



OPEN ACCESS

EDITED AND REVIEWED BY
Valerie Kouskoff,
The University of Manchester,
United Kingdom

*CORRESPONDENCE

Lin Yuan,
✉ lyuan@cmu.edu.cn
Feng Yue,
✉ fyuee@hotmail.com
Jacek Z. Kubiak,
✉ jacek.kubiak@univ-rennes1.fr
Sen Wu,
✉ swu@cau.edu.cn
Yongye Huang,
✉ huangyongye88@163.com

RECEIVED 18 May 2023
ACCEPTED 24 May 2023
PUBLISHED 30 May 2023

CITATION

Yuan L, Yue F, Kubiak JZ, Wu S and
Huang Y (2023), Editorial: Applying large
animals for developmental study and
disease modeling.
Front. Cell Dev. Biol. 11:1225060.
doi: 10.3389/fcell.2023.1225060

COPYRIGHT

© 2023 Yuan, Yue, Kubiak, Wu and
Huang. This is an open-access article
distributed under the terms of the
[Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is
permitted, provided the original author(s)
and the copyright owner(s) are credited
and that the original publication in this
journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Editorial: Applying large animals for developmental study and disease modeling

Lin Yuan^{1*}, Feng Yue^{2*}, Jacek Z. Kubiak^{3,4*}, Sen Wu^{5,6*} and Yongye Huang^{7*}

¹Laboratory of Research in Parkinson's Disease and Related Disorders, Health Sciences Institute, China Medical University, Shenyang, China, ²Key Laboratory of Biomedical Engineering of Hainan Province, School of Biomedical Engineering, Hainan University, Haikou, China, ³Faculty of Medicine, Dynamics and Mechanics of Epithelia Group, CNRS, Institute of Genetics and Development of Rennes (IGDR), University Rennes, Rennes, France, ⁴Laboratory of Molecular Oncology and Innovative Therapies, Military Institute of Medicine (WIM-PIB), Warsaw, Poland, ⁵State Key Laboratory of Animal Biotech Breeding, College of Biological Sciences, China Agricultural University, Beijing, China, ⁶Sanya Institute of China Agricultural University, Sanya, China, ⁷Key Laboratory of Bioresource Research and Development of Liaoning Province, College of Life and Health Sciences, Northeastern University, Shenyang, China

KEYWORDS

gene editing, CRISPR/Cas9, embryo, development, pig, rabbit, monkey

Editorial on the Research Topic

[Applying large animals for developmental study and disease modeling](#)

Introduction

We have a great pleasure to organize the Research Topic “Applying large Animals for Developmental Study and Disease Modeling”. It is well known that large animals show similarities in many physical and pathological characteristics with human beings and have numerous advantages in developmental and medical research. In recent years, an important breakthrough has been achieved in gene editing technique, including ZFN, TALEN, CRISPR/Cas9, and so on. Especially for the emergence of CRISPR/Cas9 mediated gene modification strategies, various types of human diseases have been recapitulated in large animal models. It has to be mentioned that the progress in establishing embryonic stem cells and inducible pluripotent stem cells is also critical for the application in diseases modeling and therapies. In our Research Topic more than ten papers have been collected, and most of them focus on pig, monkey, rabbit and horse (Figure 1).

Pig

The pig, as one of the most common livestock, exhibits several advantages in biomedical research. These are: comparable human and pig body sizes, similar anatomical and physiological characteristics, genomic composition and ordinary diets (Hou et al., 2022). It makes the pig a promising alternative animal model for humans. Rapid growth rate, early sexual maturity, short generation intervals, high number of offspring per litter, and standardized breeding techniques, also make easier the application of pigs in the study

