Fertoprotective Therapeutics:
What is on the horizon for patients?

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No commercial relationships to disclose

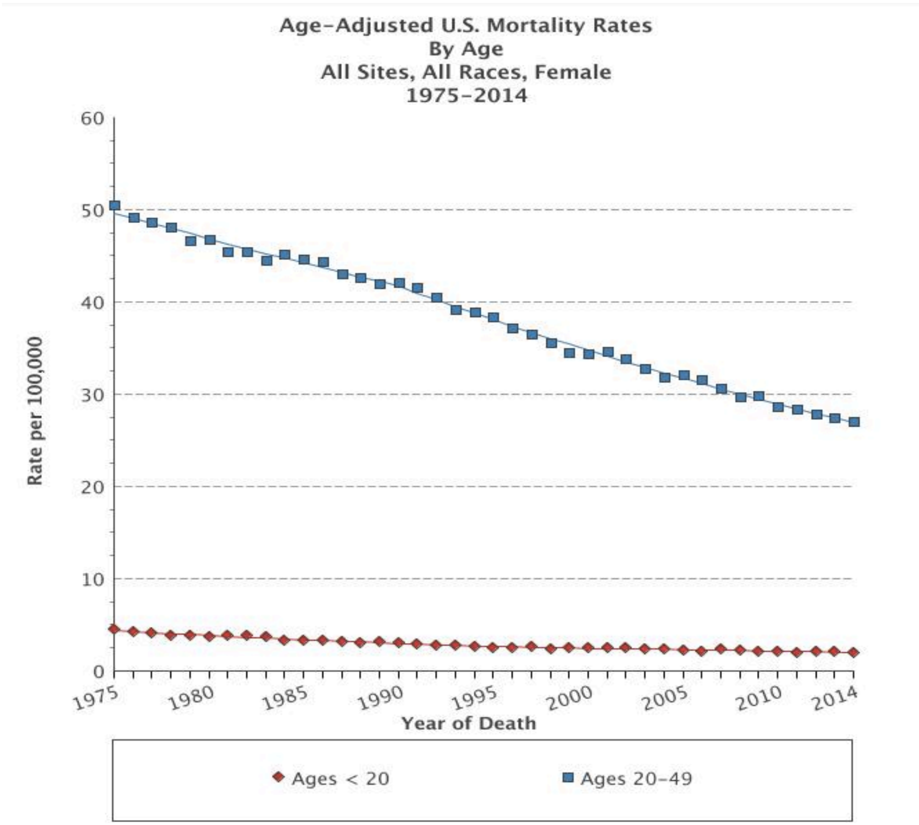
Funding sources

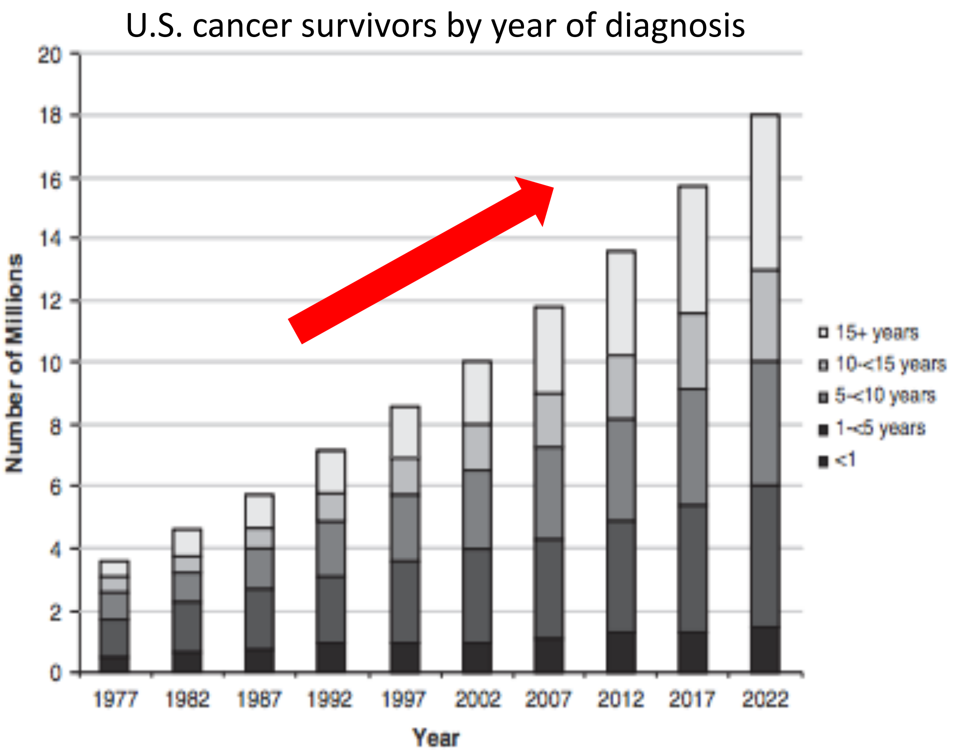
- American Society for Reproductive Medicine
- Foundation for Women's Wellness

Goals and objectives

1. Review mechanisms of iatrogenic ovarian injury
2. Discuss limitations of current approaches to fertility preservation
3. Examine experimental approaches on the horizon for pharmacologic fertoprotection

Cancer survivorship among reproductive-aged women





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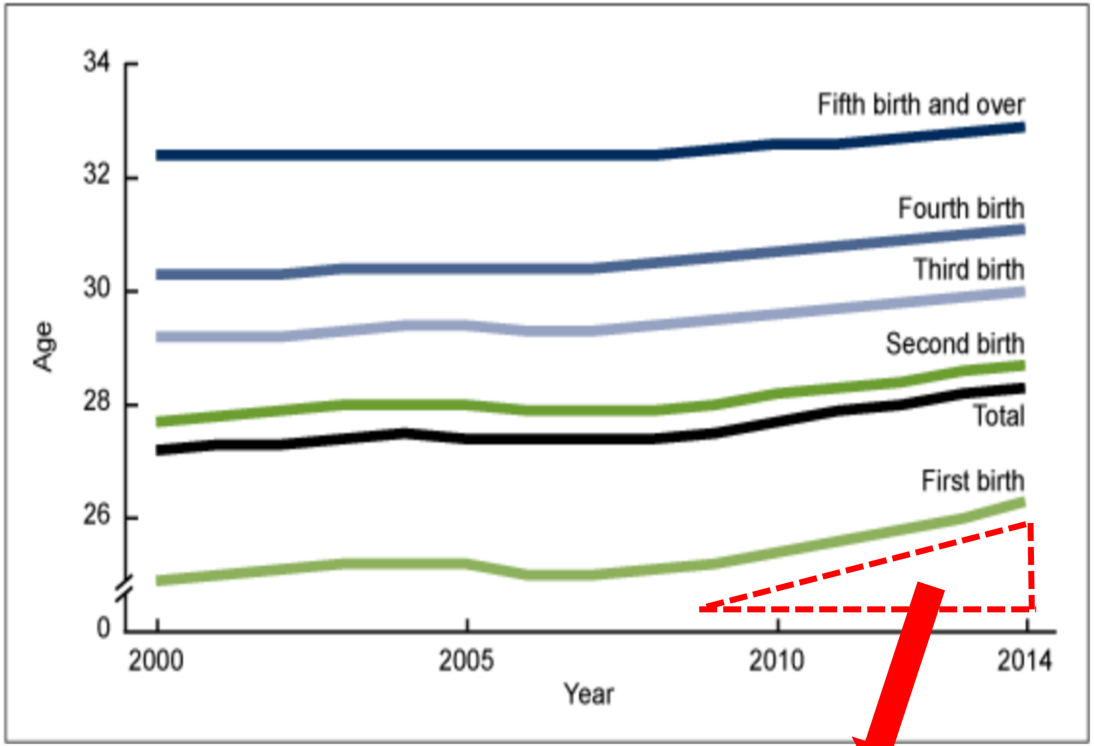
https://seer.cancer.gov/archive/csr/1975_2013
Miller et al, Am J Clin Oncol 2015

Delayed childbearing in the context of a cancer diagnosis

Mean age by birth order: United States, 2000-2014

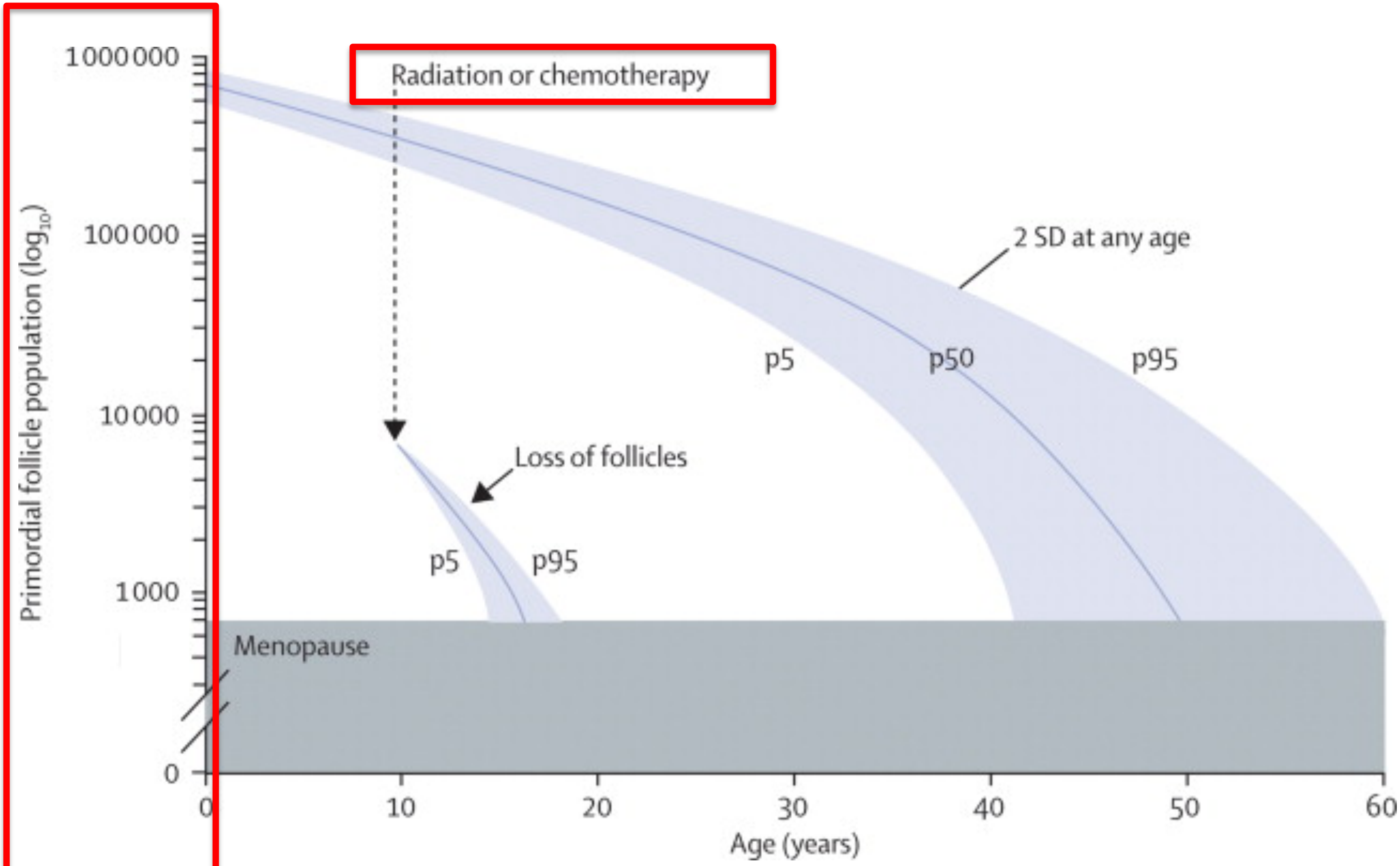


SOURCE: CDC/NCHS, National Vital Statistics System.

