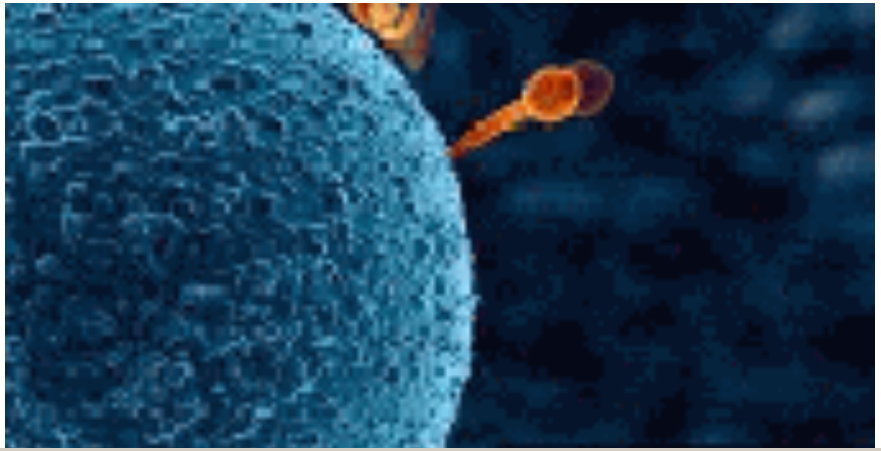
Mitochondria transfer for oocyte rejuvenation

S.M. Chuva de Sousa Lopes

Leiden University Medical Center
Department of Anatomy and Embryology
Leiden, The Netherlands

Lopes@Lumc.nl



I have nothing to disclose

What is this?

Rejuvenation (aging)

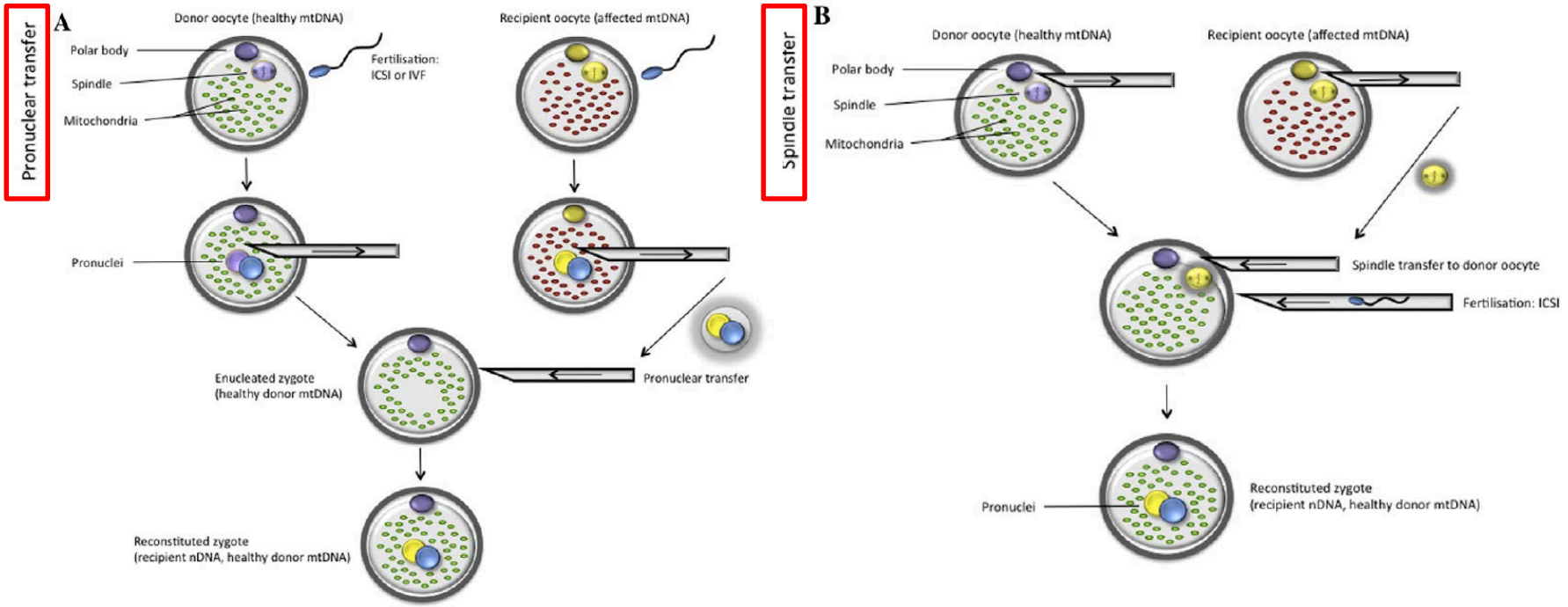
From Wikipedia, the free encyclopedia

Rejuvenation is a medical discipline focused on the practical reversal of the aging process.[1]

Rejuvenation is distinct from life extension. Life extension strategies often study the causes of aging and try to oppose those causes in order to slow aging. Rejuvenation is the *reversal* of aging and thus requires a different strategy, namely repair of the damage that is associated with aging or replacement of damaged tissue with new tissue. Rejuvenation can be a means of life extension, but most life extension strategies do not involve rejuvenation.

Oocyte rejuvenation

- Distinct from Mitochondrial Replacement Therapy (**MRT**) (three-parent babies)
- Aim is not **reverse aging**, **replace defective mitochondria**

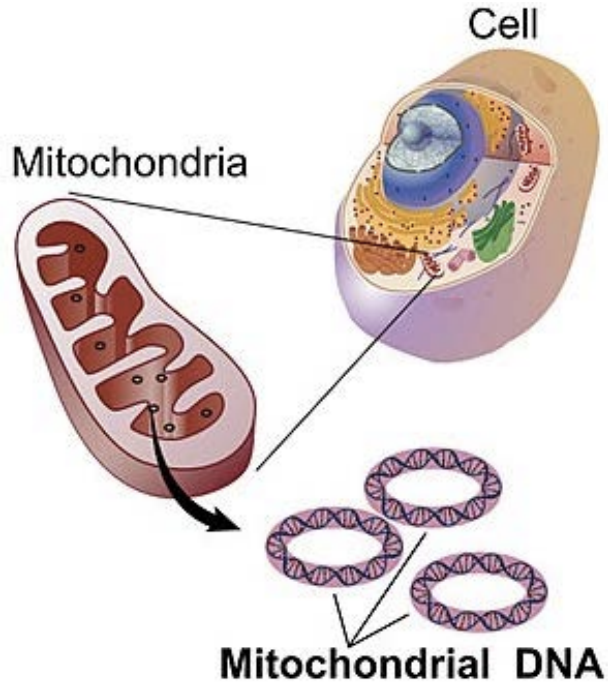


Reznichenko, Huyser, Pepper, Appl Trans genomics, 2016

Defective mitochondria?