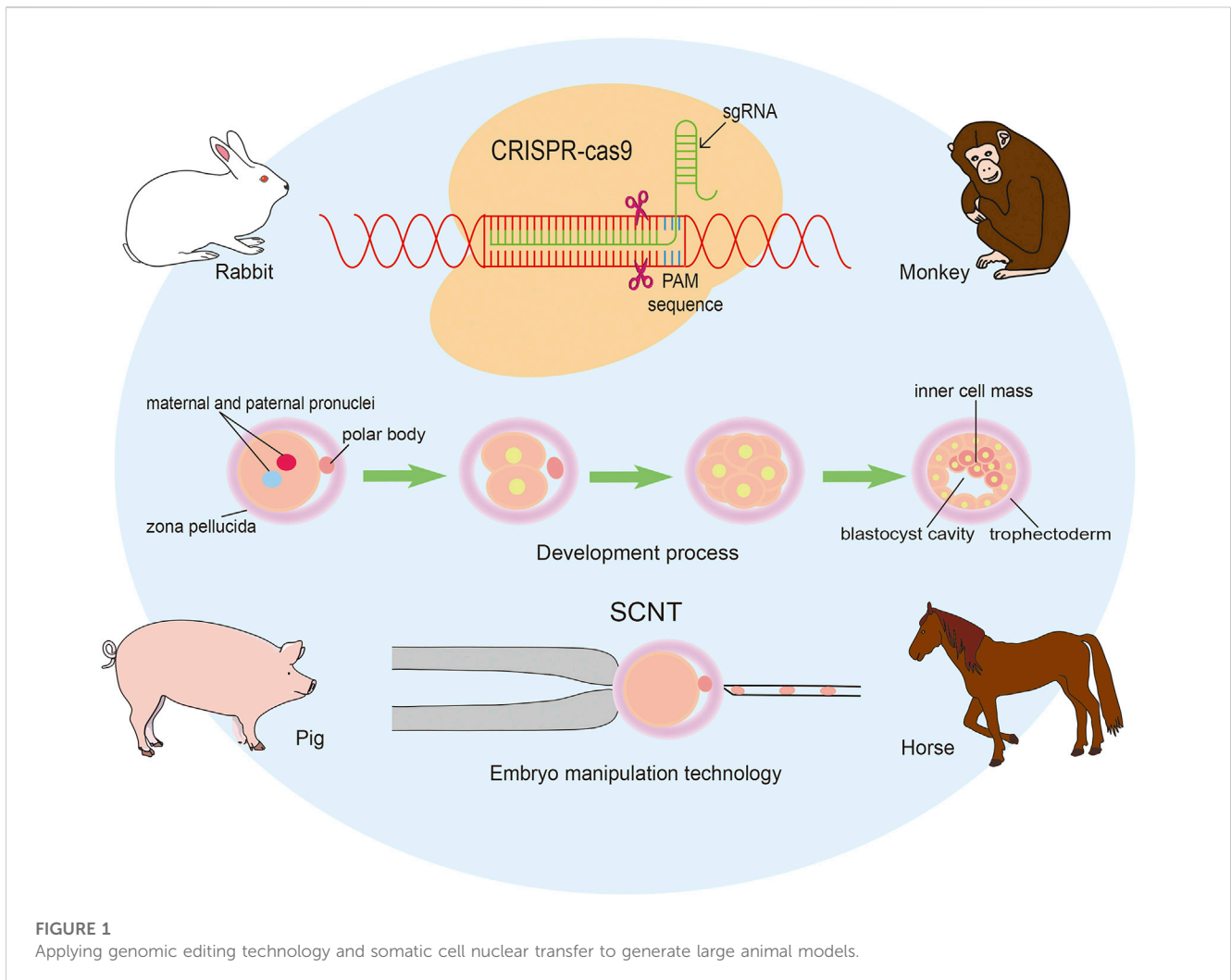


FIGURE 1
Applying genomic editing technology and somatic cell nuclear transfer to generate large animal models.