Increasing numbers of women childless at time of cancer diagnosis

Adapted from CDC.gov

Impact of treatment on ovarian reserve

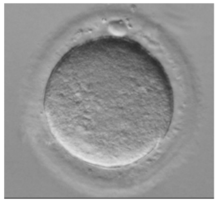


De Vos et al. Lancet 2010

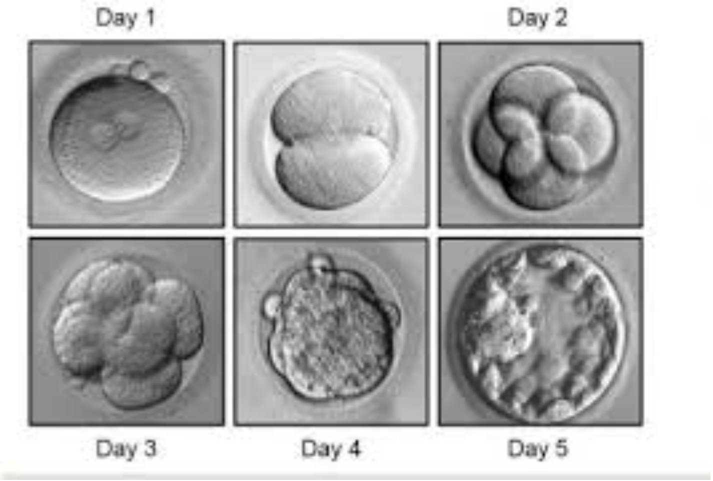
Options for female fertility preservation

Established

Oocyte cryopreservation



Embryo cryopreservation



Investigational/ experimental

Ovarian tissue cryopreservation

Pharmacologic fertoprotection

ASRM Practice Committee, Fertil Steril 2013

Limitations of oocyte/embryo cryopreservation

Hypothetical 35yo woman

Oocyte cryopreservation	Embryo cryopreservation
10 MII oocytes	
8 MII undergo ICSI	10 MII oocytes
6 2PN	8 2PN

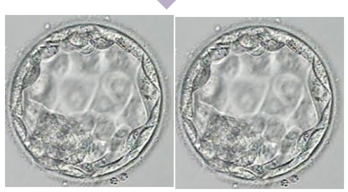
80% oocyte survival

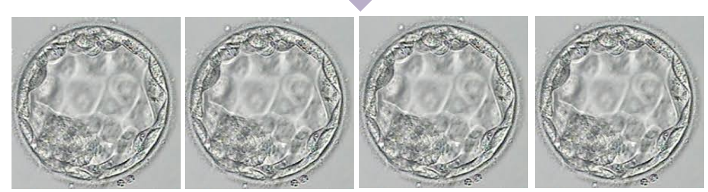
80% fertilization

30% blastocyst formation

80% fertilization

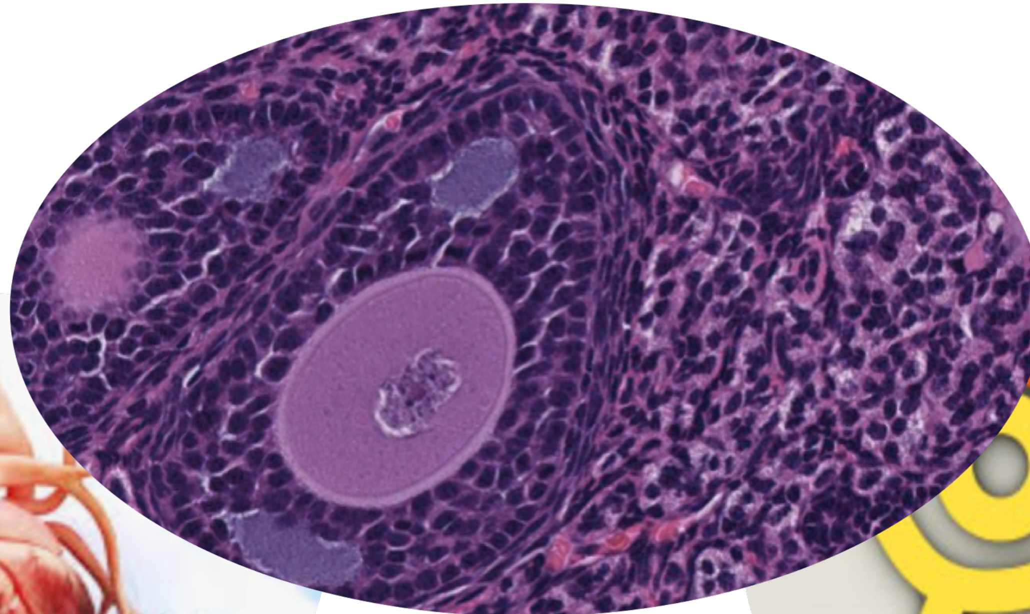
50% blastocyst formation

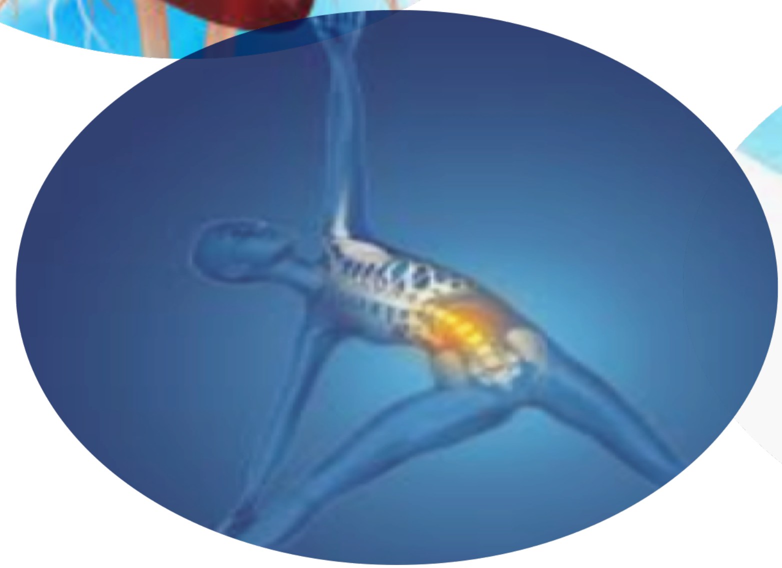




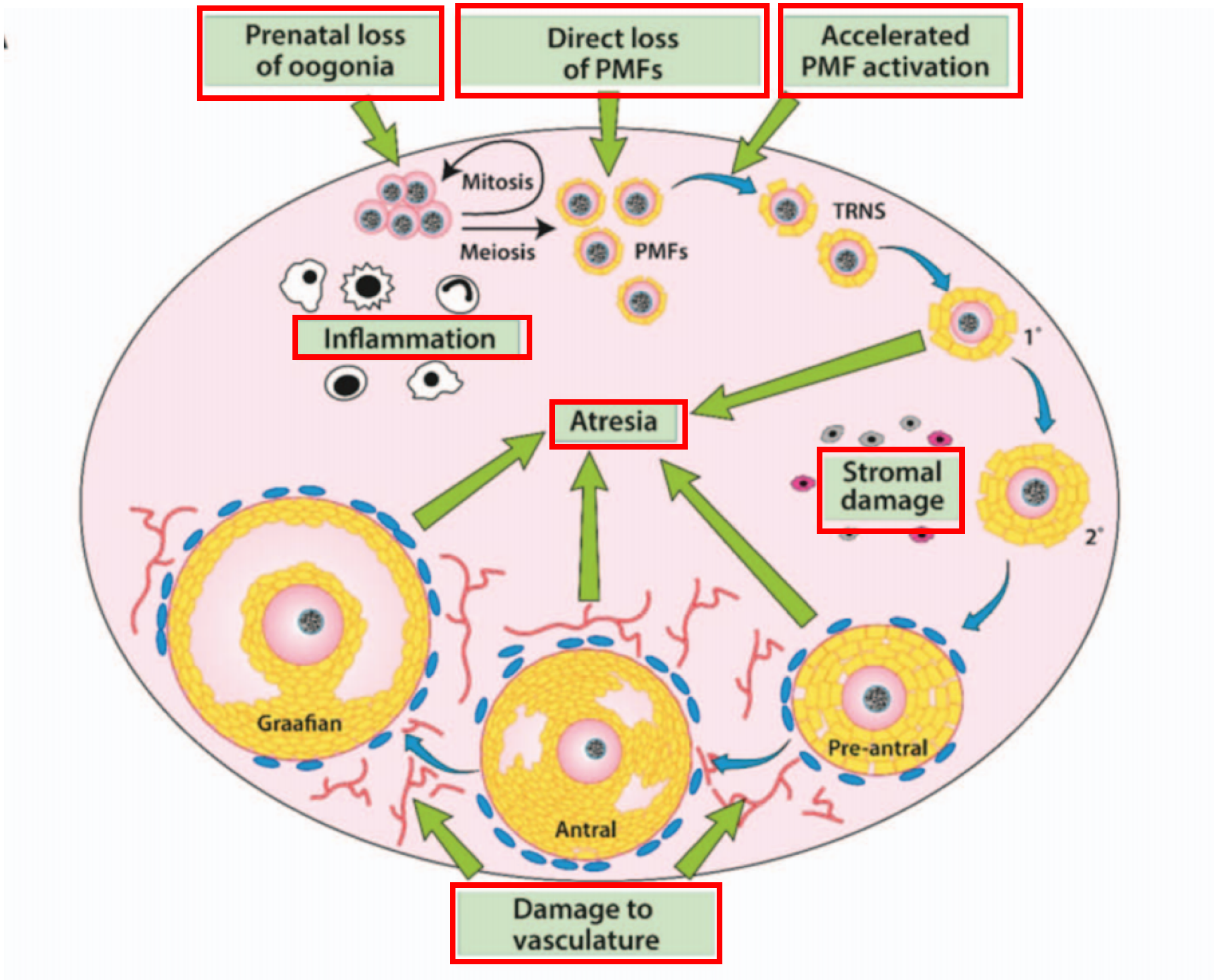
Euploidy?

Goldman et al. Fertil Steril 2013




Mechanisms of iatrogenic ovarian injury

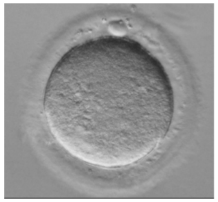


Spears et al. Hum Reprod Update 2019

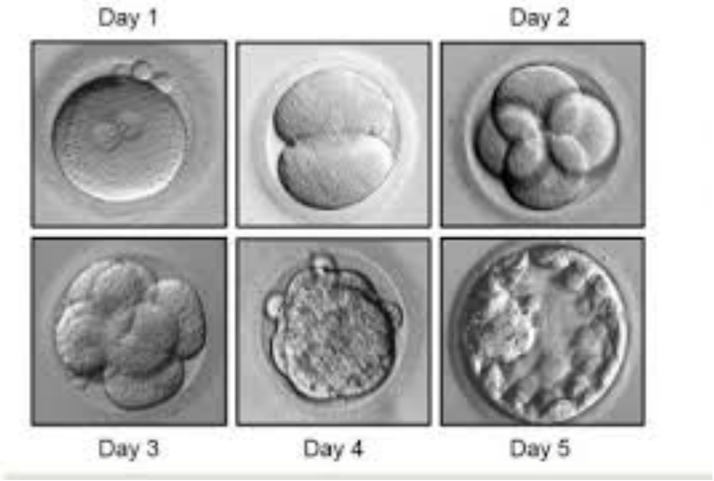
Options for female fertility preservation