Mitochondria:

- Cytoplasmic organelle (numerous)
- Function in energy production (ATP)
- Circular DNA, 37 genes, no histones, numerous
- Non-mendelian genetics, mutation-sensitive
- Maternal origin (oocyte cytoplasm); paternal degraded



Change chromosome: MT Go

Chromosome Statistics

Length (bps)	16,569
Coding genes	13
Non coding genes	24
Small non coding genes	24
Short Variants	2,831

Mitochondria *versus* Y chromosome

Change chromosome: MT Go

Chromosome Statistics

Length (bps)	16,569
Coding genes	13
Non coding genes	24
Small non coding genes	24
Short Variants	2,831

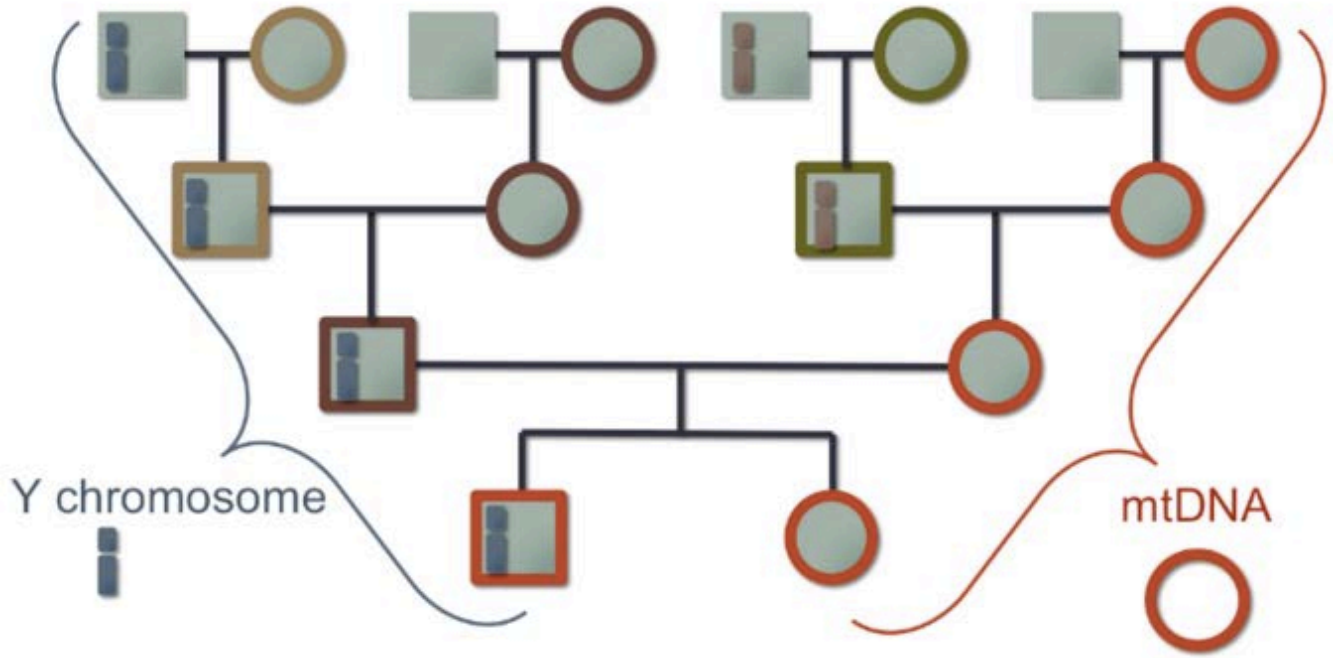
Change chromosome: Y Go

male

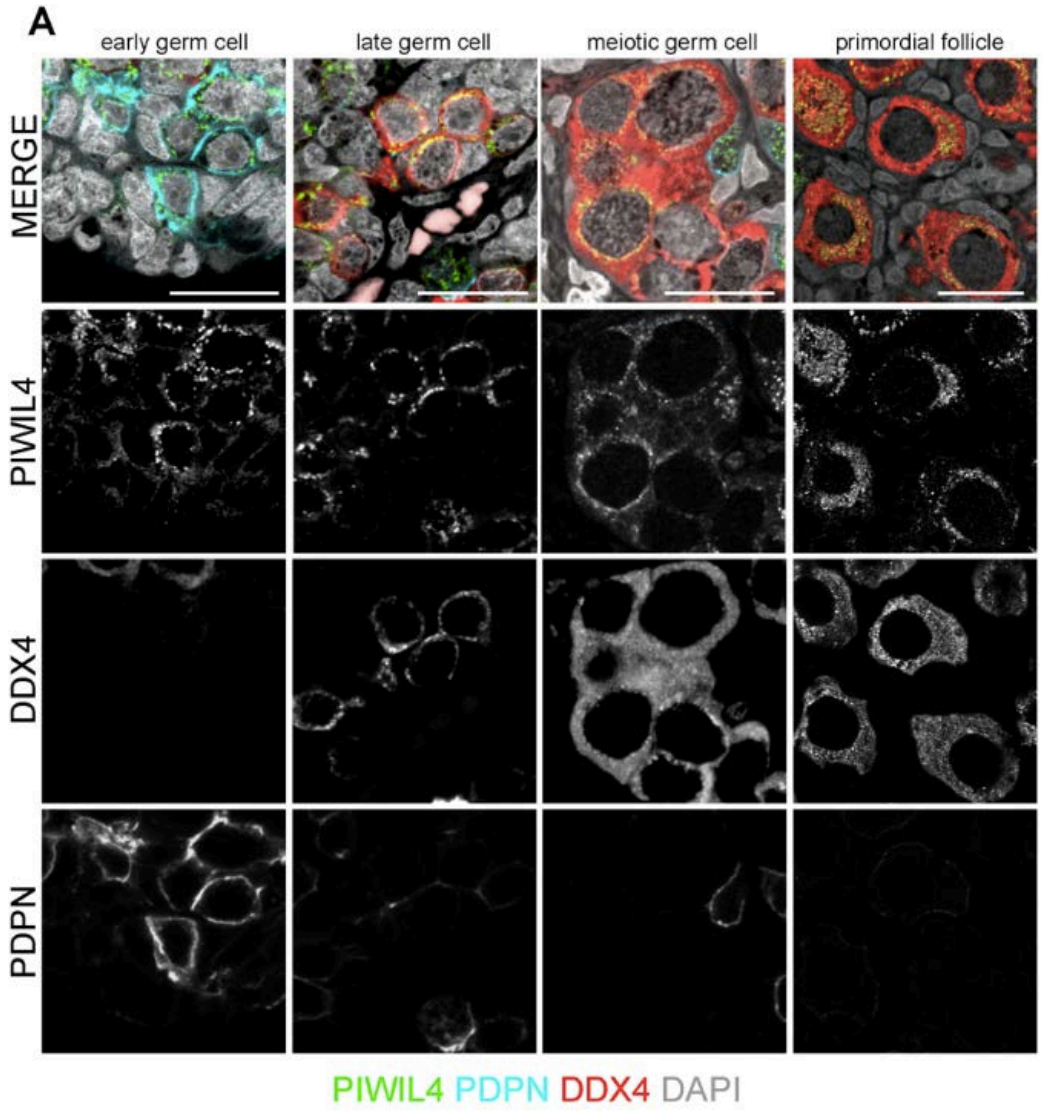
Chromosome Statistics

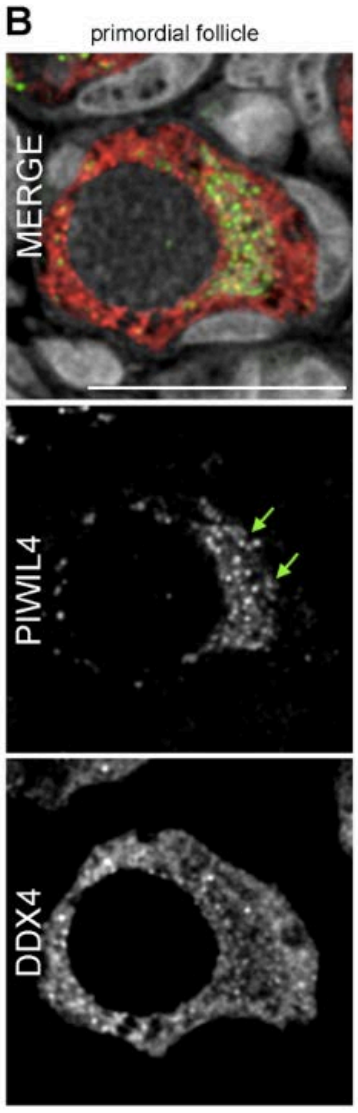
Length (bps)	57,227,415
Coding genes	63
Non coding genes	108
Small non coding genes	30
Long non coding genes	70 (incl. 2 readthrough)
Misc non coding genes	8
Pseudogenes	391
Short Variants	370,876

