strategic platform for mitigating the risk of extinction in vulnerable species (Honda 2018; Saragusty *et al.,* 2016, Lou *et al.*, 2025) and may be directed toward multiple downstream applications, including germline regeneration, *in vitro* gametogenesis (IVG), disease modeling, and stem cell based 3D embryo models or known as stembryo. In this context, iPSCs are not a replacement for habitat protection or captive breeding, but rather a complementary biotechnology that can expand the conservation toolkit for species and breeds at risk of extinction.

Germ line Reconstruction and Assisted Reproduction through IVG

A major objective in developmental and reproductive biology is the complete *in vitro* reconstruction of gametogenesis. IVG is the directed differentiation of PSC into primordial germ cell-like cells (PGCLCs) and subsequently into functional male or female gametes under controlled *in vitro* conditions, recapitulating germline development outside the organism, offering a promising route for conservation of endangered or extinct species with limited breeding populations or absence of viable gametes (Stanton *et al.,* 2019; Saragusty *et al.*, 2020; Wu *et al.*, 2024; Nogueira *et al.*, 2024). IVG is particularly valuable for species with critically low population sizes or skewed sex ratios, where conventional breeding is limited and especially relevant for endangered species with only a few surviving individuals, because somatic cells already stored in biobanks could theoretically be reprogrammed into germ cells and used for ARTs. IVG is increasingly viewed as a realistic long term strategy for genetic rescue and population recovery of endangered species and one of the pioneer examples is being extensively used for the protection of the rhinoceros species (Hayashi *et al.,* 2022; Korody and Hildebrandt, 2025). In this context, landmark studies have shown the successful reconstitution of oogenesis from mouse iPSCs under defined culture conditions (Hikabe *et al.,* 2016). Importantly, progression beyond early primordial germ cell-like stages requires a supportive niche provided by gonadal somatic cells, which supply essential signaling cues and microenvironmental factors necessary for proper germ cell maturation.

A potential strategy to address this limitation is the generation of gonadal somatic like support cells alongside germ cells *in vitro*. In line with this, studies have demonstrated that providing an appropriate ovarian niche can promote further maturation of PGCLCs. For example, prolonged culture of human PGCLCs within xenogeneic reconstituted ovarian systems, comprising mouse embryonic ovarian somatic cells, has been shown to drive their gradual progression toward oogonia-like stages over extended culture periods (Yamashiro *et al.*, 2018). Despite intensive research by multiple groups, nearly a decade elapsed between the first successful differentiation of PSCs into functional gametes in the mouse and the achievement of a comparable outcome in another rodent species, the rat (Oikawa *et al.*, 2022). Notably, the protocols enabling IVG in rats were largely adapted from those established in mice, with only minor species-specific modifications.

Different reprogramming methods, integration free protocols, different combination of factors and *in vitro* culture systems capable of reconstructing functional ovarian follicles, including oocytes, from iPSCs represent a significant advancement in reproductive biology and provide a valuable framework for elucidating the mechanisms underlying oogenesis and offer critical insights into the interactions between PGCs, oocytes, and gonadal somatic cells. In contrast to SCNT, IVG facilitates sexual reproduction through meiotic recombination, thereby generating novel allelic combinations and enhancing genetic diversity within populations (Cowl *et al.*, 2024). To date, multiple studies

have demonstrated the capacity of iPSCs to differentiate into both female and male germ cell lineages across several species, including rats, humans (Oikawa *et al.*, 2022), and mice (Nagaoka *et al.*, 2020).

Following the establishment of stable bovine ESCs (Botigelli *et al., 2*018), subsequent studies proposed *in vitro* breeding frameworks integrating stem cells, gametogenesis, and genomic selection. *In vitro* spermatogenesis from spermatogonial stem cells (SSCs) has been achieved through testicular tissue culture, with the first production of fertile sperm (Sato *et al.,* 2011). Subsequent studies across livestock species (cattle, sheep, goat, pig) and primates have demonstrated the generation of functional or sperm-like cells under optimized culture conditions (Kim *et al.*, 2015; Deng *et al.*, 2016; Deng *et al.*, 2017; Zhao *et al.*, 2018). Functional iPSC-derived gametes in rodents are a proof-of-concept for IVG and represent a promising strategy for conserving critically endangered species, such as the Indian Tibetian Sheep, Endangered camel and horse breeds. The capacity to generate a sustained supply of haploid gametes from iPSCs would constitute a valuable resource for fundamental investigations into gametogenesis and early embryonic development in endangered livestock species and Moreover, the derivation of gametes from iPSCs established using cryopreserved somatic cells of deceased individuals offers a promising avenue to reintroduce lost allelic variation and enhance genetic diversity within small or bottlenecked populations. Collectively, these attributes underscore the potential utility of iPSC-based technologies in conservation biology (Botigelli *et al.*, 2023).

