

# Modeling monkey peri-gastrulation with stem cells

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**Following implantation, coordinated progression through gastrulation is essential for establishing the vertebrate body plan, yet mechanistic insight into this process in primates has been limited by the lack of faithful morphogenetic models. In a recent study, Liu and colleagues reported an improved stem cell-derived monkey embryo model that markedly increases developmental efficiency and potential, and more closely recapitulates multi-axial organization during gastrulation, providing a powerful platform for dissecting gene regulatory and cellular dynamics in early primate development.**

Studying primate embryogenesis from the blastocyst stage through gastrulation is constrained by ethical concerns and limited access to research material. To overcome this, stem cell-derived blastocyst-like structures, or blastoids<sup>1</sup>, have been developed as *in vitro* models capable of post-implantation development and gastrulation initiation<sup>2,3</sup>. Building on a human blastoid protocol<sup>1</sup> that sequentially induces naïve embryonic stem cells (ESCs) toward hypoblast (HYP) and trophoblast (TE) lineages, Liu and colleagues previously generated cynomolgus monkey blastoids using ESCs cultured under 4 chemicals + LIF (4CL) conditions<sup>4</sup>. Notably, these blastoids showed implantation competence and triggered pregnancy-like hormonal responses when transferred into surrogate uteri. Extended *in vitro* culture to day 17 under 2D conditions led to embryoids mimicking bilaminar disc formation and producing primitive streak (PS)-like cells. Single-cell transcriptomics confirmed the presence of diverse post-implantation and early gastrulation cell types. However, generation efficiency remained low, with only ~25% forming organized blastoids and ~8% developing disc-like structures.

In their latest study, Liu and colleagues significantly enhanced blastoid generation by using low-passage monkey ESCs under 4CL conditions, achieving ~60% efficiency by day 7<sup>5</sup>. After two days in IVC1<sup>6</sup> medium within AggreWell plates, peri-gastruloid<sup>7</sup>-like structures formed by day 9 and were transferred to an optimized 3D suspension culture for continued development. By day 17, ~32% of embryoids exhibited features of peri-gastrulation-stage embryos, including bilaminar disc-, amniotic cavity-, and yolk sac-like structures. Light-sheet microscopy revealed coordinated morphogenesis between days 13–17, with PS-like cells extending across one-third of the disc. Single-cell transcriptomics of day 17–18 embryoids showed a cellular composition broadly resembling the human Carnegie stage (CS) 7 gastrula<sup>8</sup> and previously reported 2D-cultured monkey embryoids<sup>4</sup>.

Well-organized day-17 embryoids were cultured in enhanced IVC2<sup>6</sup> medium with fetal bovine serum, supporting development to day 25 in ~69.9% of the cases. These struc-

tures closely resembled day-25 *in vitro* monkey embryos<sup>9,10</sup> and CS 8–9 human embryos in size and morphology, though development did not progress beyond this stage. Single-cell analyses identified a wide array of late gastrulation cell types, including amnion-, primordial germ cell (PGC)-, extra-embryonic mesodermal cell (EXMC)-, PS-like cells, prechordal plate, mesoderm derivatives, allantois, gut, neural plate and border, epidermis, endothelial cells, and hematopoietic lineages, whereas trophoblast cells were rarely detected. Histological analysis revealed progressive neural plate morphogenesis — elongation, thickening, folding, and groove formation — though PAX6<sup>+</sup> neuroectoderm was absent. Neural crest-like cells localized to neural folds, with placode-like cells at lateral borders. Mesodermal development progressed from nascent mesoderm (day 20) to lateral mesoderm (day 25). Yolk sac hematopoiesis was evident, with progenitors in the EXMC layer. Endodermal derivatives showed axial patterning, and PGC-like cells emerged sequentially in the amnion, posterior epiblast, yolk sac, and hindgut, consistent with an amniotic origin of primate PGCs. The culture system was also effective, though variably, in an additional ESC line and an iPSC line.

As a proof-of-concept for the functional utility of the embryoid system, the authors examined the effects of the loss of function of TBXT and EOMES. TBXT knockout led to a shortened and disorganized embryonic disc, accompanied by reduced WNT signaling and impaired posterior patterning. In contrast, EOMES knockout disrupted blastoid cavitation.

