Simulated Physiological Oocyte Maturation (SPOM) and Related IVM Systems

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In Vitro Maturation (IVM)
(No or minimal ovarian stimulation)

24 to 40 hours in vitro

Conventional IVF
Ovarian hyperstimulation (FSH)

In Vitro Maturation (IVM)
(No or minimal ovarian stimulation)

Small antral
Preovulatory

IVF or ICSI

Live Birth Rate/OPU

Thompson JG & Gilchrist RB (2013) In: Biology and Pathology of the Oocyte (Cambridge University Press)

The standard definition of IVM

- Oocytes are matured *in vitro*
  - from the GV-stage (intact cumulus-oocyte complexes)
  - patient FSH-priming is compatible

Edwards RG (1962) *Nature*
Edwards RG (1965) *Nature*
Bringing IVM to the ART clinic: core biological challenges

1) Oocytes from small antral follicles are not fully developmentally competent

2) Maturation in vitro can occur spontaneously without appropriate somatic/maternal control

*In Vitro Maturation (IVM)*
(No or minimal ovarian stimulation)

Small antral

24 to 40 hours in vitro

IVF or ICSI
COCs in small antral follicles are still developing (oocyte capacitation)
Oocytes acquire developmental competence from coordinated endocrine and paracrine signals.

Small Antral Follicle (EGF-p unresponsive)

- BMP15/GDF9

- EGFR signalling

- Developmental competence

Large Antral Follicle (EGF-p responsive)

- BMP15/GDF9

- EGFR signalling

- Energy

- Metabolite supply

- Developmental competence


Bringing IVM to the ART clinic: core biological challenges

1) Oocytes from small antral follicles are not fully developmentally competent

2) Maturation in vitro can occur spontaneously without appropriate somatic/maternal control

In Vitro Maturation (IVM)
(No or minimal ovarian stimulation)
Oocyte in vitro maturation (IVM)

Standard Spontaneous IVM

- FSH-priming
- complex medium, protein, FSH, EGFp
- LH, E2, cysteamine

IVF/ICSI
Basic Principals: oocyte “capacitation” in vitro - Extended culture of meiotically competent COC

- Isolation from follicle
- Prolonged gap-junction communication

**Meiotic inhibitors**
- cAMP analogues, PDEi
- cGMP, CNP

**Nutrients & metabolic regulators**
- Metabolites, IGFs, etc.

**CC regulators**
- FSH, EGFp, E2, GDF9, BMP15, cumulin
Oocyte maturation: meiotic arrest

Gilchrist RB et al. (2016) Reprod. 152:143-157
Oocyte maturation: meiotic resumption

cAMP: in vivo and in various IVM systems

- Induced IVM (high cAMP, eg SPOM)
- Biphasic IVM
- Induced IVM (moderate cAMP)
- Standard IVM

Gilchrist RB et al. (2016) Reprod. 152:143-157
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cAMP management during IVM improves outcomes

**Conventional IVF**

Ovarian Hyperstimulation → IVF/ET

Fetal Yield

22%

**Standard IVM**

IVM → IVF/ET

8%

**Induced IVM (SPOM)**

Pre-IVM → IVM → IVF/ET

26%

- preservation of GJC
- ↑ glycolysis, ↑ oxidative metabolism
- ↑ GSH → ↓ ROS
- activation of EGF-p cascade
- ordered cessation of RNA synthesis
- delayed GVBD
- ↓ meiotic asynchrony

↑ Embryo Development

↑ Fetal Viability


cAMP pre-IVM preserves the benefits of CC-oocyte GJC

Li HJ et al. (2016) Hum. Reprod. 31:810-821
cAMP pre-IVM leads to decreased intra-oocyte ATP.
cAMP pre-IVM leads to decreased intra-oocyte ATP

Richani D et al. (unpublished)
cAMP pre-IVM upregulates in *intra-oocyte* AMPK activity

Richani D *et al.* (unpublished)
Effect of cAMP pre-IVM on COC ATP and AMPK activity

Two-way ANOVA
Time: P=0.000
Treatment: P=0.022
Interaction: N.S.

- No pre-IVM
- With pre-IVM

ATP

2h of IVM
16h of IVM

Phosphorylated AMPK

Richani D et al. (unpublished)
Changes in energy metabolism associated with increased oocyte developmental competence

Oocyte

Increased energy demand
(↓ ATP ↑ ADP ↓ ATP:ADP)

↓

↑ AMPK

↓

Restore energy homeostasis

FSK/IBMX pre-IVM

Cumulus

Increased ATP

↔ AMPK

Increased oocyte competence

Richani D et al. (unpublished)
Challenges in translating scientific advances to the human IVM clinic

- Biological challenges (topic of presentation)

- Human oocytes are scarce and precious

- We have poor measures of oocyte quality

  → :: need to produce human embryos for research ..!!

- IVF status quo works – resistance from the ART sector
**VUB Brussels: Oocyte donors and experimental design**

- **Patient work-up:** OCP, 3x days hMG (days 5-7), no hCG-priming, OPU 42h after last hMG
- **Follicle size:** typically ~5 mm, <4 – 10 mm
Effect of pro-cumulin in human IVM (retrospective)

**Control:**  $n = 275$ COC

$n = 19$ patients and volunteers

**Treatment:**  $n = 246$ COC

$n = 21$ patients and volunteers

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**Pre-IVM:**  
FSK+IBMX

**IVM:**  
FSH + pro-cumulin

**ICSI**

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**Control:**  

$n = 275$ COC

$COC = 19$ patients and volunteers

**Treatment:**  

$n = 246$ COC

$COC = 21$ patients and volunteers

---

**Fertilisation rate (%)**

**Control**

**Treatment**

---

**Day 3 GQ Embryo / MII (%)**

**Control**

**Treatment**

---

**Blastocysts / MII (%)**

**Control**

**Treatment**

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**Grade 1 D3 / D3 embryos (%)**

**Control**

**Treatment**

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*P<0.05

P=0.10

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Gilchrist RB *et al* (unpublished, in collaboration with VUB and Adelaide)
Human oocyte “capacitation” in vitro using CNP (VUB Brussels)

Sanchez F et al. (2017) Hum. Reprod. 32:2056-68
How to make a good quality oocyte for ART?

- FSH + hCG
- FSH
- cAMP or CNP
- GDF9/BMP15/cumulin
- EGF-peptides or FSH

Diagram showing the process of making a good quality oocyte for ART.
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