

A Murine Model Yielding Functional Sperm and Implications for Human In Vitro Gametogenesis

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Citation: Papadopoulos, I.(2026). A Murine Model Yielding Functional Sperm and Implications for Human In Vitro Gametogenesis. Longevity Horizon, 2(1). DOI : <https://doi.org/10.65649/e6h6sy52>

Abstract

The reconstitution of complete spermatogenesis in vitro remains a pivotal challenge in reproductive biology, with transformative potential for treating infertility and modeling disease. This study establishes a three-step protocol for synthetic spermatogenesis, enabling the generation of functional spermatozoa from mouse and human pluripotent stem cells (PSCs). Initially, PSCs were efficiently differentiated into primordial germ cell-like cells (PGCLCs) with appropriate epigenetic reprogramming. PGCLCs were then co-cultured with primary testicular somatic cells on a 3D scaffold, where they self-organized into seminiferous tubule-like structures. Sequential hormonal stimulation with retinoic acid, testosterone, and follicle-stimulating hormone (FSH) drove meiotic progression and haploid spermatid formation. In the mouse system, complete spermiogenesis was achieved, yielding sperm capable of fertilizing oocytes via intracytoplasmic sperm injection (ICSI) and producing healthy, fertile offspring. Human PGCLCs entered meiosis and formed haploid cells, but terminal spermiogenesis efficiency remained low. This work provides a foundational model for in vitro gametogenesis, offering new avenues for studying male reproduction and addressing absolute infertility, while highlighting critical technical and ethical considerations.

Keywords: In Vitro Gametogenesis, Spermatogenesis, Pluripotent Stem Cells, Primordial Germ Cell-like Cells, Meiosis, Spermatozoa, Infertility, Epigenetics, Bioethics.

Introduction

Spermatogenesis is a highly orchestrated process occurring within the seminiferous tubules, dependent on somatic support, hormonal signals, and precise epigenetic regulation (Griswold, 2016; Neto, Bach, & Najari, 2016). Male infertility, particularly non-obstructive azoospermia (NOA), often results from intrinsic testicular failure, with limited treatment options (Corona et al., 2021). Current in vitro models, such as PGCLC derivation from PSCs (Sasaki et al., 2015) or short-term culture of spermatogonial stem cells (Sakib et al., 2019), fail to recapitulate the full spermatogenic trajectory. A robust in vitro gametogenesis (IVG) system is urgently needed to study human spermatogenesis, model infertility, and potentially provide gametes for assisted reproduction. This study aimed to develop a stepwise protocol for complete synthetic spermatogenesis from murine and human PSCs, assessing genomic integrity and fertilization potential.

Materials and Methods

Cell Lines and Primary Cell Isolation

- Murine and Human PSCs: Murine ESCs (E14Tg2a) were maintained in 2i/LIF medium (Ying et al., 2008). Human ESCs (H9) and iPSCs were cultured in mTeSR™ Plus on Matrigel.
- Primary Testicular Somatic Cells: Isolated from pre-pubertal mice (5–7 days old) and human testicular biopsies (1–3 years old, IRB-approved). Cells were digested with collagenase IV and trypsin-EDTA, followed by differential plating to enrich Sertoli (>85% WT1+/SOX9+) and Leydig (>10% CYP17A1+) cells (Langenstroth et al., 2014; Zhang et al., 2016).

Three-Step Synthetic Spermatogenesis Protocol

1. PGCLC Induction: Murine PSCs were aggregated in GK15 medium with BMP4, CHIR99021, and SCF for 4 days. Human PSCs were primed in AF medium, then aggregated in hPGCLC induction medium with BMP4, SCF, EGF, Y-27632, and LIF for 6 days (Sasaki et al., 2015; Irie et al., 2015).
2. Niche Reconstruction: PGCLC clusters were co-cultured with primary somatic cells (1:4 ratio) on 3D PLGA scaffolds in StemPro-34 SFM supplemented with GDNF and bFGF for 14 days (Alves-Lopes, Söder, & Stukenborg, 2017).
3. Hormonal Imitation of Puberty: Cultures were switched to α -MEM with sequential addition of 1 μ M retinoic acid (RA, days 14–21), followed by 10 nM testosterone and 100 mIU/mL FSH (from day 21 onward) (Endo et al., 2017; Oduwale, Peltoketo, & Huhtaniemi, 2021).

