CO-TRANSPLANTATION OF HUMAN OVARIAN TISSUE WITH IGF-1-PRODUCING ENDOTHELIAL CELLS IMPROVES SURVIVAL OF EARLY STAGE FOLLICLES AND IS ASSOCIATED WITH ACCELERATED FOLLICULAR GROWTH IN VIVO

LIMOR MAN M.D, M.Med.Sc
ASSISTANT PROFESSOR OF RESEARCH IN OBSTETRICS AND GYNECOLOGY
RONALD O. PERELMAN AND CLAUDIA COHEN CENTER FOR REPRODUCTIVE MEDICINE
WEILL CORNELL MEDICINE, NYC, NY, USA
IMPROVING POST-TRANSPLANTATION SURVIVAL OF HUMAN OVARIAN TISSUE

- Major loss of oocytes during transplantation occurs due to ischemia before revascularization
- Massive global activation of follicles upon transplantation
MINIMIZE ISCHEMIC INJURY TO THE TRANSPLANT BY REDUCING THE LATENCY PERIOD BEFORE NEOVASCULARIZATION TO IMPROVE SURVIVAL.

- **Graft ischemia in a 5 to 7 day window post-transplant remains a significant obstacle to maintaining tissue viability.**

- **Minimize ischemic injury to the transplant by reducing the latency period before neovascularization to improve survival.**
TRANSPLANTATION CAUSE GLOBAL ACTIVATION

• AFTER GRAFTING OF SHEEP CORTICAL TISSUE, FOLLICULAR ACTIVATION WAS OBSERVED AFTER FIRST DAYS

• MASSIVE IN VIVO FOLLICULAR ACTIVATION AFTER TRANSPLANTATION OF GRAFTED FRAGMENTS OF HUMAN OVARY AND ISOLATED FOLLICLES
AN EXOGENOUS CELL IMPETUS IMPROVES THE SURVIVAL OF CO-TRANSPLANTED OVARIAN TISSUE

- Patients undergoing ovarian tissue cryopreservation
- Thawed ovarian cortical strips
- Cultured ExECs
- ExEC-imbedded plasma clot
- Control plasma clot
- Oophorectomized NSG mice

2 weeks (short term) 14-22 weeks (long term)

Harvest

Graph showing % Total Follicles:
- No EC: 20
- ExEC: 80

p = 0.03
FOLLICULAR DEVELOPMENT

- Primordial
- Primary
- Preantral
- Antral

AMH
FSH

Metabolic demands
Most significant benefit to the retention of the quiescent follicular pool by AMH-ECS and AMH-MSC.
FROM INITIAL RECRUITMENT TO THE GONADOTROPIN DEPENDENT STAGE

Controlled Ovarian Hyperstimulation (COH)

In vitro activation protocols

-Gougeon et al. Human Reproduction 1986

INSULIN LIKE GROWTH FACTOR 1 (IGF-1)

• IGF-1 is expressed in most tissues, a mediator of the anabolic and mitogenic activity of GH

• IGF-1 receptor (IGF-1R), a tyrosine kinase receptor, mediates most of the GH-like actions via activation of PI3K/Akt pathway

• Akt pathway in the ovarian tissue has been associated with increased recruitment of dormant primordial follicles, accelerated follicular growth and “burn out” of follicles


• In vitro activation protocols: disruption of Hippo signaling by fragmenting ovaries followed by Akt stimulator treatment and autografting

ROBUST ENRICHMENT OF IGF-1 IN CULTURE

Vectors-IGF-1

Human Endothelial Cells

![Diagram showing the enrichment of IGF-1 in culture with vectors and human endothelial cells.]

![Bar graph showing the concentration of IGF-1 in ECs and IGF-ECs with a p-value of <0.001.]

P<0.001
EXPERIMENTAL DESIGN

CONTROL GROUP

- Human Ovarian Tissue
- Fibrin clot
- n=8

STUDY GROUP

- Human Ovarian Tissue
- Fibrin clot
- n=6

END POINT 3 WEEKS
CO-TRANSPLANTATION WITH IGFR-1-ECS SHIFTS FOLLICLE TOWARDS GROWTH

\[
P_{\text{Primordial}} = 0.41 \\
P_{\text{Primary}} = 0.03 \\
P_{\text{Secondary}} = 0.05
\]
IGF-1 SUPPORTS GROWTH OF FOLLICLES INTO A MORE ADVANCED STAGE
CELL-BASED STRATEGY
MOLECULAR STIMULATION CYCLE

IGF-1
Co-
Transplantation

In Vitro
Activation
Protocols

-Gougeon et al. Human Reproduction 1986
ACKNOWLEDGMENTS

Daylon James
Laura Park
Jovana Lekovich
Glenn Schattman
Zev Rosenwaks
Nikica Zaninovic
Richard Bodine
Michael Ginsberg