on human diseases. In recent decades, the advances in technologies contribute to the development of genetically engineered pig models of human diseases. The emergence of somatic cell nuclear transfer (SCNT) and reliable genome editing techniques make possible for the generation of porcine models of human diseases. The efficacy of porcine SCNT has been largely improved and several kinds of small molecular inhibitors have been applied to enhance the developmental competence of SCNT embryos (Ouyang et al., 2021; Hou et al., 2022). CRISPR/Cas9-mediated gene editing strategies are widely used in the establishment of porcine models of human diseases. Various genomic genetically engineered pigs have been generated, including chimeric gene knock in, point mutations, large genome fragment deletions, multifunctional live cell sensors, etc. One of the most promising potential application of pigs in the biomedical field is xenotransplantation. In 7 January 2022, the medical school of the University of Maryland in the United States conducted the first-ever life-saving cardiac xenotransplantation and it was successful in extending the patient's life for about 8 weeks (Rothblatt, 2022). The breakthrough sheds light on xenotransplantation using porcine organs as donors. Actually, corneas, lungs, nerve cells, kidneys, livers, and islets of pigs are also potential candidates for

xenotransplantation. In the Research Topic, Junliang Li et al. evaluated the methylation status of IG-DMR and gene expression profile in the DLK1-DIO3 region (Li et al.); Lin et al. revealed that intravenous injection of AAV9-GFP could result in widespread expression of transgene in various porcine organs (Lin et al.); Hilansi Rawat et al. found that porcine expanded pluripotent stem cells could differentiate into cardiovascular progenitor cells, functional cardiomyocytes, epicardial cells and epicardial-derived cells, and they established an enhanced system for whole-embryo culture allowing *ex utero* development of porcine post-implantation embryos from ED14 up to ED17 (Hilansi et al.); and many papers review the progress of applying pigs in xenotransplantation and biomedical research.

Nonhuman primates

Nonhuman primates (NHP) emerge increasingly as excellent models for translational research, due to even closer proximity to human beings in terms of physiology, biochemistry, immunology, pathology and genetic evolution. For example, NHP models are widely used in studies on Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-CoV-2). In fact, NHP models of HIV, ZIKV or Ebola virus infection mirror closely the pathogenesis in human patients. SCNT monkeys have been successfully produced using fetal fibroblasts as donor cells in recent years (Liu et al., 2018). Furthermore, BMAL1 gene-edited monkeys via the CRISPR/Cas9 technique were generated with both intracytoplasmic sperm injection and SCNT method (Liu et al., 2019; Qiu et al., 2019). Cynomolgus monkey blastoids resembling blastocysts in morphology and transcriptomics using naive ESC develop to embryonic disk with the structures of yolk sac, amnion cavity, chorionic cavity and primitive streak via prolonged *in vitro* culture (Li et al., 2023), making it possible to investigate primate embryonic development without the same ethical concerns associated humans. Various NHP models of human diseases have been established in recent years, including bilaterally delivering synthetic A β oligomers into the cerebral parenchyma of cynomolgus monkeys to drive early pathological progression of Alzheimer's disease (Yue et al., 2021). However, in the near future, researchers might face monkey shortage crisis (Grimm, 2023). In the Research Topic, Liang et al. summarizes the recent progress in using genomic editing technology in the establishment of NHP models and discusses the factors limiting the wide application of NHP models of human diseases (Liang et al.).

Rabbit

Rabbit is another commonly used experimental model for investigating equivalents of human diseases. With the emergence of microinjecting, SCNT and genomic editing technology, a large number of rabbit models of human diseases were established. The pronuclear microinjection is still the most common method in the generation of transgenic rabbit models. Novel genomic editing technologies, such as CRISPR/Cas9, remarkably promote precision in rabbit genome manipulation (Song et al., 2020). In previous studies, CRISPR/Cas9 technique was applied to introduce mutation of α A-Crystallin or GJA8 gene to induce congenital cataracts in Rabbits (Yuan et al., 2016; Yuan et al., 2017). Recently, SpRY-ABEmax mediated base substitution has been used to generate YIPF5 (p.W218R) mutation to generate rabbit primary microcephaly model, which precisely recapitulate the typical symptoms of human primary microcephaly (Liu et al., 2023). With recent technological innovations in genomic editing techniques, rabbit models will certainly play a much more important role in the study on human diseases. In our Research Topic, a carrageenan-induced abdominal aortic adventitial inflammatory model in hypercholesterolemic rabbits is described (Chen et al.). It determines the role of MMP-12 secreted from adventitial macrophages in the pathogenesis of this diseases (Chen et al.).