Established

Oocyte cryopreservation



Embryo cryopreservation



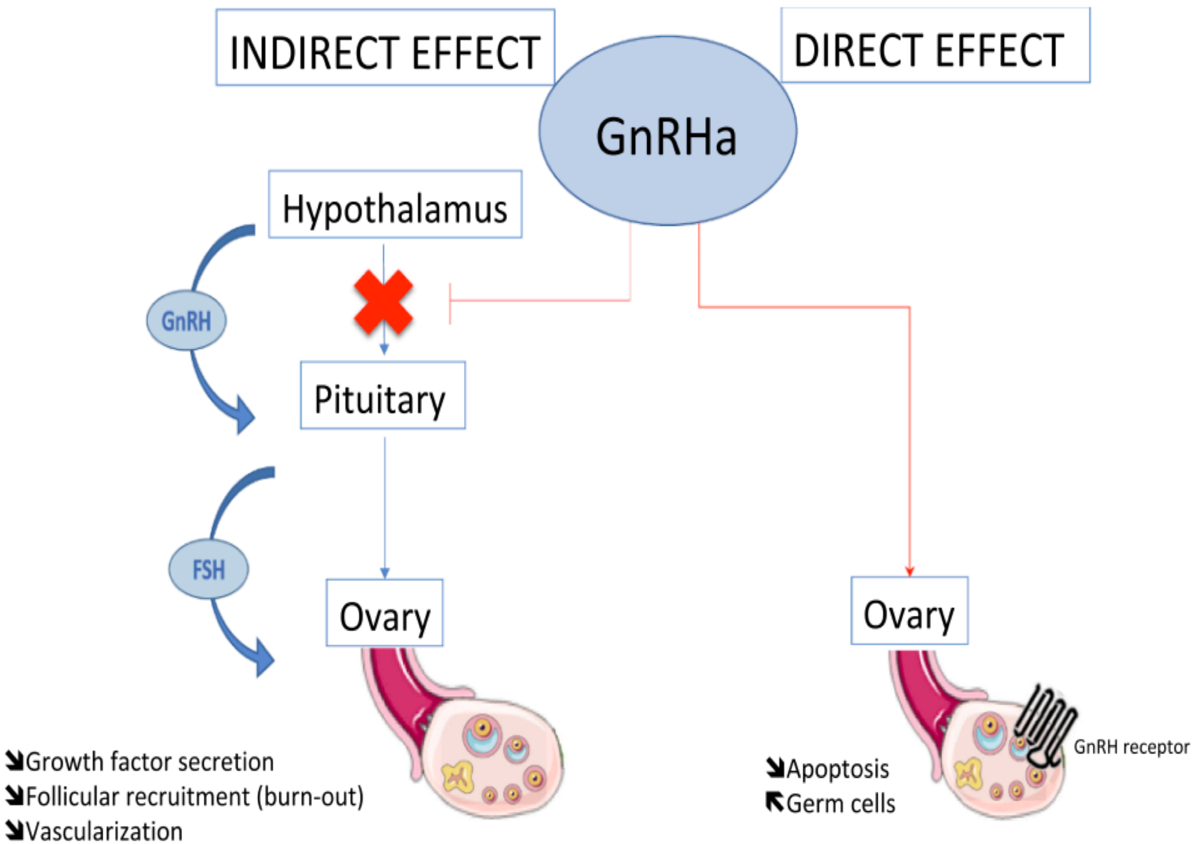
Investigational/ experimental

Ovarian tissue cryopreservation

Pharmacologic fertoprotection

ASRM Practice Committee, Fertil Steril 2013

GnRH agonist mechanism of action in fertility preservation



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Lambertini et al, Cancer Treatment Reviews 2019

GnRH agonist pre-clinical data: murine models

Table 1
Preclinical studies in female mice evaluating temporary ovarian suppression with GnRHa during chemotherapy.

Authors	Type of gonadotoxic treatment	Main results	Overall results
Yuce et al., 2004	Cyclophosphamide	* Small protection of primordial follicles	Protection (only against high dose of cyclophosphamide)
Danforth et al., 2005; Kishk et al., 2013; Hasky et al., 2015; Kanter et al., 2016	Cyclophosphamide	* Dose-dependant protection of the ovarian reserve * Slight protection of growing follicles * Preservation of AMH levels * Preservation of fertilization rate, early embryo development and improvement of oocyte quality	Protection
Tan et al., 2010	Busulfan	* Protection of primordial and primary follicles	Protection
Lin et al., 2012; Zhang et al., 2013	Cisplatin	* Protection of quiescent and growing follicles * Preservation of AMH levels * No difference in proliferation and apoptosis in the ovaries	Protection
Detti et al., 2014; Horicks et al., 2015; Horicks et al., 2018	Cyclophosphamide	* No protection of quiescent and growing follicles * No protection of FSH and AMH levels * FSH deficiency does not protect ovarian reserve * *In vitro* exposure to GnRHa does not preserve follicular survival * No difference in proliferation and apoptosis in the ovaries	No protection
Hasky et al., 2015	Doxorubicin	* Compromise vascular recovery * No preservation of AMH levels	No protection
Park et al., 2017	Docetaxel	* Protection of total follicles * Preservation of proliferation within follicles * Decrease of double-strand DNA breaks	Protection

Lambertini et al, Cancer Treatment Reviews 2019

GnRH agonist pre-clinical data: rat models

Table 2
Preclinical studies in female rats evaluating temporary ovarian suppression with GnRHa during chemotherapy.

Authors	Type of gonadotoxic treatment	Main results	Overall results
Ataya et al., 1985; Ataya et al., 1988; Bokser et al., 1990; Ataya et al., 1993; Knudtson et al., 2017	Cyclophosphamide	* Protection of quiescent and growing follicles * Preservation of LH and E2 levels * Preservation of pregnancy, implantation and live birth rates	Protection
Montz et al., 1991	Cyclophosphamide	* Improvement of fertility only with agonist twice a day	Partial protection
Letterie et al., 2004; Li et al., 2015; Parlakgumus et al., 2015	Cyclophosphamide	* No protection of ovarian reserve and growing follicles * No preservation of fertility * Increase in liver, pulmonary and splenic hemorrhage * No preservation of AMH levels	No protection
Matsuo et al., 2007; Li et al., 2013	Cisplatin	* Protection of ovarian reserve * Preservation of cyclicity	Protection
Ozcelik et al., 2010	Paclitaxel and/or cisplatin	* Protection of ovarian reserve (paclitaxel) * No protection of ovarian reserve (cisplatin)	Protection only against paclitaxel
Wang et al., 2014	5-fluorouracil	* Protection of ovarian reserve * Preservation of AMH and FSH levels * Decrease of apoptotic factors	Protection

Lambertini et al, Cancer Treatment Reviews 2019

Pre-clinical data: female primates, human models

Table 3
Preclinical studies in female primates and human models evaluating GnRHa effect during chemotherapy.

Authors	Model	Type of gonadotoxic treatment	Main results	Overall results
Ataya et al., 1995	*In vivo* study in rhesus monkeys	Cyclophosphamide	* Protection of ovarian reserve * Preservation of FSH, E2 and P levels * Interruption of cyclicity	Protection
Imai et al., 2007	*In vitro* study on human granulosa cells	Doxorubicin	* Direct preservation of E2 levels after FSH stimulation	Protection
Bildik et al., 2015	*In vitro* study on human granulosa cells and ovarian tissue fragments	Cyclophosphamide Paclitaxel 5-fluorouracil TAC regimen	* No protection of ovarian reserve * No preservation of AMH, E2 and P levels * No upregulation of anti-apoptotic genes * No preservation of the vascular density	No protection

Lambertini et al, Cancer Treatment Reviews 2019

30 + years of clinical data in GnRH agonists:

- 14 randomized studies in breast cancer:
  - Potential prolongation of ovarian function/ possible decreased POI
  - No clear benefit in fertility preservation
- 2 RCTs in lymphoma: No benefit
- 12 meta-analyses: Potential benefit in preventing POI
- Clear benefit: menstrual suppression in women at bleeding risk

Moore et al, NEJM 2015
DeMesteere et al, J Clin Oncol 2016
Behringer et al, Ann Oncol 2010
Lambertini et al, Cancer Treatment Reviews 2019

Gonadotropin releasing hormone agonists (GnRHa)

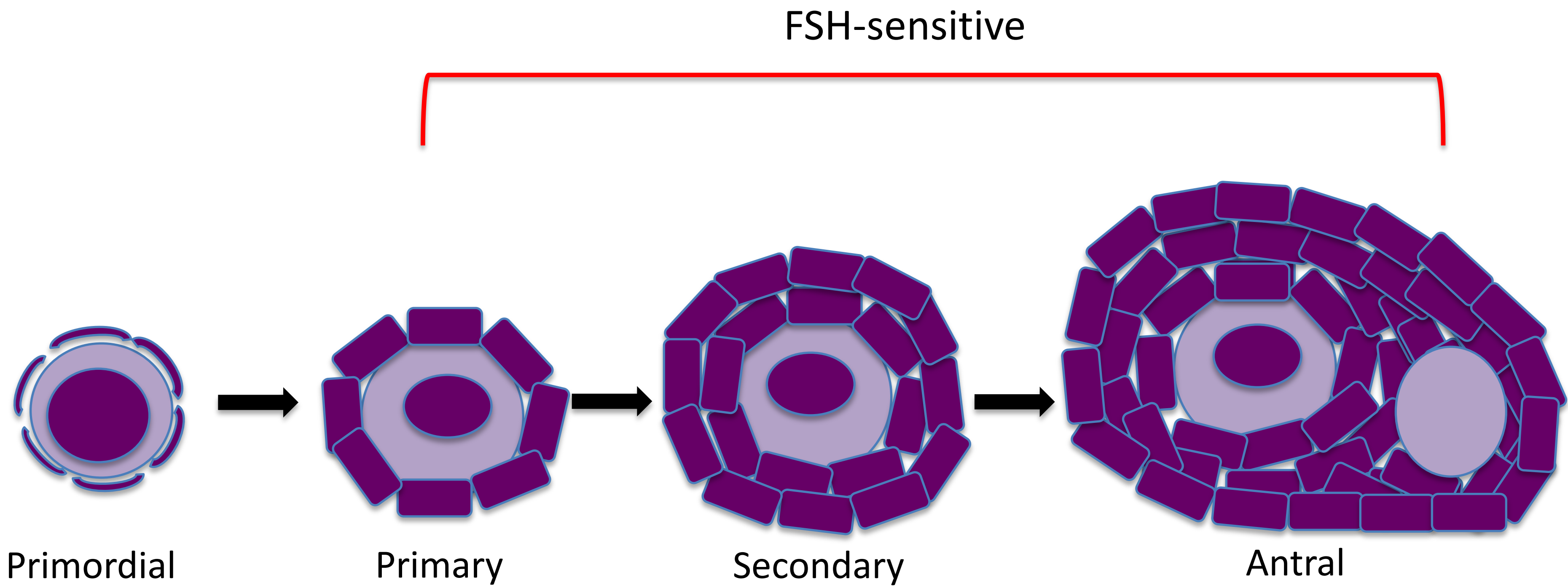
ASCO statement 2013

- Present both embryo and oocyte cryopreservation as established fertility preservation methods
- Discuss the option of ovarian transposition (oophoropexy) when pelvic radiation therapy is performed as cancer treatment
- Inform patients of conservative gynecologic surgery and radiation therapy options
- Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method, and these agents should not be relied on to preserve fertility
- Inform patients that other methods (eg, ovarian tissue cryopreservation, which does not require sexual maturity, for the purpose of future transplantation) are still experimental