Synthetic embryology for conservation of endangered species

The Stem Cell Based Embryo Modelinghas gained significant attention towards the generation of *in vitro* 3D culture embryo like models also known as Stembryo derived exclusively from iPSCs. One of the most promising applications of SCBEMs for endangered speciesconservation is the generation of pre-implantation blastocyst-like models, termed "blastoids" (Oura *et al.*, 2023) and encompass diverse configurations, including blastoids and gastruloids, which recapitulate distinct stages of early embryonic development depending on the cellular states and culture conditions employed (Terhune *et al.*, 2022). Such models offer unprecedented access to developmental processes that are otherwise difficult to investigate *in vivo*. In recent years, iPSCs derived embryo models or blastoid models have been generated across multiple mammalian species, including mice, humans, cattle, pigs, monkeys, and bats (Li *et al.*, 2019; Rivron *et al.*, 2018; Ai Z *et al.*, 2023, Sozen *et al.*, 2018; Kagawa *et al.*, 2021; Yanagida *et al.*, 2021; Yu *et al.* , 2021; Pinzón-Arteaga *et al.,* 2023; Xiang *et al.*, 2024; Li *et al.*, 2023; Déjosez *et al.*, 2023). Blastoids recapitulate key embryonic and extraembryonic lineages, including the trophectoderm and hypoblast, and can be generated via iPSC-only systems, co-culture with support-lineage cells, or from reprogrammed somatic cell derived iPSCs. In mice, monkeys, and cattle, transferred blastoids can initiate early pregnancy, but none have produced live offspring, with implantation likely a key bottleneck (Du and Wu, 2024; Aguilera-Castrejon, *et al.*, 2021). *In vitro* platforms may help optimize embryo-endometrium interactions and reprogramming methods (Shibata *et al.*, 2024; MacCarthy *et al.*, 2024).

These synthetic *in vitro* embryo-like models have further demonstrated the emergence of PGCLCs within biologically relevant cellular niches, thereby closely recapitulating early germline development through the high resolution single cell transcriptomic analyses, which can be leveraged to refine and optimize differentiation protocols. Notably, PGCLCs derived from such embryo models exhibit epigenetic and transcriptional profiles that more closely resemble their *in vivo* counterparts than those generated through conventional directed differentiation approaches (Cooke *et al.*, 2023; Weatherbee *et al.,* 2023; Liu *et al.*, 2023). In addition, these platforms provide a tractable system to evaluate the consequences of genetic manipulation in iPSCs, including strategies aimed at enhancing genetic diversity. Importantly, stem cell derived embryo models may ultimately serve as a direct source for embryo transfer into surrogate females, thereby potentially circumventing the need for donor oocytes or *in vitro* derived gametes supporting broader efforts in biodiversity conservation (Korody and Hildebrandt, 2025).

The use of embryo models in well-characterized model organisms, where direct comparison with *in vivo* embryos is possible, provides a robust framework for assessing developmental fidelity. This comparative approach is particularly valuable for extrapolating findings to endangered species, in which access to *in vivo* embryos is highly limited or ethically constrained (Hutchinson *et al.*, 2024). No blastoids have yet been developed for endangered or critical livestock or wildlife species, highlighting a major gap that will require improved understanding of early development, enhanced embryo culture and iPSC conditions. This gap may reflect limited knowledge of species-specific reprogramming requirements, incomplete understanding of reproductive physiology, and constraints in infrastructure and funding. Importantly, the reprogramming process is associated with risks,

including chromosomal instability, accumulation of genetic mutations, and epigenetic aberrations. Accordingly, rigorous evaluation of genomic and epigenomic integrity through approaches such as karyotypic analysis and molecular profiling is essential to ensure the safety and reliability of iPSCs for downstream applications. Further mechanistic studies are therefore required to optimize reprogramming fidelity and facilitate the translational deployment of iPSC-based strategies in conservation programs (Pera, 2011).