Horse

Horses are commonly used as animal models for studying several human diseases, including neurodegenerative diseases, mental and behavioral disorders, neuropsychiatric disorders and spontaneous sepsis. Using SCNT and genomic editing technology to generate horse models of human diseases seems to be less attractive than porcine and rabbit models. However, the rapid development in

horse models have been achieved in recent years. A recent report has revealed that a total of 12 SCNT foals were born (Cortez et al., 2023), and gene-edited horse embryos have been generated by CRISPR/Cas9 technology (Maniego et al., 2022). In our Research Topic, Neil Marr et al. utilized immunolabelling for CD146 to determine horse tendon cell population, providing the intrinsic evidences for the relationships between local interfascicular matrix vascular and basement membrane constituents (Marr et al.).

In conclusion, the Research Topic "Applying large Animals for Developmental Study and Disease Modeling" delivers a whole plethora of excellent examples of the fascinating progress made recently in this field of biomedical research.

Author contributions

LY and YH drafted the manuscript, YH revised the draft, FY, JK and SW made substantial contributions to the work through in-depth discussion. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the National Natural Science Foundation of China (Nos. 82201594 and 81502582). Funding was also provided by the Fundamental Research Funds for the Central Universities (N182004002 and N2220002), Natural Science Foundation of Liaoning Province (2021-MS-104, 2022-YGJC-39 and 2022-MS-228), Fundamental Scientific Research Fund of Liaoning Provincial Education Department (LJKQZ2021002), Key Laboratory of Bioresource Research and Development of Liaoning Province (2022JH13/10200026), Hainan Key Research and Development Project (ZDYF2021SHFZ049), and JK was supported by an internal grant nr. 612/2023 from Wojskowy Instytut Medyczny-Panstwowy Instytut Badawczy, Warsaw, Poland.