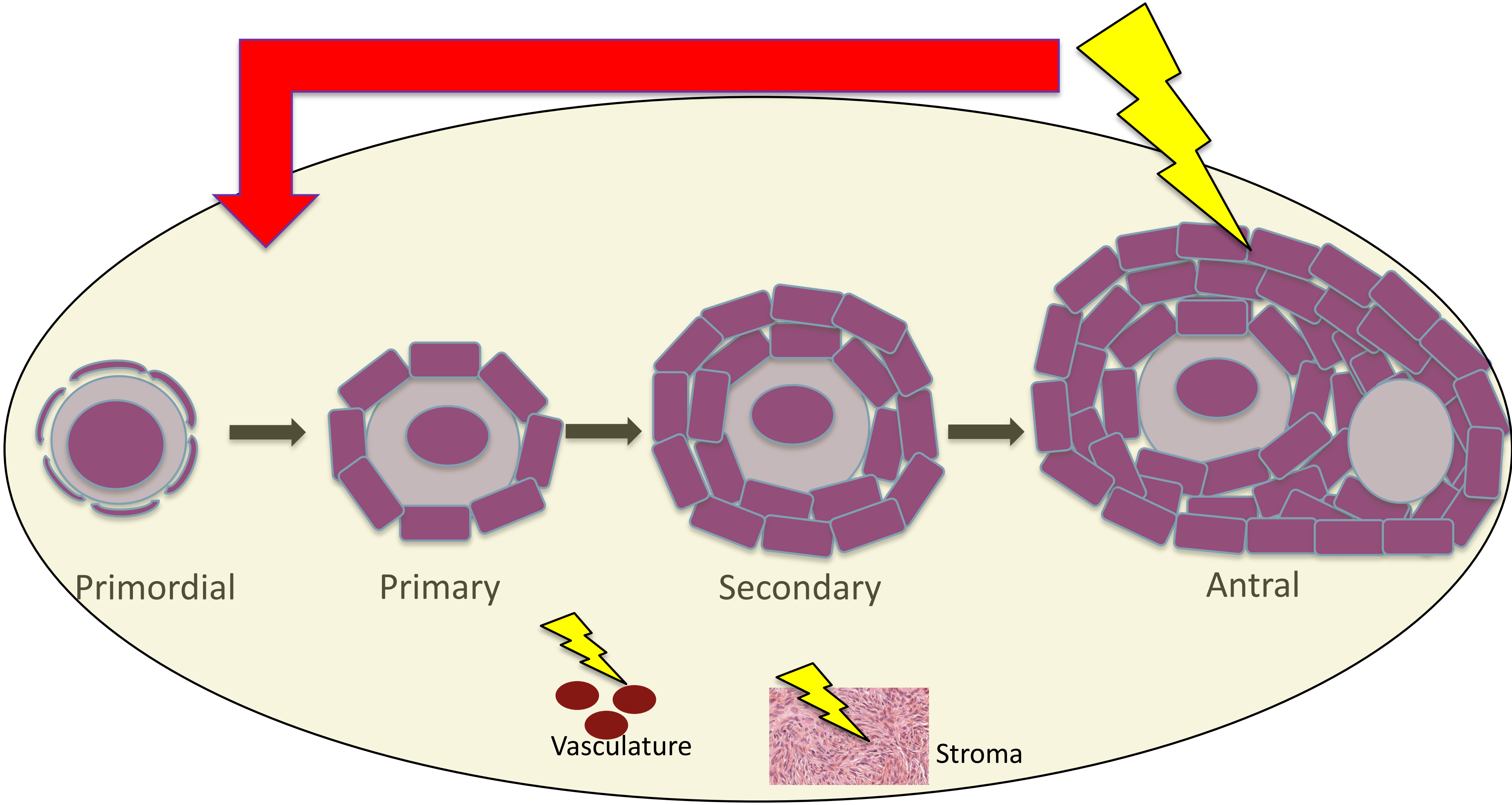
NCCN revised guidelines 2015:
“Randomized trials have shown that suppression with GnRH agonist therapy during adjuvant chemotherapy in **premenopausal women with ER-negative tumors**…may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea”… “smaller historical experiences in patients with ER-positive disease… **conflicting results regarding protective effect on fertility**”

Loren et al, J Clin Oncol 2013
www.nccn.org

Physiologic ovarian folliculogenesis

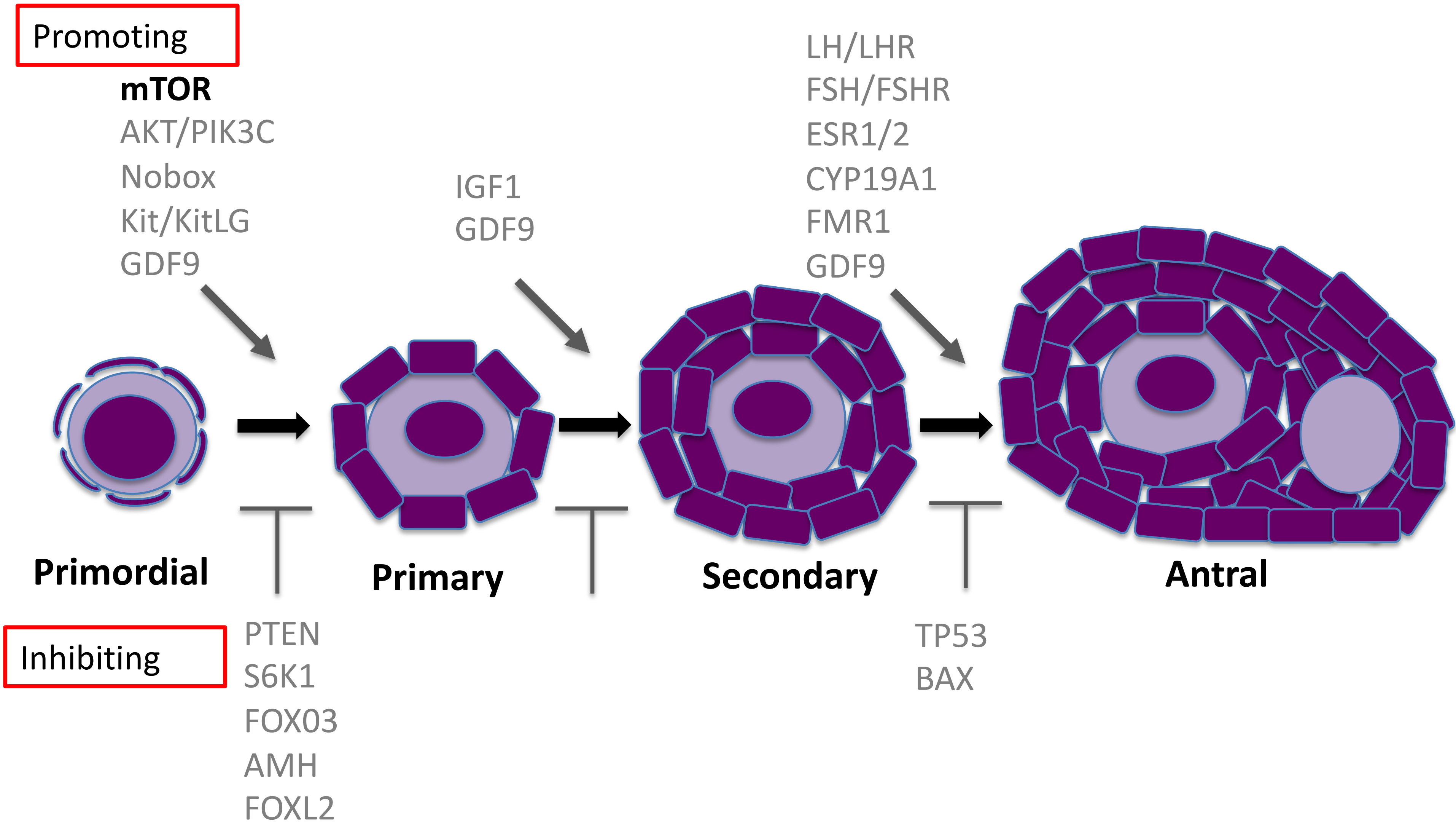


Mechanisms of ovarian damage



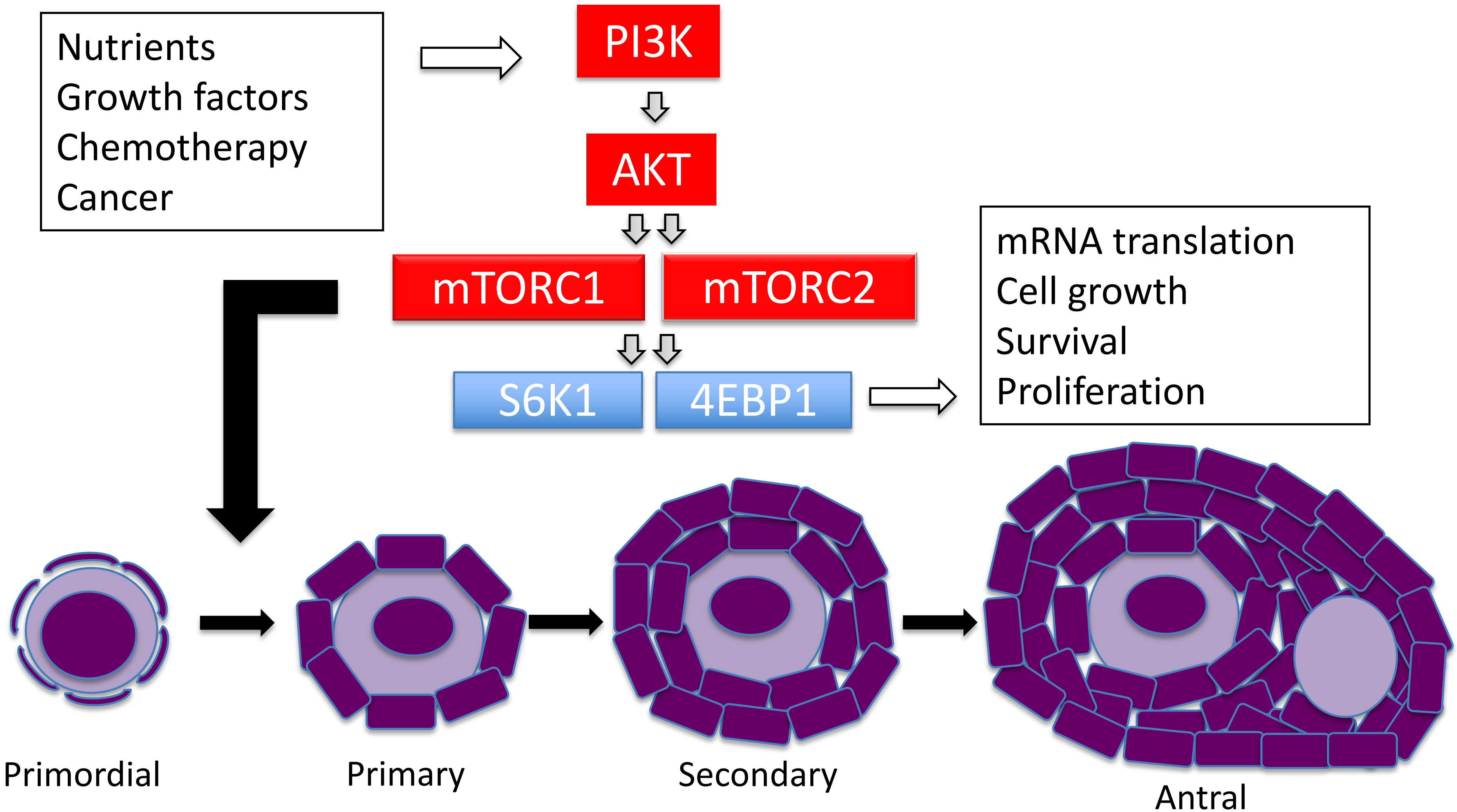
Kalich-Philosoph et al. Sci Transl Med 2013