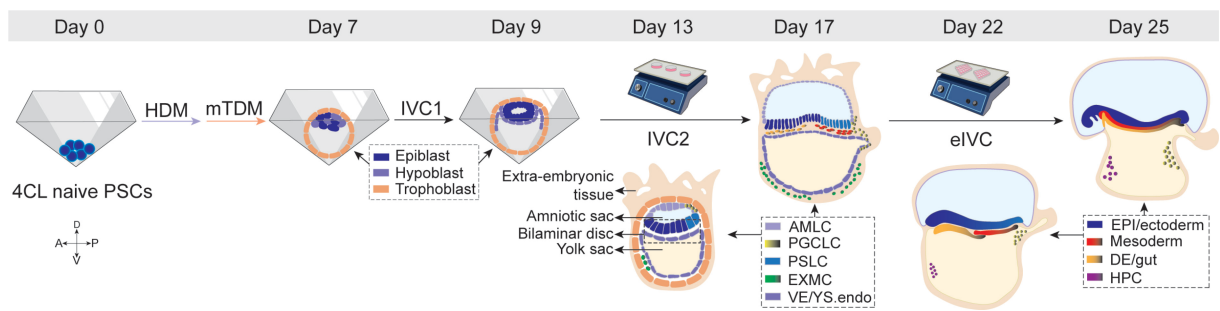
This monkey embryoid system provides a continuous *in vitro* model of development from the blastocyst stage through gastrulation and early organogenesis. A major strength of the model is its ability to capture epiblast- and yolk sac-related lineages alongside coordinated morphogenesis of the embryonic disc. However, several critical features of early primate development remain absent or underrepresented. Notably, anterior visceral endoderm (AVE)-like cells were not detected, possibly due to limited HYP-like cell function or limitations of suspension culture — unlike prior work where AVE markers (LEFTY1<sup>+</sup>, CER1<sup>+</sup>, OTX2<sup>+</sup>) emerged under attached conditions<sup>4</sup>. Similarly, TE development is poorly represented, raising questions about whether this reflects species-specific differences or limitations of the culture system. Consequently, the system's applicability to human blastoids remains uncertain.

Moreover, although the embryoids recapitulate several aspects of gastrulation, their developmental potential beyond this stage remains limited. This is evidenced by the absence of PAX6<sup>+</sup> mature neuroectoderm, neuro-mesodermal progenitors (NMPs), NKX2-5<sup>+</sup> cardiac mesoderm, and the node, the organizer of the body axis. Despite these limitations, this

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**Fig. 1 A stem cell-derived monkey embryo model of peri-gastrulation development.** Li *et al.* developed stem cell-derived monkey embryoids that model gastrulation and early organogenesis over a 25-day culture period. Using a two-step induction protocol, 4CL naïve pluripotent stem cells formed blastoids by day 7 in AggreWell plates. Culture in IVC1 medium produced peri-gastruloid-like structures by day 9, followed by suspension culture in IVC2 medium, which supported post-implantation-like development, including bilaminar disc formation (day 13) and PS extension (day 17). Extended culture in enhanced IVC conditions promoted features of late gastrulation, such as neural plate formation, mesoderm and endoderm specification, and embryonic disc organization (days 22–25). These embryoids generated advanced cell types and structures, including neural crest cells, mesodermal derivatives, hematopoietic progenitors, patterned gut, and migrating PGC-like cells.

system provides a valuable and experimentally tractable platform for interrogating poorly understood lineage decisions and morphogenetic events in early primate development. In particular, it enables the generation of sequential developmental atlases and lineage-tracing studies to address questions such as the biphasic development of the yolk sac and the emergence of amniotic cells and EXMCs, underscoring the conceptual and practical importance of modeling development from the blastocyst through gastrulation.

#### COMPETING INTERESTS

The authors declare no competing interests.

#### REFERENCES

1. Yu, L.Q. *et al.* *Nature* **591**, 620–626 (2021).
2. Yu, L.Q. *et al.* *Cell Stem Cell* **30**, 1246–1261.e9 (2023).
3. Karvas, R.M. *et al.* *Cell Stem Cell* **30**, 1148–1165.e7 (2023).

4. Li, J. *et al.* *Cell Stem Cell* **30**, 362–377.e7 (2023).
5. Li, J. *et al.* *Nature* **649**, 161–172 (2026).
6. Bedzhov, I., Leung, C.Y., Bialecka, M. & Zernicka-Goetz, M. *Nat. Protoc.* **9**, 2732–2739 (2014).
7. Liu, L.Z. *et al.* *Cell* **186**, 3776–3792.e16 (2023).
8. Tyser, R.C.V. *et al.* *Nature* **600**, 285–289 (2021).
9. Zhai, J.L. *et al.* *Cell* **186**, 2078–2091.e18 (2023).
10. Gong, Y.D. *et al.* *Cell* **186**, 2092–2110.e23 (2023).

#### ADDITIONAL INFORMATION

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