Mitochondria *versus* Y chromosome

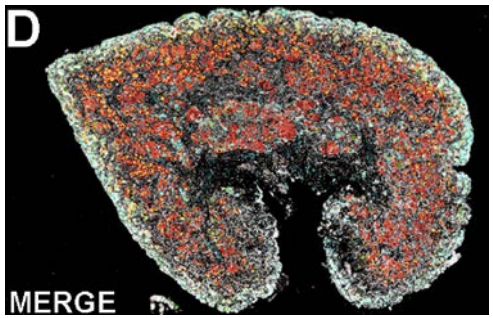


Mitochondria during human oogenesis



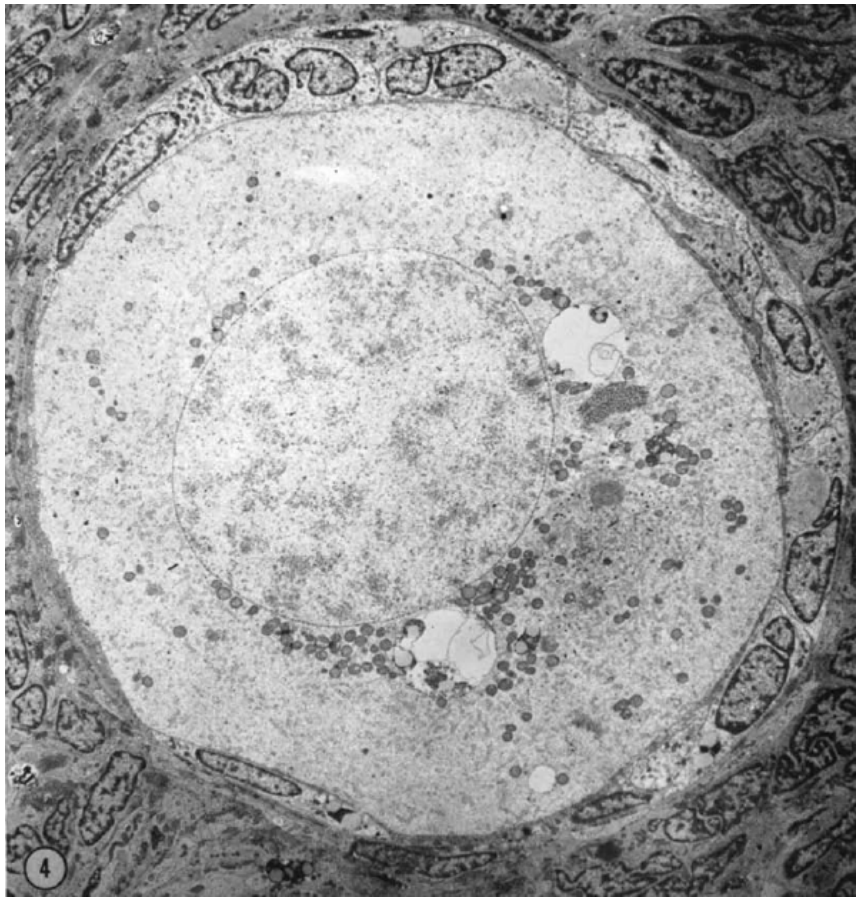


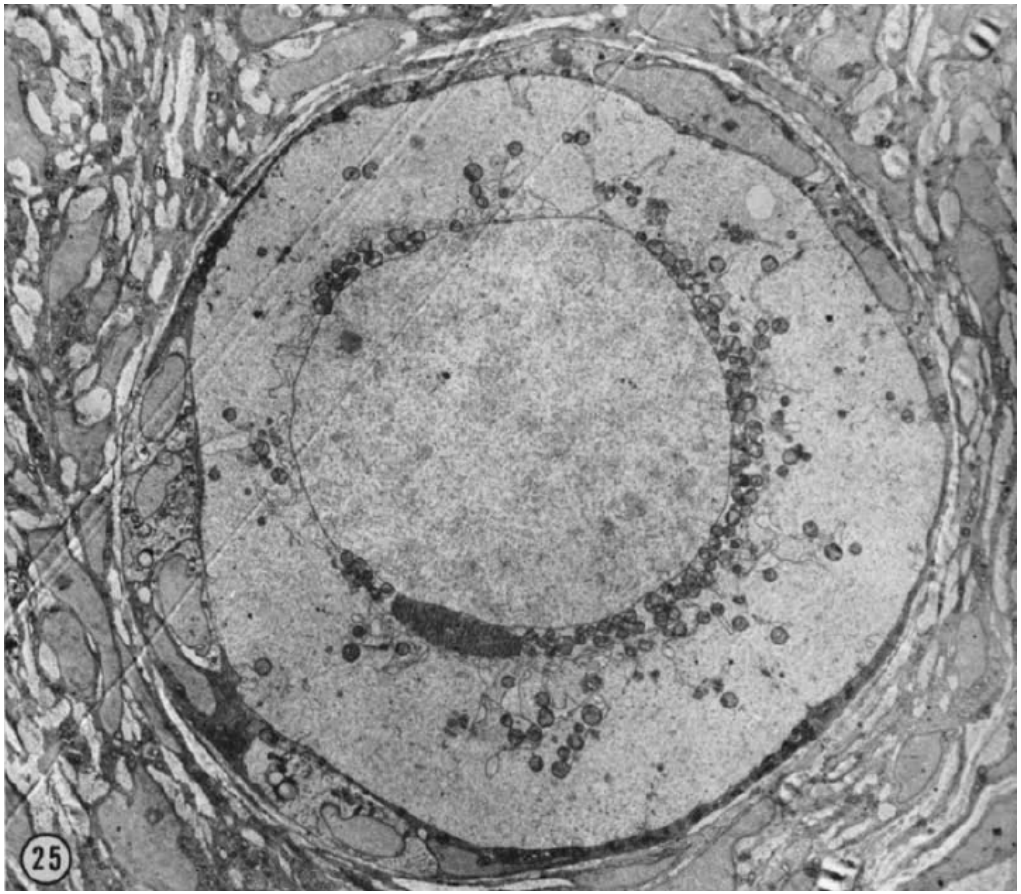
W22 ovary



Gomes Fernandes et al, HR, 2018

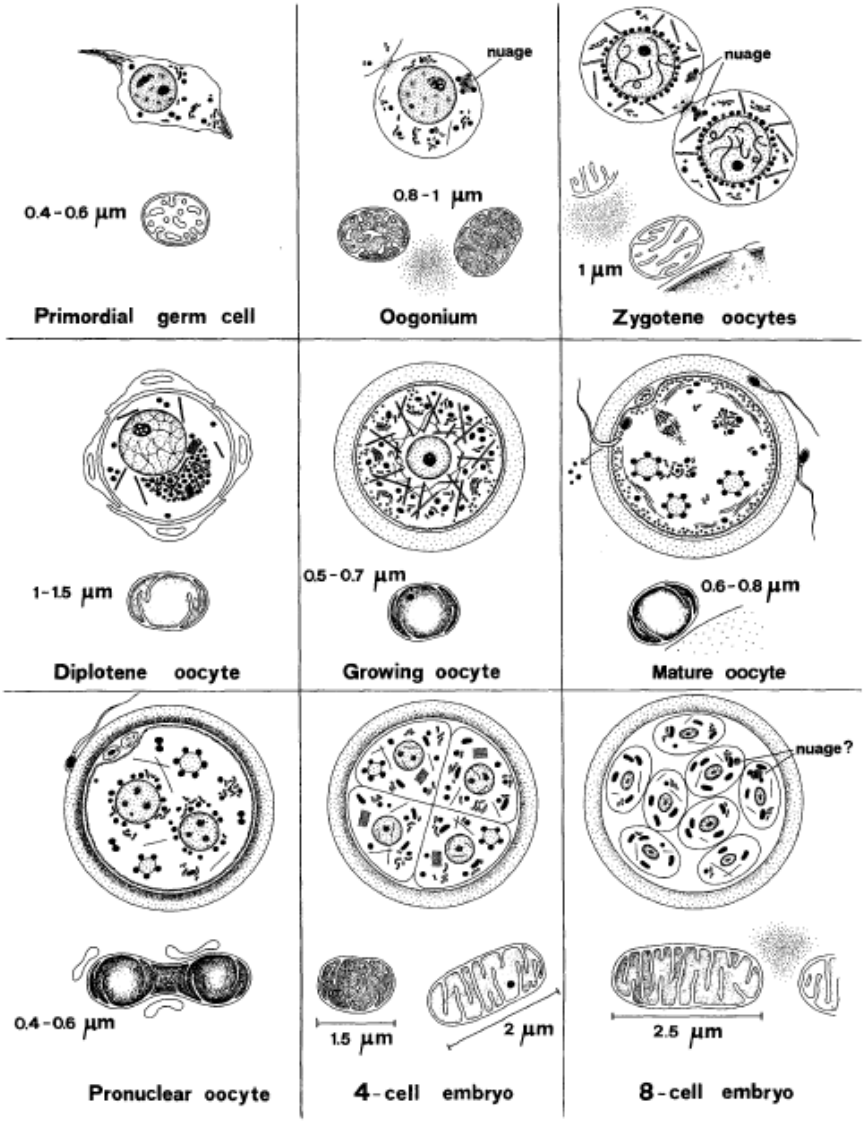
Mitochondria during human oogenesis

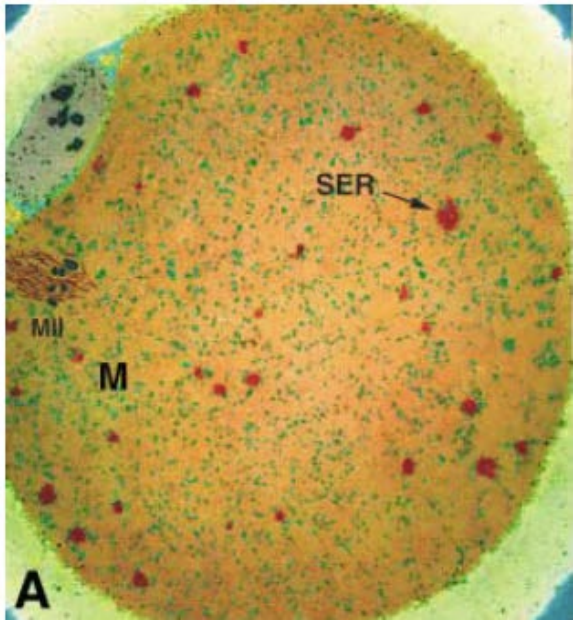




Hertig and Adams, JCB, 1967

Mitochondria during human oogenesis



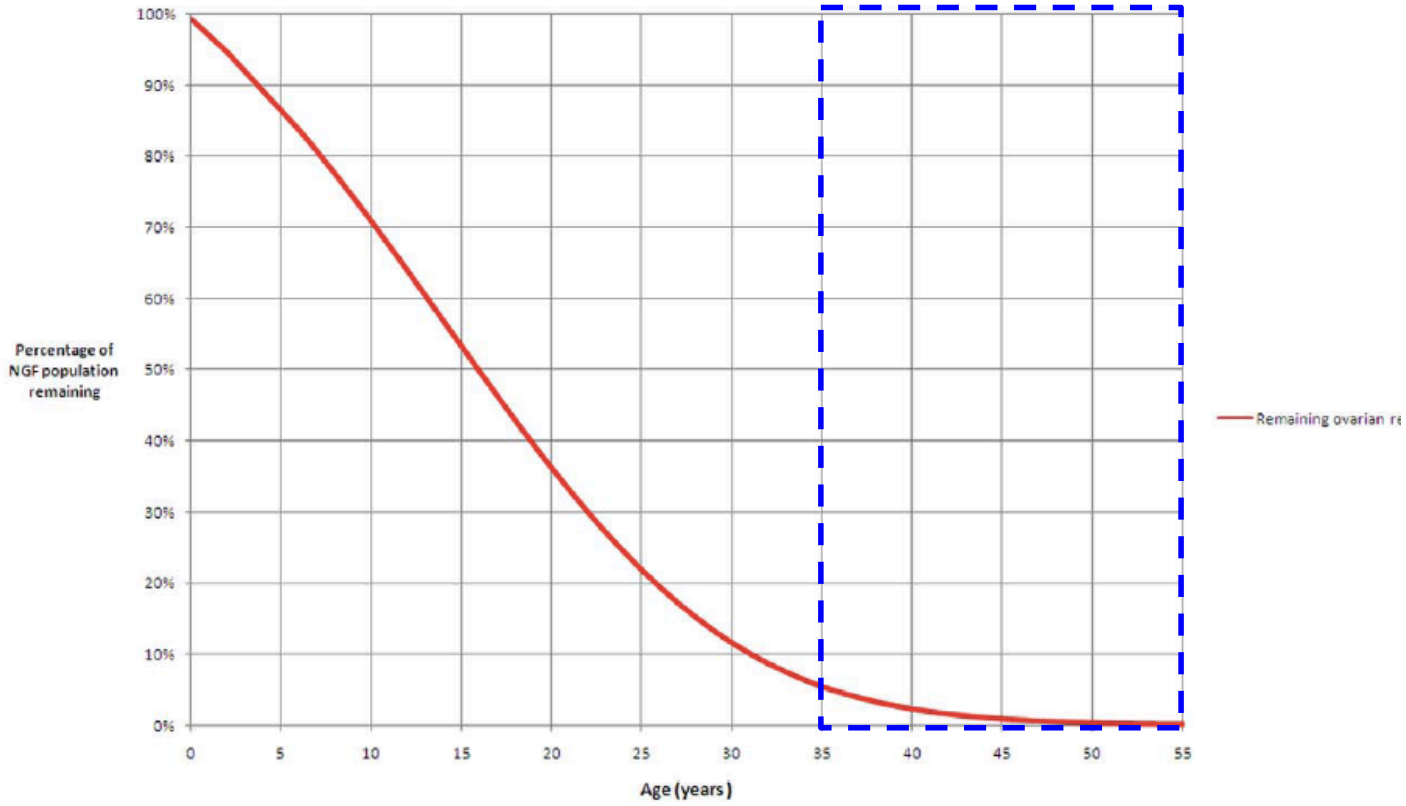


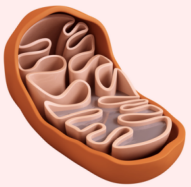
Motta et al, HR, 2000
Blerkom, reproduction, 2004