Promoting and inhibitor factors



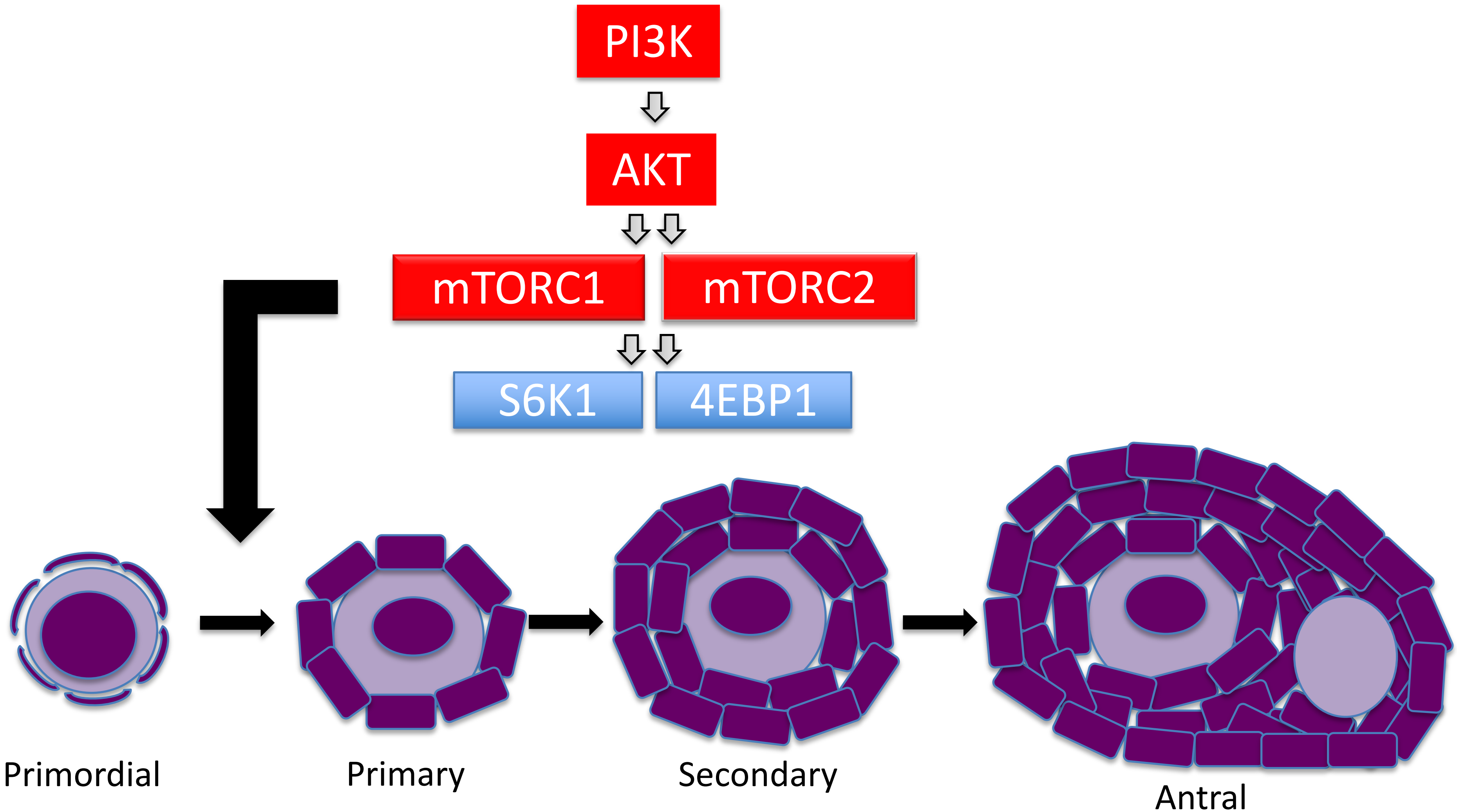
Adapted from Wood-Trageser M, Rajkovic A. Sem Reprod Med 2013

mTOR pathway



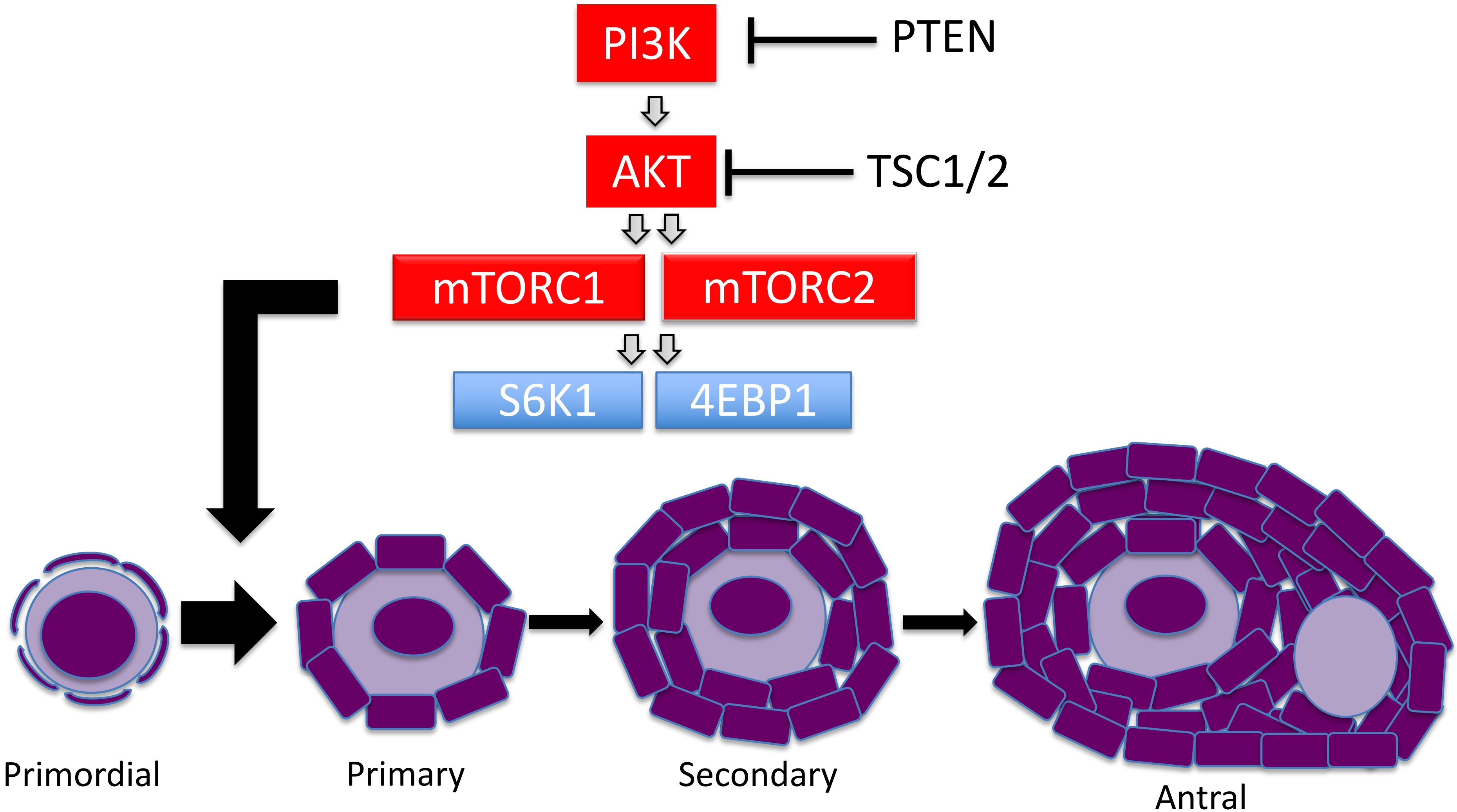
Reddy et al., Science, 2008; Adhikari et al., Mol. Hum. Reprod. 2009; Zhang et al., Gene, 2013; Castrillon DH et al., Science, 2013

mTOR pathway critical to primordial follicle activation



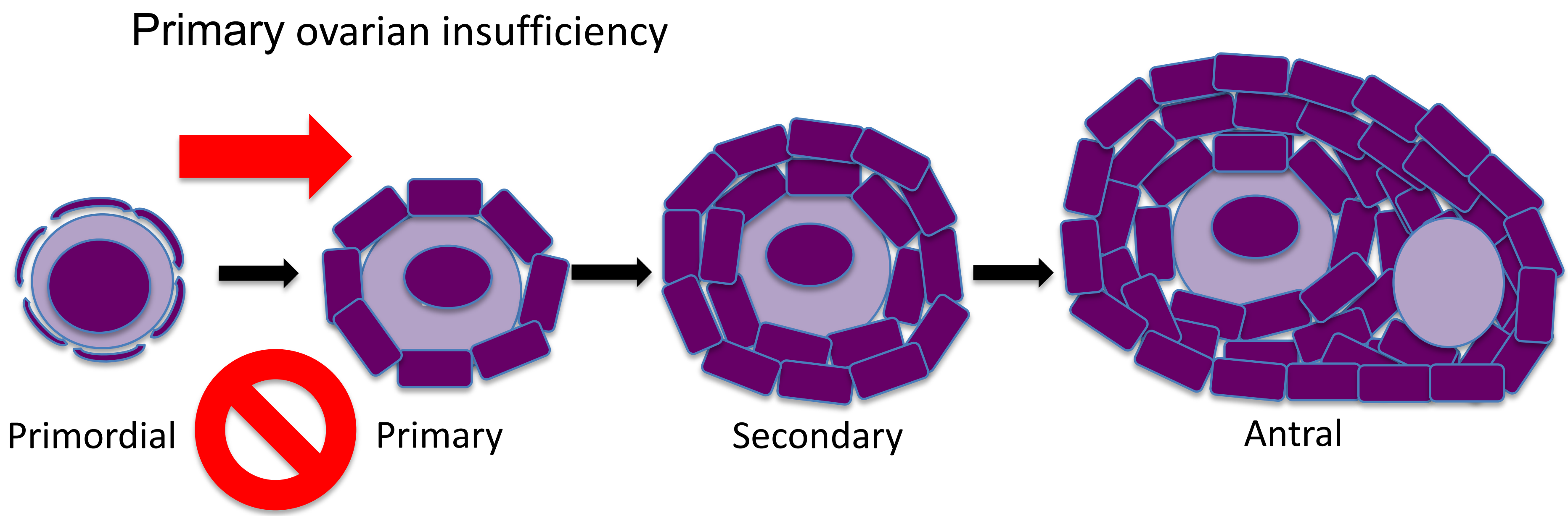
Reddy et al., Science, 2008; Adhikari et al., Mol. Hum. Reprod. 2009; Zhang et al., Gene, 2013; Castrillon DH et al., Science, 2013

Up-regulated PI3K/AKT results in follicular depletion



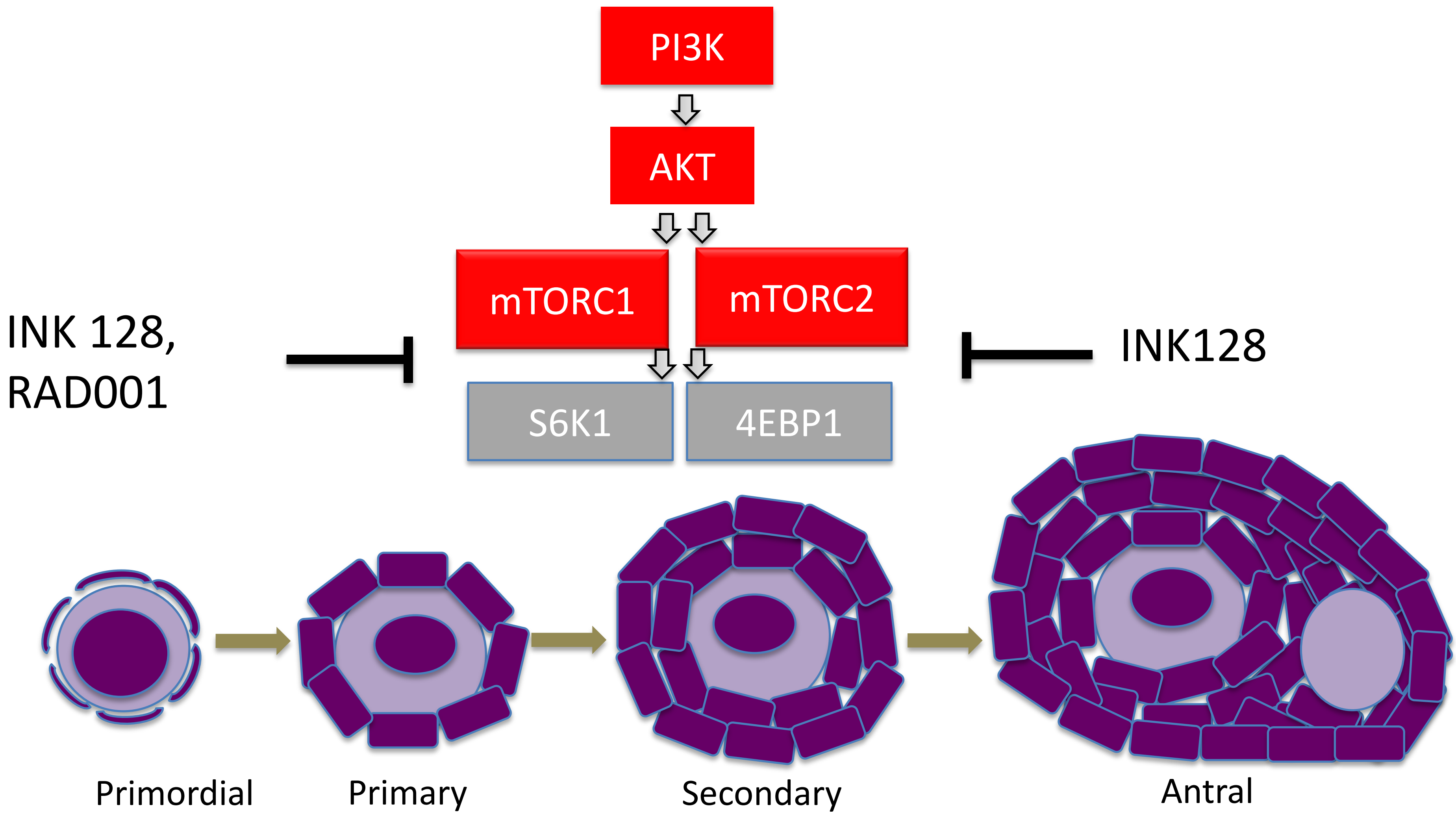
Reddy et al., Science, 2008; Adhikari et al., Mol. Hum. Reprod. 2009