Acknowledgments

We would like to thank Wanlu Zhang in Northeastern University for assistance.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Cortez, J. V., Hardwicke, K., Cuervo-Arango, J., and Grupen, C. G. (2023). Cloning horses by somatic cell nuclear transfer: Effects of oocyte source on development to foaling. *Theriogenology* 203, 99–108. Epub 2023/04/04PubMed PMID: 37011429. doi:10.1016/j.theriogenology.2023.03.018
- Grimm, D. U. S. (2023). U.S., European researchers face monkey shortage crisis. *Science* 380 (6645), 567–568. Epub 2023/05/11PubMed PMID: 37167380. doi:10.1126/science.adi6512
- Hou, N., Du, X., and Wu, S. (2022). Advances in pig models of human diseases. *Anim. Model Exp. Med.* 5 (2), 141–152. Epub 2022/03/29PubMed PMID: 35343091; PubMed Central PMCID: PMC8291534. doi:10.1002/ame2.12223
- Li, J., Zhu, Q., Cao, J., Liu, Y., Lu, Y., Sun, Y., et al. (2023). Cynomolgus monkey embryo model captures gastrulation and early pregnancy. *Cell Stem Cell* 30 (4), 362–377.e7. Epub 2023/04/08PubMed PMID: 37028403. doi:10.1016/j.stem.2023.03.009
- Liu, X., Yang, J., Li, Z., Liu, R., Wu, X., Zhang, Z., et al. (2023). YIPF5 (p.W218R) mutation induced primary microcephaly in rabbits. *Neurobiol. Dis.* 182, 106135. Epub 2023/05/05PubMed PMID: 37142085. doi:10.1016/j.nbd.2023.106135
- Liu, Z., Cai, Y., Liao, Z., Xu, Y., Wang, Y., Wang, Z., et al. (2019). Cloning of a gene-edited macaque monkey by somatic cell nuclear transfer. *Natl. Sci. Rev.* 6 (1), 101–108. Epub 2019/01/01PubMed PMID: 34691835; PubMed Central PMCID: PMC6291622. doi:10.1093/nsr/nwz003
- Liu, Z., Cai, Y., Wang, Y., Nie, Y., Zhang, C., Xu, Y., et al. (2018). Cloning of macaque monkeys by somatic cell nuclear transfer. *Cell* 174 (1), 245. Epub 2018/06/30PubMed PMID: 29958110. doi:10.1016/j.cell.2018.01.036
- Maniego, J., Pesko, B., Habershon-Butcher, J., Hincks, P., Taylor, P., Tozaki, T., et al. (2022). Use of mitochondrial sequencing to detect gene doping in horses via gene editing and somatic cell nuclear transfer. *Drug Test. Anal.* 14 (8), 1429–1437. Epub 2022/04/02PubMed PMID: 35362263. doi:10.1002/dta.3267
- Ouyang, H., Han, J., and Huang, Y. (2021). Pig cloning using somatic cell nuclear transfer. *Methods Mol. Biol.* 2239, 1–18. Epub 2020/11/24PubMed PMID: 33226609. doi:10.1007/978-1-0716-1084-8_1
- Qiu, P., Jiang, J., Liu, Z., Cai, Y., Huang, T., Wang, Y., et al. (2019). BMAL1 knockout macaque monkeys display reduced sleep and psychiatric disorders. *Natl. Sci. Rev.* 6 (1), 87–100. Epub 2019/01/01PubMed PMID: 34691834; PubMed Central PMCID: PMC6291534. doi:10.1093/nsr/nwz002
- Rothblatt, M. (2022). Commentary on achievement of first life-saving xenohart transplant. *Xenotransplantation* 29 (3), e12746. Epub 2022/04/27PubMed PMID: 35471736. doi:10.1111/xen.12746
- Song, J., Zhang, J., Xu, J., Garcia-Barrio, M., Chen, Y. E., and Yang, D. (2020). Genome engineering technologies in rabbits. *J. Biomed. Res.* 35 (2), 135–147. Epub 2020/09/17PubMed PMID: 32934190; PubMed Central PMCID: PMC7555133. doi:10.7555/JBR.34.20190133
- Yuan, L., Sui, T., Chen, M., Deng, J., Huang, Y., Zeng, J., et al. (2016). CRISPR/Cas9-mediated GJA8 knockout in rabbits recapitulates human congenital cataracts. *Sci. Rep.* 6, 22024. Epub 2016/02/26PubMed PMID: 26912477; PubMed Central PMCID: PMC4766569. doi:10.1038/srep22024
- Yuan, L., Yao, H., Xu, Y., Chen, M., Deng, J., Song, Y., et al. (2017). CRISPR/Cas9-mediated mutation of α -crystallin gene induces congenital cataracts in rabbits. *Invest. Ophthalmol. Vis. Sci.* 58 (6), BIO34–BIO41. Epub 2017/05/06PubMed PMID: 28475701. doi:10.1167/jovs.16-21287
- Yue, F., Feng, S., Lu, C., Zhang, T., Tao, G., Liu, J., et al. (2021). Synthetic amyloid-beta oligomers drive early pathological progression of Alzheimer's disease in nonhuman primates. *iScience* 24 (10), 103207. Epub 2021/10/28PubMed PMID: 34704001; PubMed Central PMCID: PMC8524197. doi:10.1016/j.isci.2021.103207