Oocyte rejuvenation: why do we need it?

Problem:

- Decline in number oocytes with age
- Decline in quality of oocytes (low potential being fertilized, etc)





mitochondrial dysfunction

Wallace and Kelsey, Plos One 2010
Kristensen et al., HR, 2017

Oocyte rejuvenation: historical context

90s-00s:

- non-autologous cytoplasmic transfer to oocytes
- synchronous and asynchronous
- ~3% volume, young donors, ~50 live births
- heteroplasmy (3 parents, different from MRT)
- suspended US in 2002

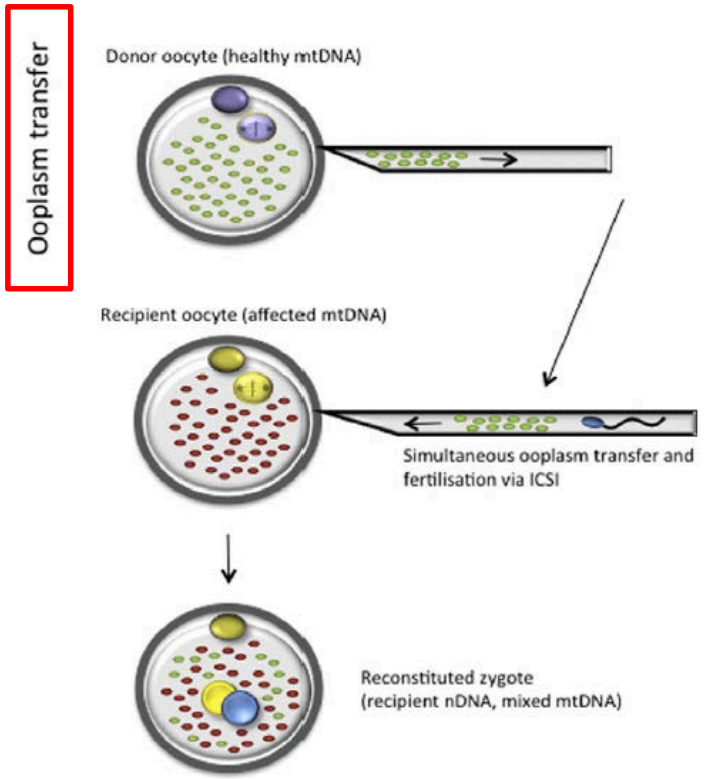


Table I. Cytoplasmic transfer cases performed

Type of cytoplasm transferred to recipient oocytes	No. of procedures	Pregnancies achieved	Offspring delivered	Reference(s)
Synchronized fresh oocytes by electrofusion	3	0	0	Cohen *et al.* (1998)
Synchronized fresh oocytes by injection (USA)	30	13[a]	16	Cohen *et al.* (1997, 1998); Brenner *et al.* (2000); Barritt *et al.* (2000, 2001)
Synchronized fresh oocytes by injection (Israel)	15	5	6	J.Levron *et al.* (pers. commun.)
Synchronized frozen oocytes by injection	4	1	2	Lanzendorf *et al.* (1999)
Asynchronous 3-PN zygotes by injection	9	4	5	Huang *et al.* (1999)

[a]One pregnancy resulted in a miscarriage.

