Co-transplantation of human ovarian tissue with AMH-producing cells inhibits recruitment of primordial follicles in a short and long term grafts.

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Major Obstacle Undermining Viability and Endocrine Output of Ovarian Tissue Post-Transplantation

• Loss of oocytes during transplantation occurs due to ischemia before revascularization

• Massive global activation of follicles upon transplantation is an obstacle to maintaining long-term endocrine output and salvaging a robust pool


Loss of Oocytes After Transplantation due to Ischemia
An Exogenous Cell Impetus Improves the Survival of Co-Transplanted Ovarian Tissue
Long-Term Viability and Function of Ovarian Tissue Grafts are Improved by ExECs
Massive Global Activation of Follicles upon Transplantation

![Graph showing follicle activation percentages over time.

- Primordial follicles:
  - 2W: Low percentage
  - 3W: Moderate percentage
  - 14W: Low percentage

- Primary follicles:
  - 2W: Low percentage
  - 3W: High percentage
  - 14W: High percentage

- Secondary follicles:
  - 2W: Low percentage
  - 3W: Moderate percentage
  - 14W: High percentage]
AMH Exert a Repressive Input on Activation and/or Growth of Follicles
Anti-Mullerian Hormone AMH

- Mullerian Inhibiting Substance/Factor-MIS/MIF
- A dimeric glycoprotein, member of the transforming growth factor beta superfamily – TGFβ
- In females, not expressed during ovarian sex differentiation
- Produced exclusively by granulosa cells of growing follicles from the late antenatal stage till menopause
- Pool of the primordial follicles decreased faster in AMH-Knockout than WT mice

AMH Dual Effect on Follicular Development

Efficient Transduction of Cultured ECs/MSC

Vectors-AMH

Human Endothelial Cells


AMH Conc. (ng/ml)

- GC
- EC
- AMH EC
Experimental Design

cultured ExECs

control ExECs
AMH ExECs

control ExEC or MSC fibrin clot
AMH ExEC or MSC fibrin clot

2 weeks (short term) 14 weeks (long term)

Harvest

Muscle
Fibrin Clot
Ovarian Graft
Confocal Microscopy

Endothelial Cells

Lectin-Functional Vessels

AMH-Ab

Colocalization
Most Significant Benefit to the Retention of the Quiescent Follicular Pool

**AMH-ECs**

- Ctl ExEC
- AMH ExEC

**AMH-MSCs**

- Ctl MSC
- AMH MSC

Percent of total follicles

Prim 1° 2°

Prim 1° 2°
Highest Percentage of Primordial Follicles AMH Producing ECs
A Significant Retention of Primordial Follicles was Noted Also at 14 Weeks

![Graph showing significant retention of follicles at 14 weeks.](image-url)

- Primordial: P=0.01
- Primary: P=0.05
- Secondary:
Conclusions

• Comparison of different treatments AMH-ExECs revealed the most significant benefit to the retention of the quiescent follicular pool in short and long term grafts.

• These findings present a cell-based strategy that combines accelerated perfusion with a direct paracrine delivery of a bioactive payload to transplanted ovarian tissue.

• Improved tissue viability and enforced retention of quiescent follicles can be combined to increase productivity and longevity of ovarian tissue grafts.
Future Directions

• Utilizing engineered ECs expressing secreted factors to interrogate their impact on human ovarian physiology, using our unique In vivo model
• Using a non-cellular method of delivering secreted factors for future clinical use
• Testing AMH as a chemo protectant agent
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