Potential clinical implications



Fertility preservation
Ovarian aging

Hypothesis: mTOR inhibitors preserve ovarian reserve and fertility in mice treated with CY



mTOR inhibitors widely used for benign and malignant conditions

mTORC 1 Inhibitors
(Everolimus, RAD001)

- **Breast cancer (ER+, HER2 neg) ****
- Advanced renal cell carcinoma **
- Subependymal Giant Cell Astrocytoma **
- Tuberous Sclerosis **
- Metastatic pancreatic neuroendocrine tumors **
- Diffuse Large B-Cell Lymphoma
- Epilepsy
- Melanoma
- Cholangiocarcinoma

mTORC 1/2 (Dual) Inhibitors
(INK128, MLN0128)

- Breast cancer
- Neuroblastoma
- Pancreatic cancer
- Renal cell carcinoma
- Thyroid cancer
- Acute lymphoblastic leukemia
- Non-Hodgkin's Lymphoma

**FDA approved: trade name Afinitor (Novartis)

Rahmani et al., Clin Cancer Res, 2014; Nguyen et al. Epilepsia 2015; Rosenberg et al. Transl Oncol 2015; Yang et al. Oncotarget 2015; Strosberg et al. World J Gastroenterol 2015; Zhang et al. Apoptosis 2015; Lou et al. Biochem Biophys Res Comm 2014; Ingels et al. Int J Cancer 2014; Gild et al. Endocr Relat Cancer 2013; Janes et al. Leukemia 2013

C57BL/6
8 weeks

Control (PVP) *
RAD001 2.5mg/kg * (mTORC1 inhibitor)
INK128 0.3 mg/kg * (mTORC1/2 inhibitor)
Cyclophosphamide (CY 75mg/kg)
RAD + CY
INK + CY

* Oral gavage

Aim 1:
Ovarian reserve

CY

Daily RAD
Daily INK
Weeks 1-3

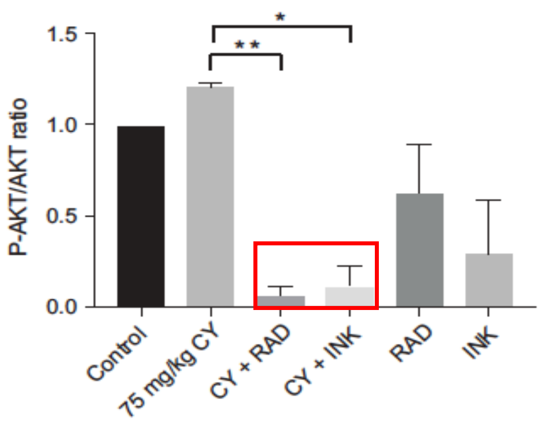
Sacrifice

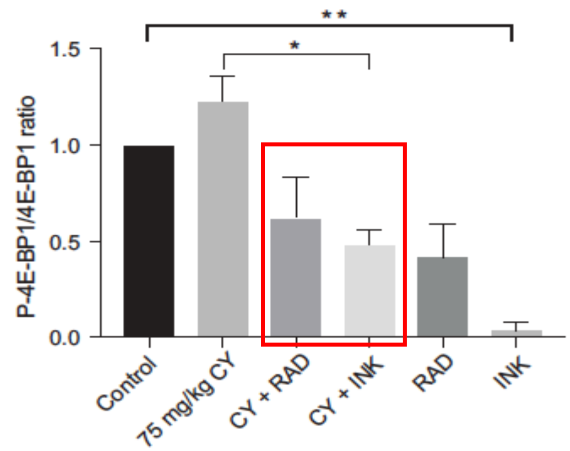
Daily RAD
Daily INK
Week 4

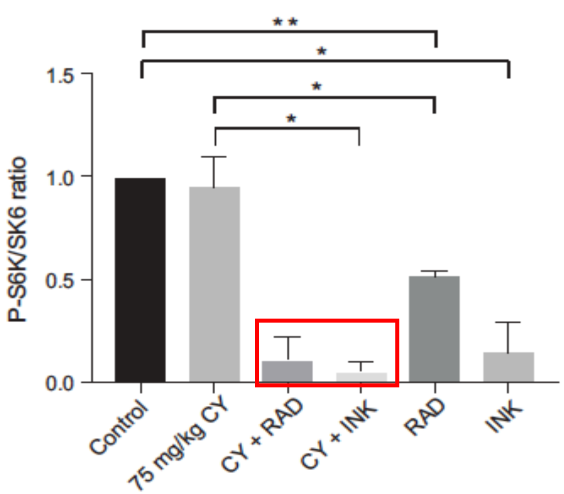
Aim 2:
Fertility

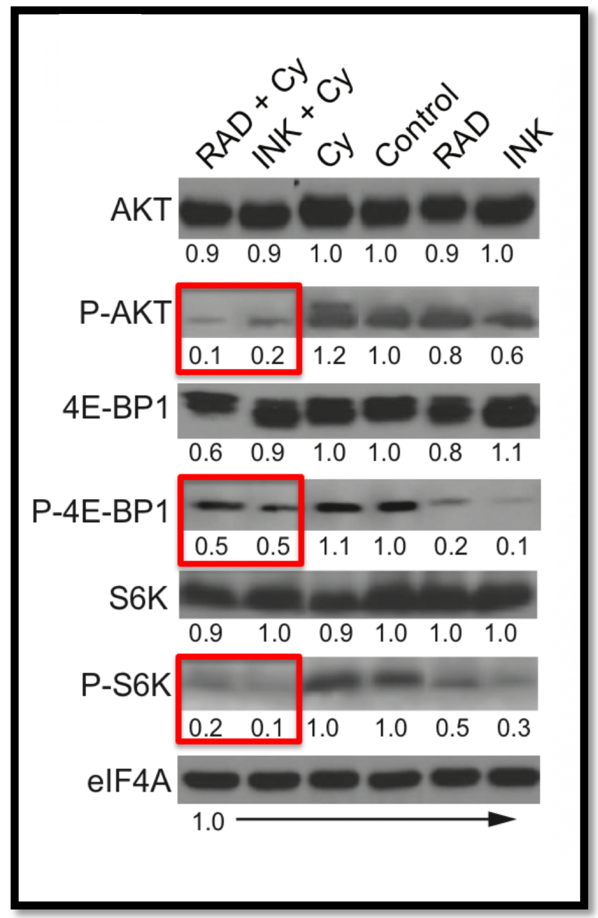
Daily RAD
Daily INK
Weeks 1-4

Down-regulation of mTOR activity in whole ovary lysates of co-treated mice



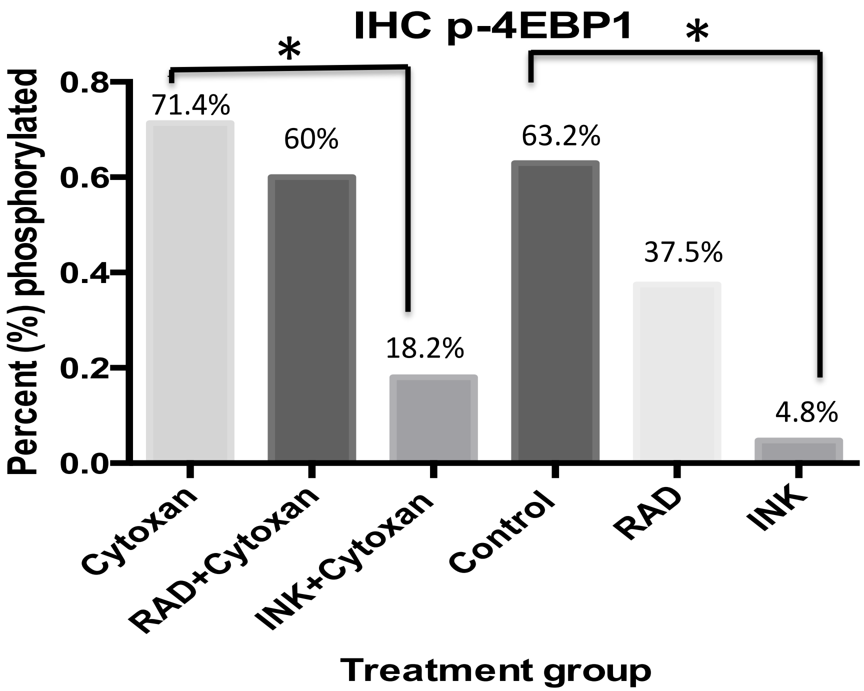


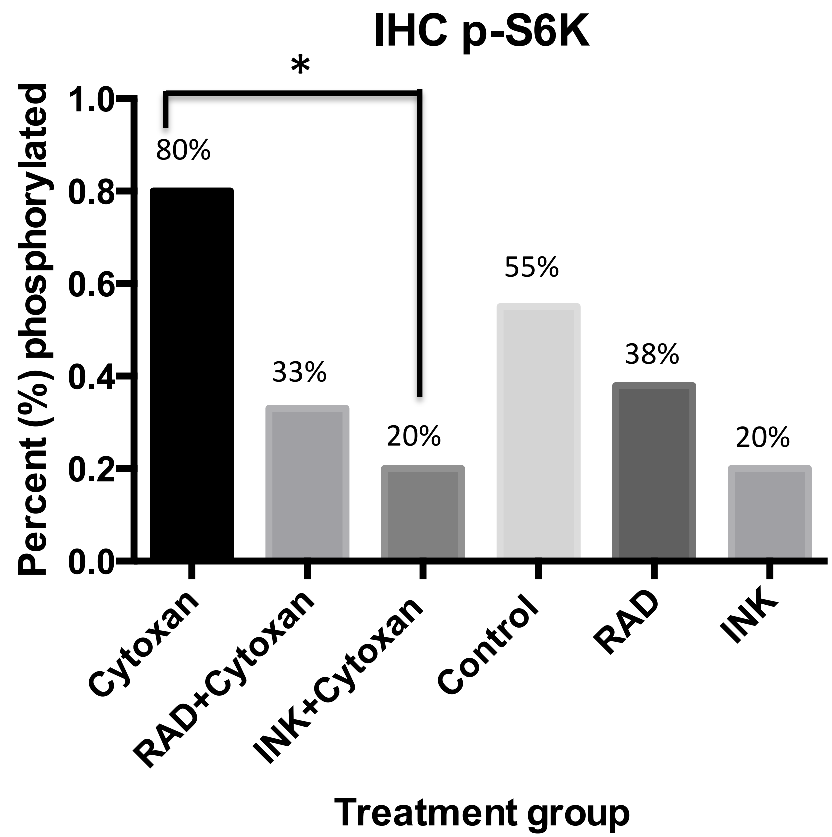




Goldman et al. PNAS 2017

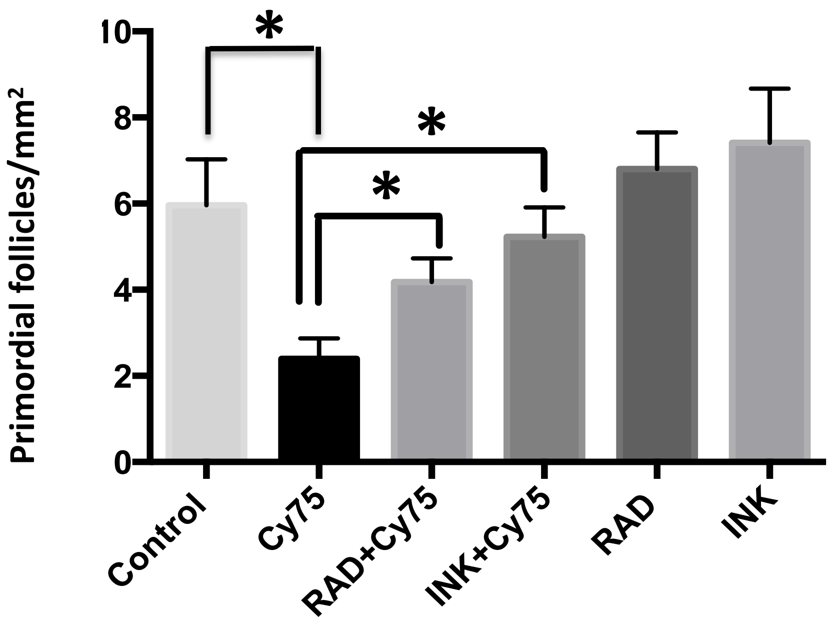
Phosphorylation of 4EBP-1 and S6 kinase within primordial follicles is decreased after mTOR inhibition