Barritt and Cohen et al, HRU 2001
Reznichenko, Huyser, Pepper, Appl Trans genomics, 2016

Oocyte rejuvenation: "oogonial stem cells"

2012: population of adult oocyte-producing stem cells in human ovaries

ARTICLES

nature medicine

Oocyte formation by mitotically active germ cells purified from ovaries of reproductive-age women

Yvonne A R White[1,2,4], Dori C Woods[1,2,4], Yasushi Takai[3], Osamu Ishihara[3], Hiroyuki Seki[3] & Jonathan L Tilly[1,2]

- population stem cells in the adult ovaries
- FACS-sorted DDX4 (surface marker)
- proliferate in culture
- differentiate to oocytes

White and Tilly et al, Nature Medicine 2012

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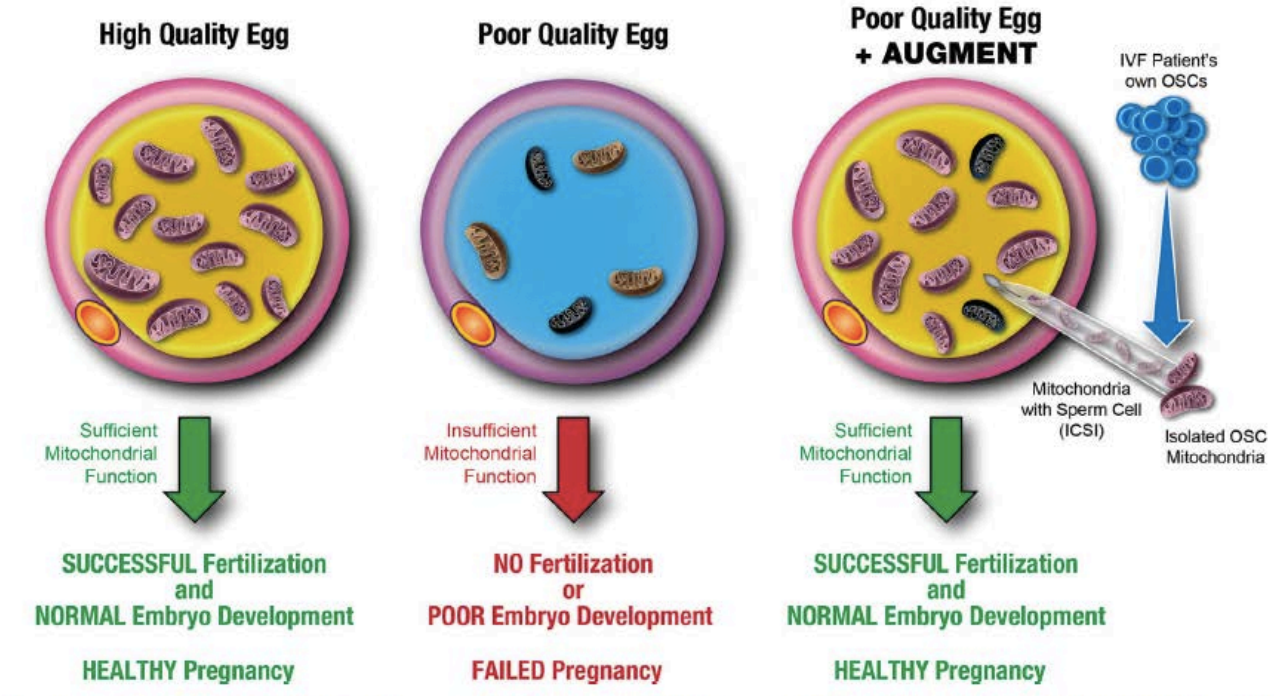
- population stem cells in the adult ovaries
- FACS-sorted DDX4 (surface marker)
- proliferate in culture – acquire DDX4
- differentiate to oocytes

White and Tilly et al, Nature Medicine 2012

Oocyte rejuvenation: AUGMENT

2015:
- Autologous Germline Mitochondrial Energy Transfer (AUGMENT)
- patent 2014 (8,642,329 and 8,647,869)
- ~12 live births



- autologous
- uses OSCs
- purified mitochondria transfer

Woods and Tilly, Semin Reprod Med, 2015
Kristensen et al., HR, 2017

Oocyte rejuvenation: in the clinic

OvaScience techniques. The future of IVF?

10/26/2016

0 Comments

Authors: **Shuyana Deba Rementeria, Javier Del Río Riego** and **Sara Sanz Juste**

Sources: OvaScience, http://www.ovascience.com/

Status: Comercial

Serving patients in a total of **six countries**: Canada, Spain, Japan, Panama, Turkey and United Arab Emirates.

https://embryologistmedia.weebly.com/news/archives/10-2016

Oocyte rejuvenation: OvaScience

Rejuvenating the Chance of Motherhood?

MIT Technology Review

An audacious startup thinks it can give 40-ish women a better shot at having children. Should desperate would-be parents believe it?

by Karen Weintraub | December 9, 2016

Zain Rajani enjoys his first birthday cake in April.