Ethical regulation

Appropriate application of iPSCs based methods has the potential to significantly advance our understanding of early developmental processes; however, their use must be carefully regulated to avoid ethical concerns and public apprehension (Rossant and Fu 2023; Segers, 2023). The application of iPSCs, PGCLC- 3D embryo models, genetic engineering, and ARTs must adhere to internationally recognized frameworks, particularly those established by ISSCR, as well as national regulatory authorities governing animal research and biotechnology. These guidelines emphasize scientific validity, transparency, traceability, and the prohibition of premature or unproven applications, especially in areas involving germline modification and embryo manipulation and promote scientifically rigorous, ethically sound, and responsibly regulated stem cell research, while discouraging premature clinical or commercial exploitation (Anthony *et al.,* 2021; Lovell-Badge *et al.,* 2021; Turner 2021).

A key regulatory priority is ensuring animal welfare across all stages of research and application. Procedures such as tissue collection, oocyte/semen retrieval, embryo transfer, cloning, and interspecies surrogacy must comply with strict welfare standards, minimizing pain, stress, and developmental risks. Implementation of the 3Rs principle; Replacement, Reduction, and Refinement, is essential to limit animal use and improve experimental design. In addition, long term health monitoring of animals produced through advanced technologies is required to assess potential physiological or genetic abnormalities. Ethical considerations also extend to population and ecosystem levels. Regulatory bodies increasingly stress the importance of risk benefit assessment, stakeholder engagement, and societal acceptance before deploying such technologies. Overall, robust ethical governance, coupled with continuous scientific evaluation, is essential to ensure that iPSCs based conservation strategies are both responsible and sustainable.

Future perspectives and challenges

Despite substantial progress in iPSCs from diverse species, significant technical and translational limitations continue to constrain their broader application in conservation biology. A major challenge lies in the incomplete understanding of cellular reprogramming mechanisms, which contributes to low efficiency, variability among iPSC lines, and the occurrence of partially reprogrammed cells with reduced differentiation potential. Additionally, the widespread reliance on heterologous reprogramming factors limits reproducibility across species, particularly in non-model and endangered animals, where species specific regulatory networks remain poorly characterized. Genomic instability and safety concerns represent further critical barriers. Reprogramming and prolonged culture can introduce chromosomal abnormalities, copy number variations, and point mutations, thereby compromising genetic fidelity and increasing the risk of tumorigenicity and functional heterogeneity. Residual expression of exogenous reprogramming factors and incomplete silencing of transgenes also remain persistent issues, raising concerns for downstream applications such as germline transmission and therapeutic use (Weeratunga *et al.,* 2023).

From a conservation perspective, additional constraints include the lack of standardized criteria for validating pluripotency across species, limited availability of appropriate culture systems, and difficulties in accessing high quality biological material from endangered species. Although recent frameworks emphasize integration of iPSC biobanking with ARTs and genome engineering, their practical implementation remains in early stages due to technical inefficiencies and species specific bottlenecks. Finally, ethical and regulatory considerations continue to evolve alongside technological advances. International guidelines increasingly emphasize the need for rigorous validation, transparency, and responsible translation, particularly in the context of embryo modeling, germline manipulation, and potential de-extinction efforts. Collectively, these challenges underscore the need for species specific optimization, improved mechanistic insights, and robust regulatory frameworks to enable safe and effective deployment of iPSC based technologies in livestock and wildlife conservation.

CONCLUSION

iPSC biobanking represent a transformative platform in conservation biology, offering unprecedented opportunities to preserve, restore, and utilize genetic resources from threatened livestock and wildlife

species. Their capacity for indefinite self-renewal and differentiation into germline lineages places them at the core of next-generation conservation strategies, particularly when integrated with IVG, genome editing, and ARTs. Despite significant progress, several challenges limit their practical application, including low reprogramming efficiency, genomic instability, incomplete germ cell maturation, and species-specific constraints. Ethical, regulatory, and animal welfare considerations must also be addressed, alongside the current lack of standardized protocols and limited availability of high-quality biological material for many endangered species. Biobanking of iPSCs should be regarded as a complementary strategy rather than a replacement for species conservation, operating in close integration with ART and hold strong potential for enhancing genetic diversity, enabling genetic rescue, and strengthening both ex situ and in situ conservation programs. Overall, while iPSCs are not a standalone solution, they constitute a powerful and versatile component of a multidisciplinary framework for sustainable biodiversity conservation and long-term genetic management, with their future impact driven by continued innovation, collaboration, and strategic investment.

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