Goldman et al. PNAS 2017

Two-fold increase in PMFs per surface area when CY-treated mice are co-treated with mTOR inhibitors



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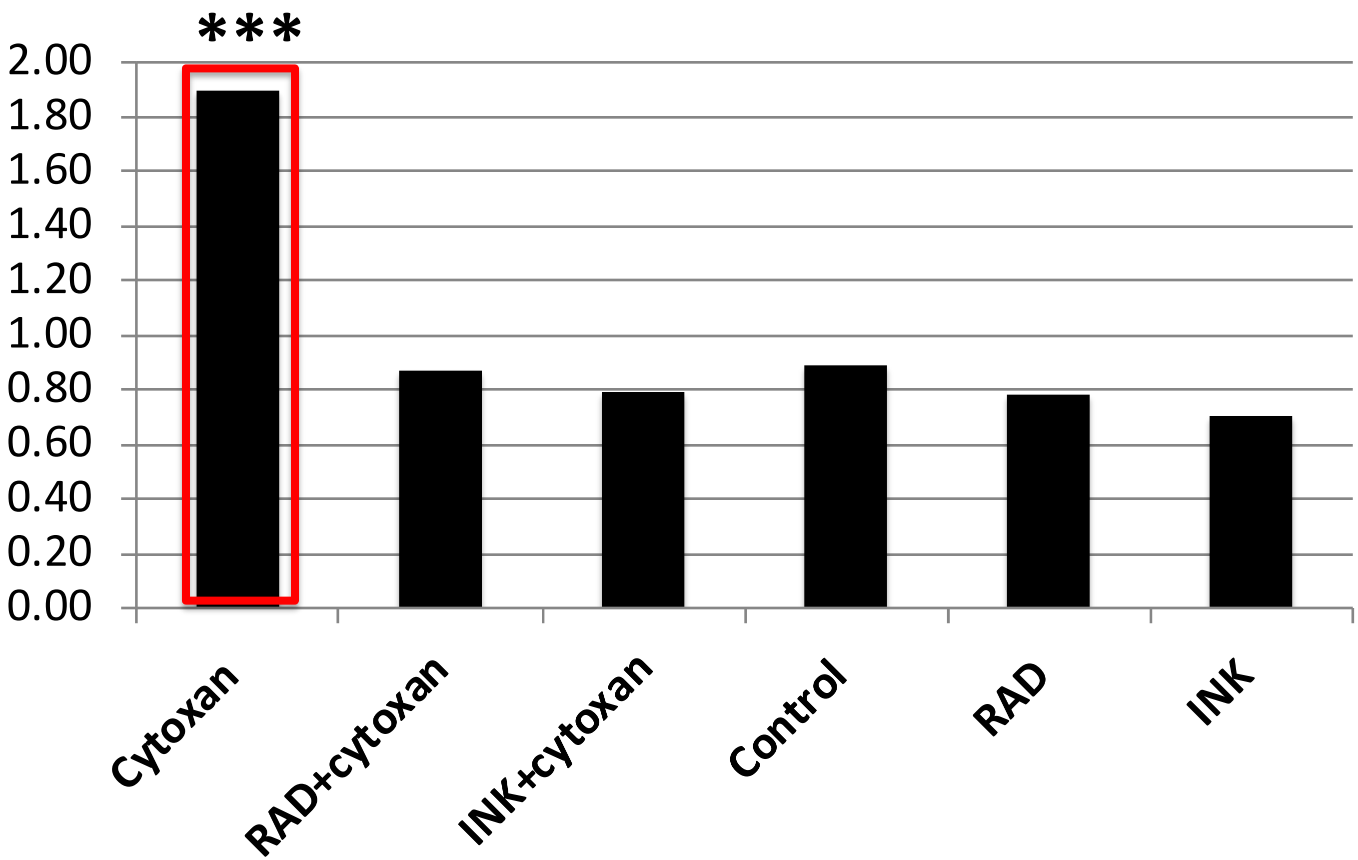
Goldman et al. PNAS 2017

Cytoxan causes follicular burn-out; co-treatment with RAD and INK attenuate this effect



Ratio of total growing to primordial follicles

C57BL/6
8 weeks

Control (PVP) *
RAD001* (mTORC1 inhibitor)
INK128 * (mTORC1/2 inhibitor)
Cyclophosphamide (CY 75mg/kg)
RAD + CY
INK + CY

* Oral gavage

**Aim 1:
Ovarian reserve**

CY

Daily RAD
Daily INK
Weeks 1-3

Sacrifice

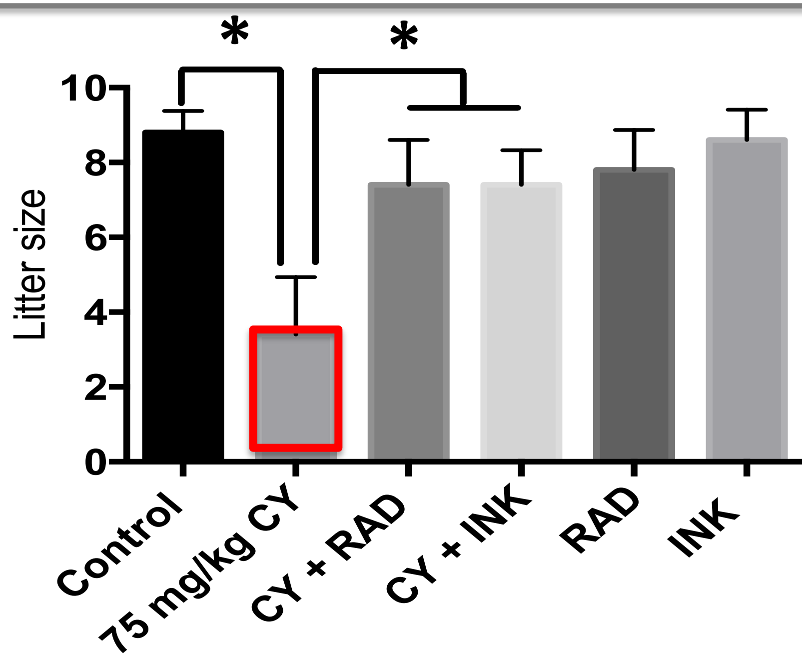
Daily RAD
Daily INK
Week 4

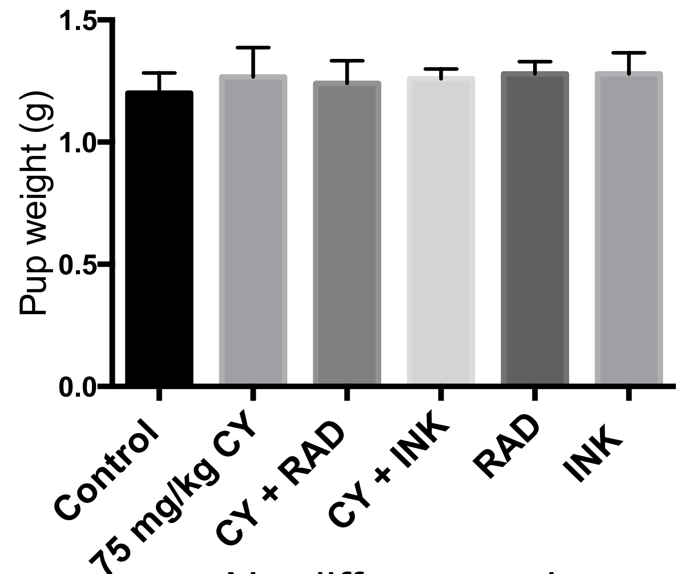
**Aim 2:
Fertility**

Daily RAD
Daily INK
Weeks 1-4

mTORC1/2 inhibition preserves ovarian function and fertility during genotoxic chemotherapy

Kara N. Goldman[a], Devon Chenette[b], Rezina Arju[b], Francesca E. Duncan[c], David L. Keefe[a], Jamie A. Grifo[a], and Robert J. Schneider[b,d,1]