In a pristine lab overlooking a busy highway in the Boston suburbs, OvaScience researchers identify and count what they believe are egg-precursor cells. These constitute, OvaScience says, about 6 percent of the cells on the surface of the ovarian cortex. In the Augment procedure, an IVF surgeon laparoscopically removes a section of this layer about half the size of a dime. The tissue is shipped to an OvaScience lab, where the mitochondria are extracted and shipped back to the fertility clinic. Just before fertilization, the mitochondria are inserted into the egg alongside the sperm. Then IVF proceeds as usual.

https://www.technologyreview.com/s/603065/rejuvenating-the-chance-of-motherhood/

Oocyte rejuvenation: OvaScience

MIT Technology Review

Rewriting Life

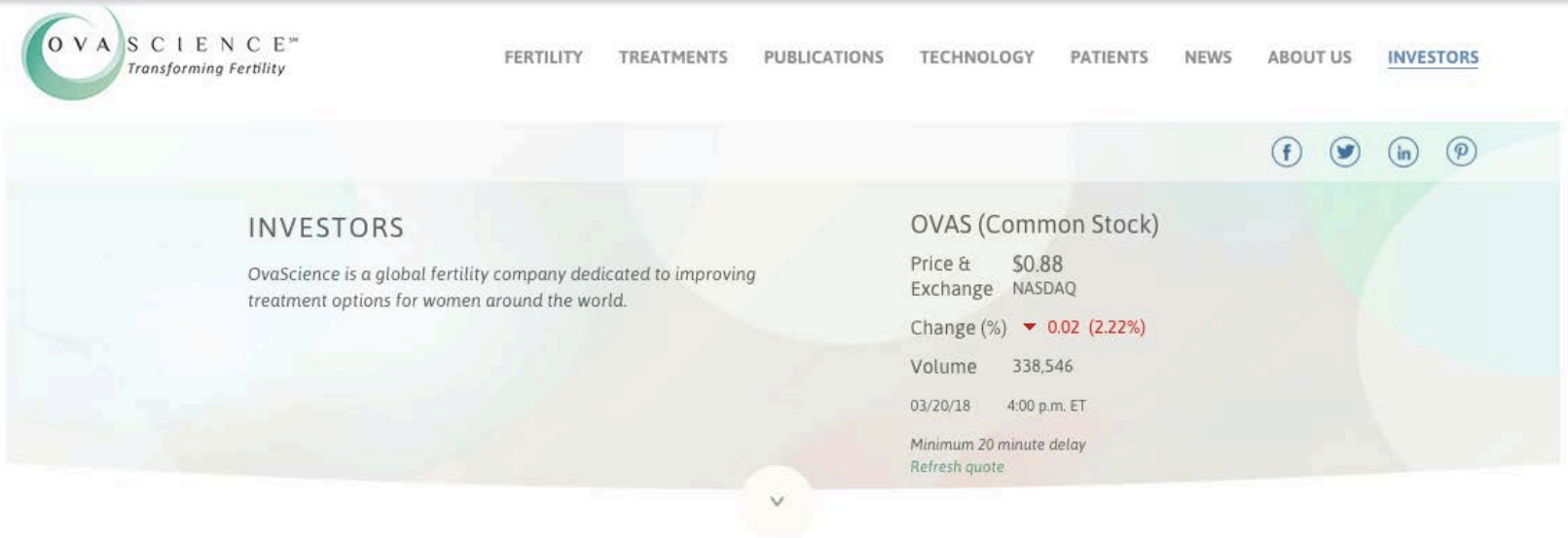
Turmoil at Troubled Fertility Company Ovascience

A pioneering biotech scales back plans to rejuvenate women's eggs for IVF.

by Karen Weintraub December 29, 2016

https://www.technologyreview.com/s/603274/turmoil-at-troubled-fertility-company-ovascience/

Oocyte rejuvenation: OvaScience today

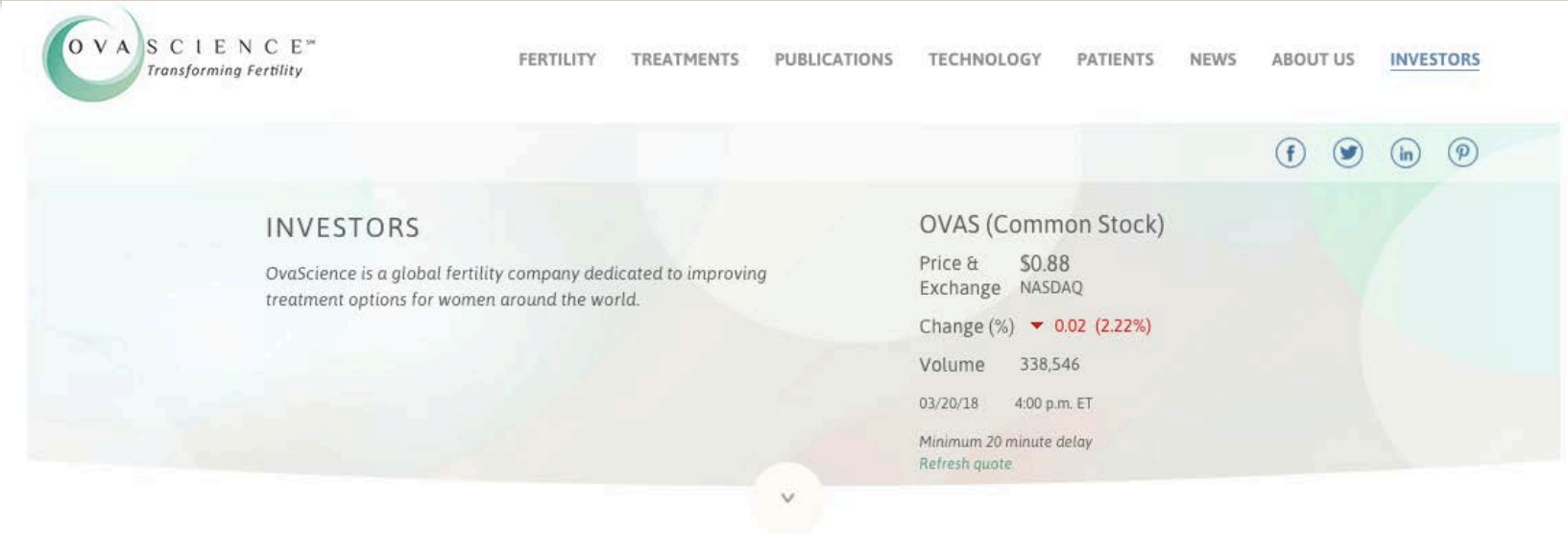


OvaPrime℠ Treatment: OvaPrime is a potential fertility treatment that could help restore a woman's egg production. With OvaPrime, a woman's own egg precursor (EggPC℠) cells are isolated from a niche within her ovary where they are quiescent and repositioned such that they receive the appropriate signals to mature *in vivo* into healthy, fertilizable eggs.