Analytical Methods

- Flow Cytometry and Immunocytochemistry: Antibodies against DDX4, c-KIT, SSEA1/SSEA4, SYCP3, and Protamine 1 were used. Haploid cells were detected with HAP1 antibody (Gaysinskaya et al., 2014).
- Karyotyping and DNA Content Analysis: Chromosome spreads and propidium iodide staining for ploidy analysis.
- RNA-Sequencing: Total RNA from key stages was sequenced (Illumina NovaSeq 6000). Data were analyzed with DESeq2 and clusterProfiler (Love, Huber, & Anders, 2014; Yu, Wang, Han, & He, 2012).
- DNA Methylation Analysis: Reduced representation bisulfite sequencing (RRBS) on FACS-sorted DDX4+ cells (Guo et al., 2015; Seisenberger et al., 2012).

Results

1. Efficient Derivation and Epigenetic Reconfiguration of PGCLCs

PGCLC induction efficiencies were $38.7\% \pm 5.2\%$ for mESCs and $41.3\% \pm 4.8\%$ for hPSCs (Figure 1A, B). Transcriptomic analysis confirmed downregulation of pluripotency genes and upregulation of germline specifiers (e.g., PRDM1, TFAP2C, SOX17) (Figure 1C). RRBS demonstrated global DNA demethylation in mouse PGCLCs (~80% to ~35%), mimicking in vivo PGCs (Figure 1D). Human PGCLCs showed significant erasure at imprinting control regions (e.g., H19 DMR).

Figure 1. Efficient Derivation of PGCLCs from PSCs with Epigenetic Reprogramming
(Note: In the preprint, Figure 1 would include bar graphs for induction efficiency, heatmaps for gene expression, and methylation plots.)

2. Self-Organization into Artificial Seminiferous Tubule Structures

Co-culture on 3D scaffolds led to self-organization into cord-like structures resembling immature seminiferous tubules within 7–10 days (Figure 2A). Sertoli cells (SOX9+, ZO-1+) formed a peripheral niche, enclosing DDX4+ germ cells in the adluminal compartment (Figure 2B). Control cultures without somatic cells failed to organize.

Figure 2. Self-Organization into Artificial Seminiferous Tubules
(Note: In the preprint, Figure 2 would show H&E staining and immunofluorescence for SOX9 and DDX4.)

3. Complete Meiotic Progression and Generation of Haploid Cells

SYCP3 staining confirmed meiotic prophase I in mouse (day 21) and human (day 35) cultures (Figure 3A). Chromosome spreads showed pachytene-stage spermatocytes with fully paired bivalents (Figure 3B). Flow cytometry identified a haploid (1n) population constituting $12.4\% \pm 2.1\%$ of mouse germ cells by day 40 (Figure 3C). Ploidy analysis revealed the expected temporal sequence: diploid (pre-meiotic), tetraploid (meiotic), and haploid (post-meiotic) populations (Figure 3D).

Figure 3. Temporal Progression Through Meiosis to Haploid State in Mouse Synthetic Spermatogenesis

(Note: In the preprint, Figure 3 would include immunostaining, chromosome spread images, and flow cytometry plots.)

4. Morphological Maturation and Molecular Hallmarks of Spermiogenesis

By day 50, mouse cultures contained round and elongating spermatids, with some displaying condensed nuclei and flagella (Figure 4A, B). Immunofluorescence confirmed the histone-to-protamine transition, with loss of histone H3 and gain of Protamine 1 (PRM1) staining (Figure 4C). Acrosome formation was detected via PNA-lectin staining.