OvaTure℠ Treatment: OvaTure is a potential fertility treatment that eliminates the need for hormone stimulation. With OvaTure, a woman's own EggPC cells are isolated from her ovary and matured *in vitro* into healthy, fertilizable eggs.

http://phx.corporate-ir.net/phoenix.zhtml?c=251343&p=RssLanding&cat=news&id=2338353

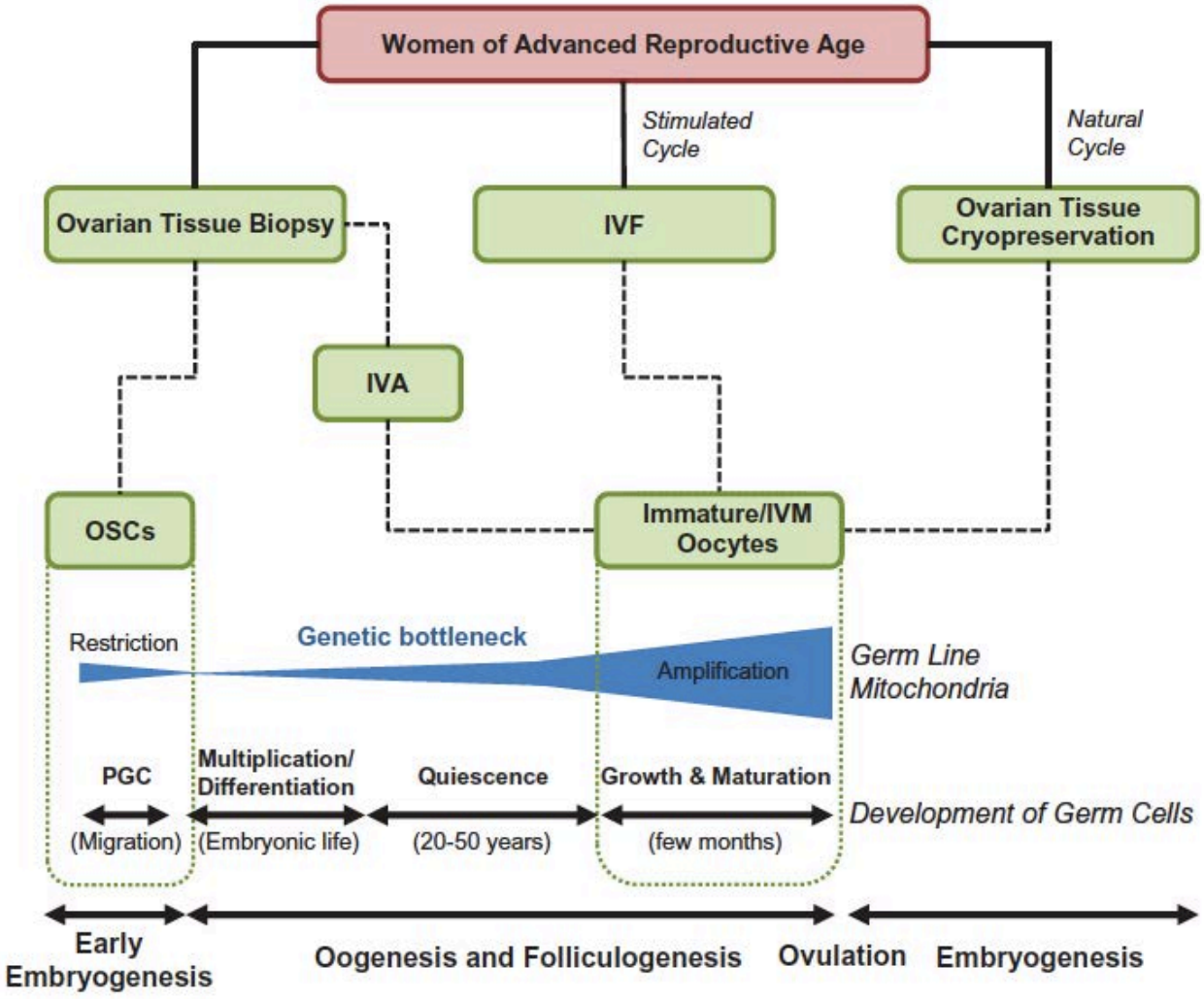
Oocyte rejuvenation: OvaScience today

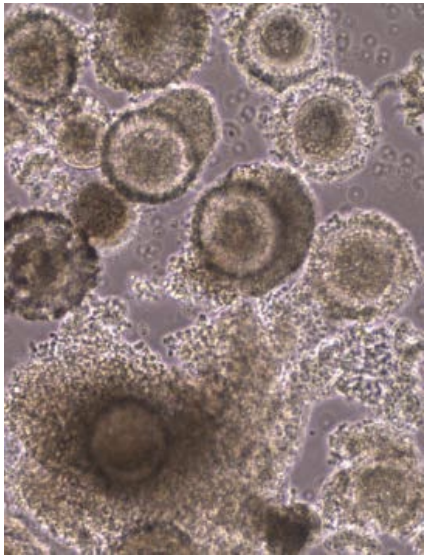


AUGMENT℠ Treatment: AUGMENT is a fertility treatment designed to improve fertilization and pregnancy rates. With AUGMENT, mitochondria from a woman's own EggPC cells are isolated and injected into the egg during *in vitro* fertilization (IVF). AUGMENT is currently offered to patients through an exclusive license to IVF Japan Group in Japan. OvaScience retains worldwide commercialization rights for AUGMENT outside of Japan and continues to work with the U.S. Food and Drug Administration under its available procedures to determine the most appropriate regulatory pathway for potential entry into the United States.

http://phx.corporate-ir.net/phoenix.zhtml?c=251343&p=RssLanding&cat=news&id=2338353

Oocyte rejuvenation: alternatives?





Kristensen et al., HR, 2017

Conclusions

- Autologous mitochondria transfer
- Using OSCs (?) or (immature) oocytes
- Safety concerns and RCTs – ESHRE SIG Stem Cells
- Other factors that could play a role?

Stem cells

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Unresolved issues:

- Is having more mitochondria good or bad?
- Are mitochondria equal (after bottleneck)?
- Place of injection (connection to other organelles in the cell)?

Thank you!

LEIDS UNIVERSITAIR MEDISCH CENTRUM

Dept. Anatomy and Embryology, LUMC
Susana Chuva de Sousa Lopes
Maaike Nieveen
Monika Bialecka
Vanessa Torrens-Juaneda
Xueying Fan
Ioannis Moustakas

Dept. Gynaecology, LUMC
Lucette van der Westelaken
Leoni Louwe

Dept. Reproductive Medicine, UZ Gent
Petra De Sutter
Susana Chuva de Sousa Lopes
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