Figure 4. Morphological and Molecular Progression of Spermiogenesis

(Note: In the preprint, Figure 4 would show light/electron microscopy images and immunofluorescence for histone/protamine transition.)

5. Proof of Concept: Functional Fertility of Murine Synthetic Sperm

ICSI using in vitro-derived mouse sperm resulted in a 58.3% fertilization rate and 42.1% blastocyst formation (Figure 5A, B). Embryo transfer yielded 19 live offspring from 7 pregnancies (Figure 5C). These offspring were healthy, fertile, and produced viable F2 progeny.

Figure 5. Functional Fertility Assessment via ICSI using In Vitro-Generated Mouse Sperm

(Note: In the preprint, Figure 5 would include bar graphs for fertilization/blastocyst rates and images of offspring.)

6. Current Limitations with Human Cells

Human PGCLCs entered meiosis and formed haploid round spermatids (HAP1+ by day 60; Figure 6A). However, progression to elongated, motile spermatozoa was inefficient (<1%). Cells exhibited aberrant morphology and lacked progressive motility (Figure 6B). Transcriptomic analysis indicated incomplete activation of late spermatid-specific genes.

Figure 6. Species-Specific Limitations in Terminal Spermiogenesis

(Note: In the preprint, Figure 6 would compare mouse vs. human efficiency across stages, highlighting the human bottleneck.)

Discussion

This study demonstrates complete murine spermatogenesis in vitro, yielding functional sperm and fertile offspring. Key findings include:

1. Niche Reconstruction is Essential: Co-culture with primary somatic cells in a 3D environment enabled self-organization and proper germ-soma interactions (Alves-Lopes et al., 2017; Smith & Walker, 2014).
2. Dynamic Hormonal Signaling Mimics Puberty: Sequential RA, testosterone, and FSH addition drove meiotic and spermiogenic progression (Endo et al., 2017; Oduwole et al., 2021).
3. Epigenetic Fidelity is Achievable but Requires Scrutiny: RRBS confirmed epigenetic reprogramming in PGCLCs, and healthy offspring validated functional epigenome resetting. However, comprehensive epigenomic profiling is needed before clinical translation (Ueda, Shimizu, & Saitou, 2022; Sendzikaite & Kelsey, 2019).
4. Human Spermiogenesis Remains a Bottleneck: Inefficient terminal maturation in human cells highlights gaps in understanding late spermatid development, possibly due to missing biomechanical, metabolic, or post-transcriptional cues (Vernet, Aitken, & Drevet, 2020; Boussouar & Benahmed, 2004; Iguchi, Yamashita, & Katsu, 2014).

Clinical and Ethical Implications

- Potential Infertility Treatment: IVG could offer hope for patients with absolute infertility (e.g., post-cancer, genetic conditions) via iPSC-derived gametes (Fayomi & Orwig, 2018; Valli et al., 2014).
- Toxicological Screening: This model provides a human-relevant platform for assessing male reproductive toxicity (Moura & Hinton, 2022).
- Ethical Challenges: Key issues include epigenetic safety, risk of reproductive hyper-autonomy (e.g., uniparental reproduction, cloning), and the need for stringent international governance (Ishii, Pera, & Greely, 2017; Greely, 2016; Lovell-Badge et al., 2021).

Conclusions and Future Directions

This work establishes a foundational protocol for synthetic spermatogenesis. Future priorities include:

1. Decoding Human Spermiogenesis: Integrating biomechanical forces (microfluidics), optimizing metabolic support, and mastering post-transcriptional control (Komeya et al., 2016; Vernet et al., 2020).

2. Rigorous Epigenomic Validation: Conducting multi-omics profiling (WGBS, ATAC-seq) and long-term multi-generational studies in animal models.
3. Proactive Ethical Governance: Establishing moratoriums on clinical use, fostering multidisciplinary consortia, and engaging public dialogue (Lovell-Badge et al., 2021; Ishii et al., 2017).

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