No differences in pup weight or anomalies

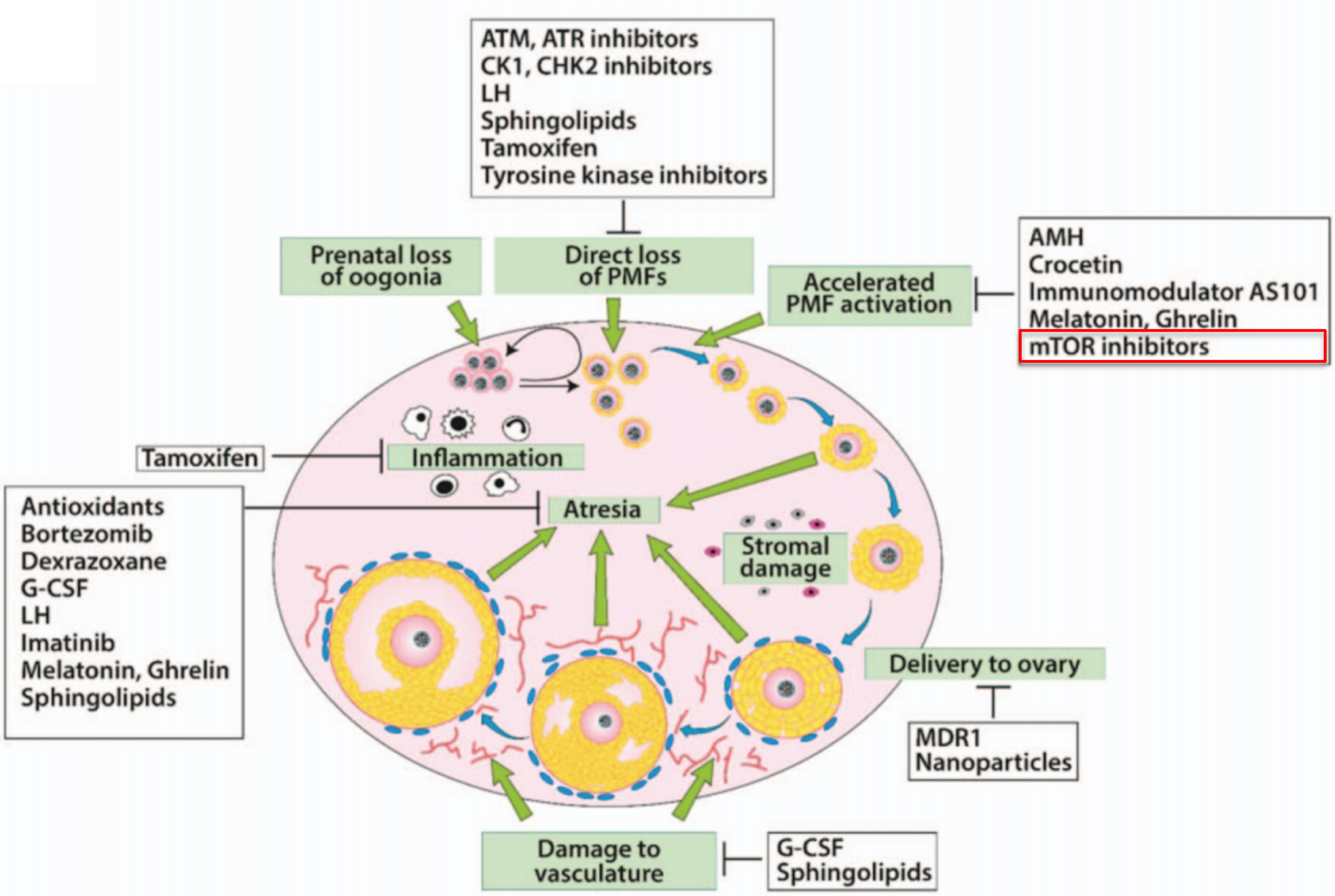
CY

CY + RAD

CY + INK

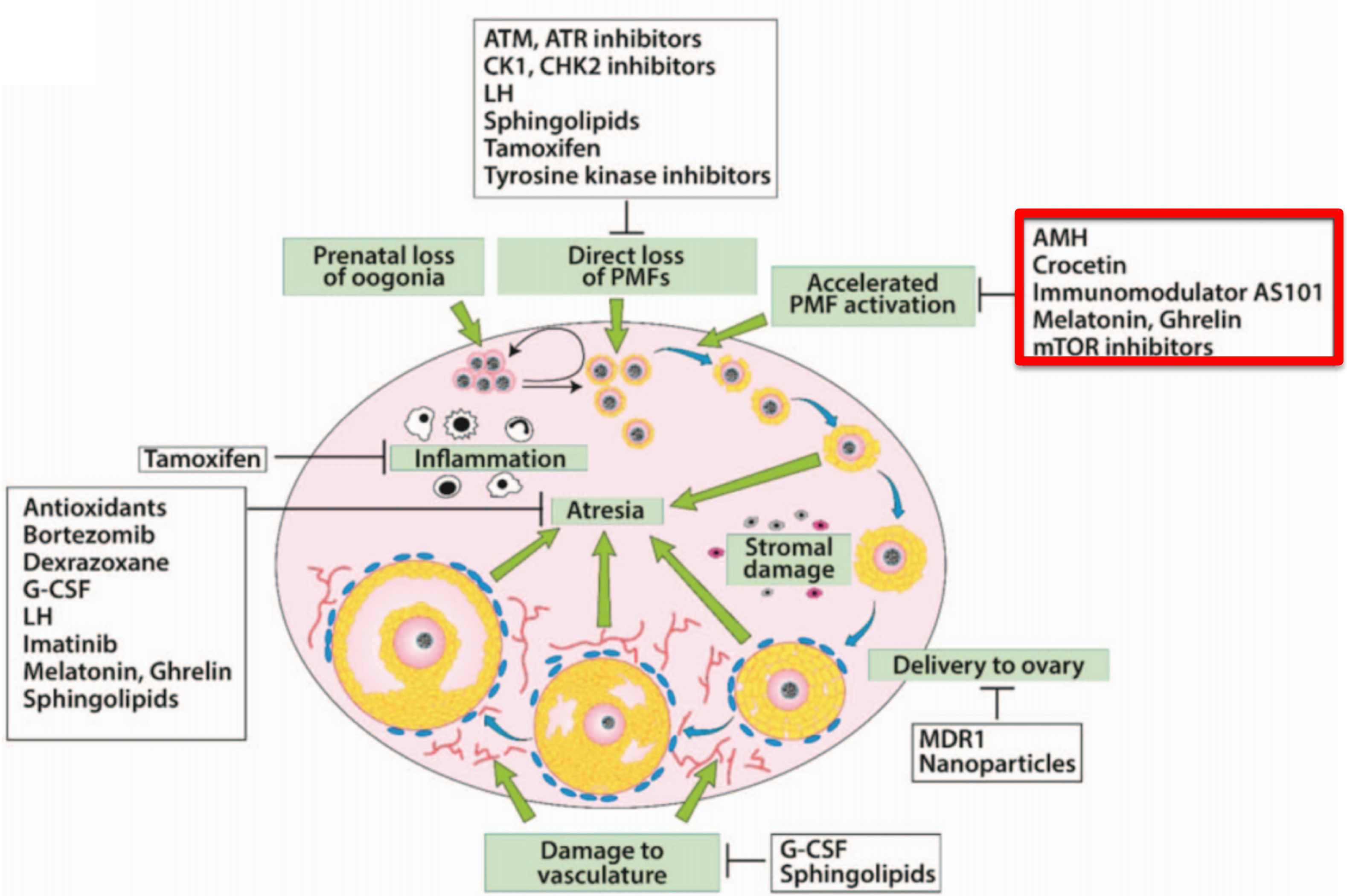
Goldman et al. PNAS 2017

Growing landscape of pharmacologic fertoprotection



Spears et al. Hum Reprod Update 2019

Growing landscape of pharmacologic fertoprotection



Spears et al. Hum Reprod Update 2019

Cyclophosphamide Triggers Follicle Activation and "Burnout"; AS101 Prevents Follicle Loss and Preserves Fertility

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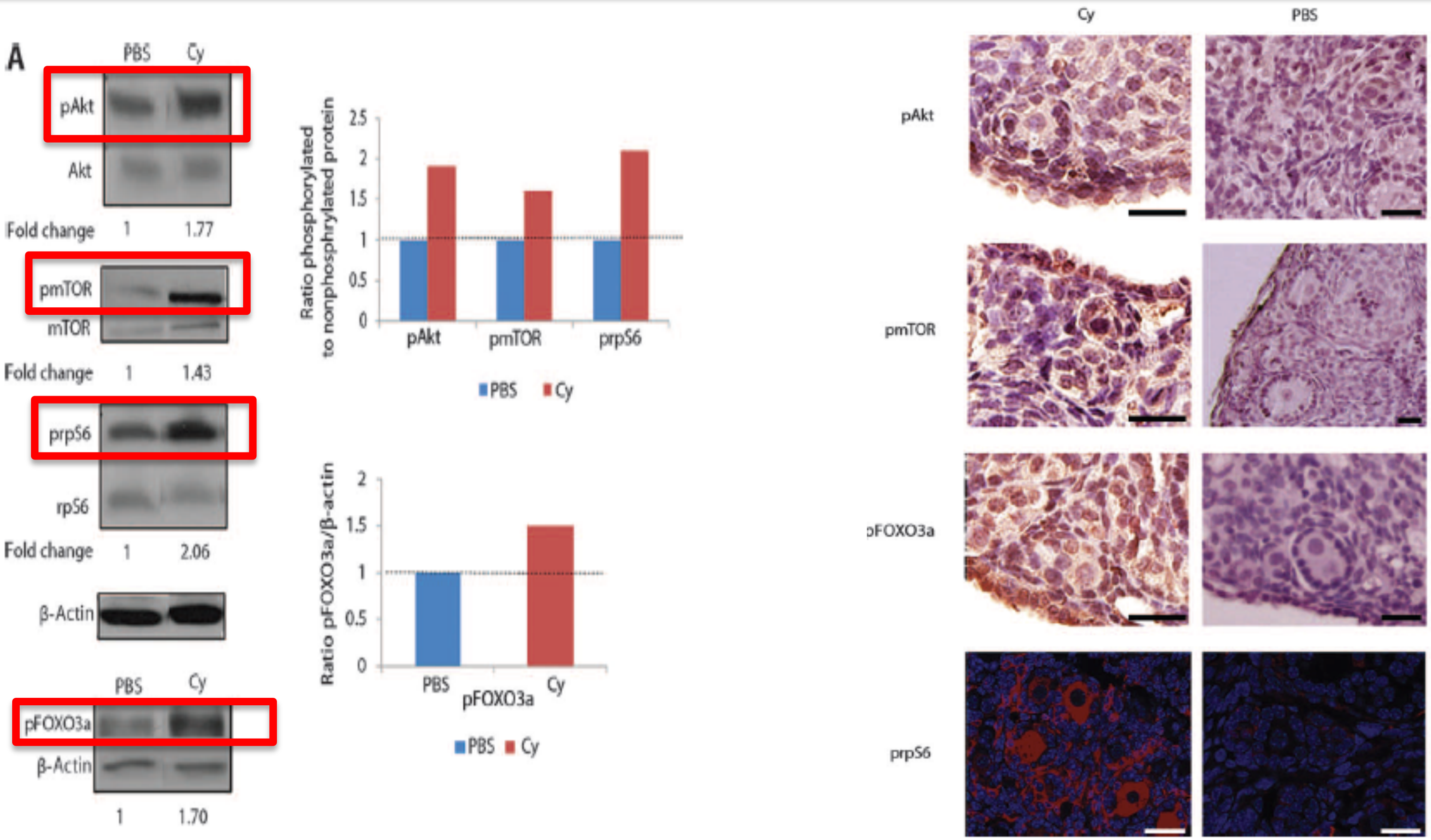
www.ScienceTranslationalMedicine.org 15 May 2013 Vol 5 Issue 185 185ra62



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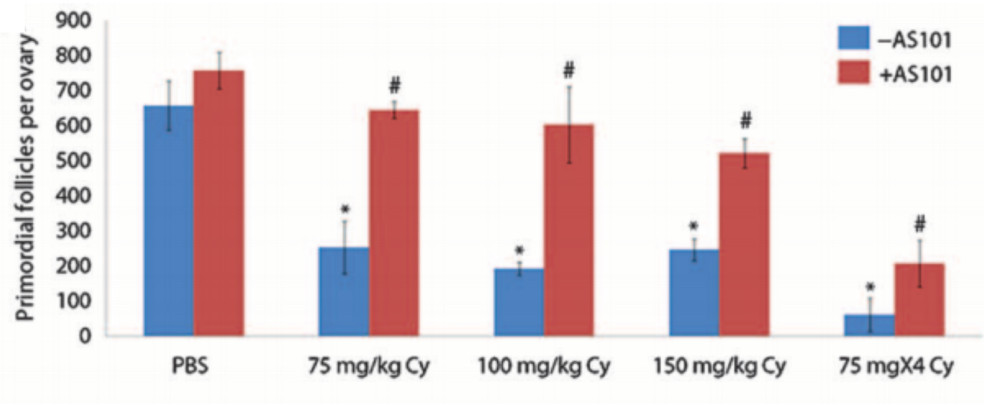
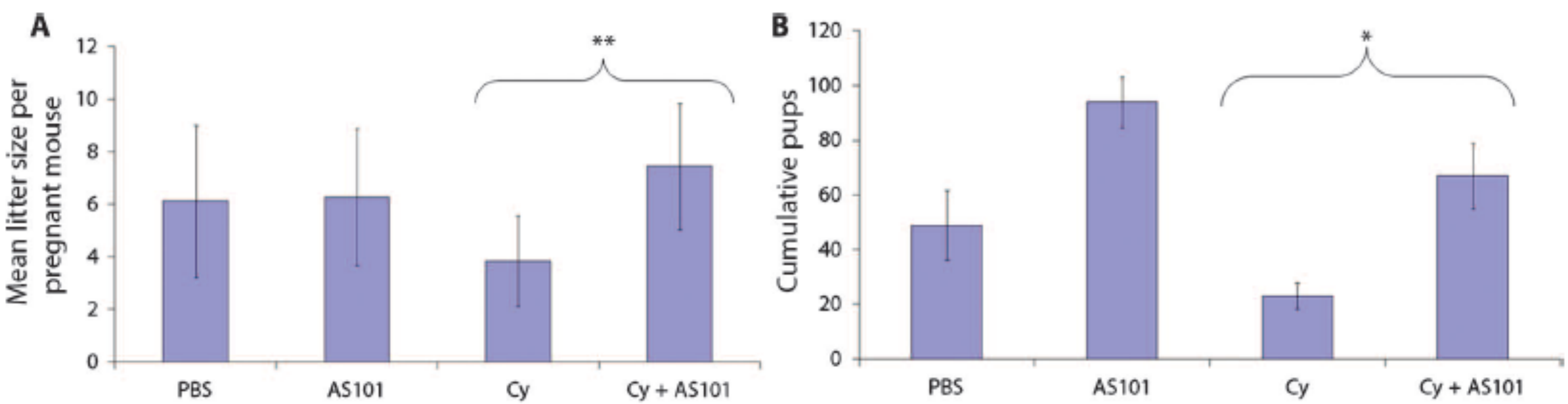
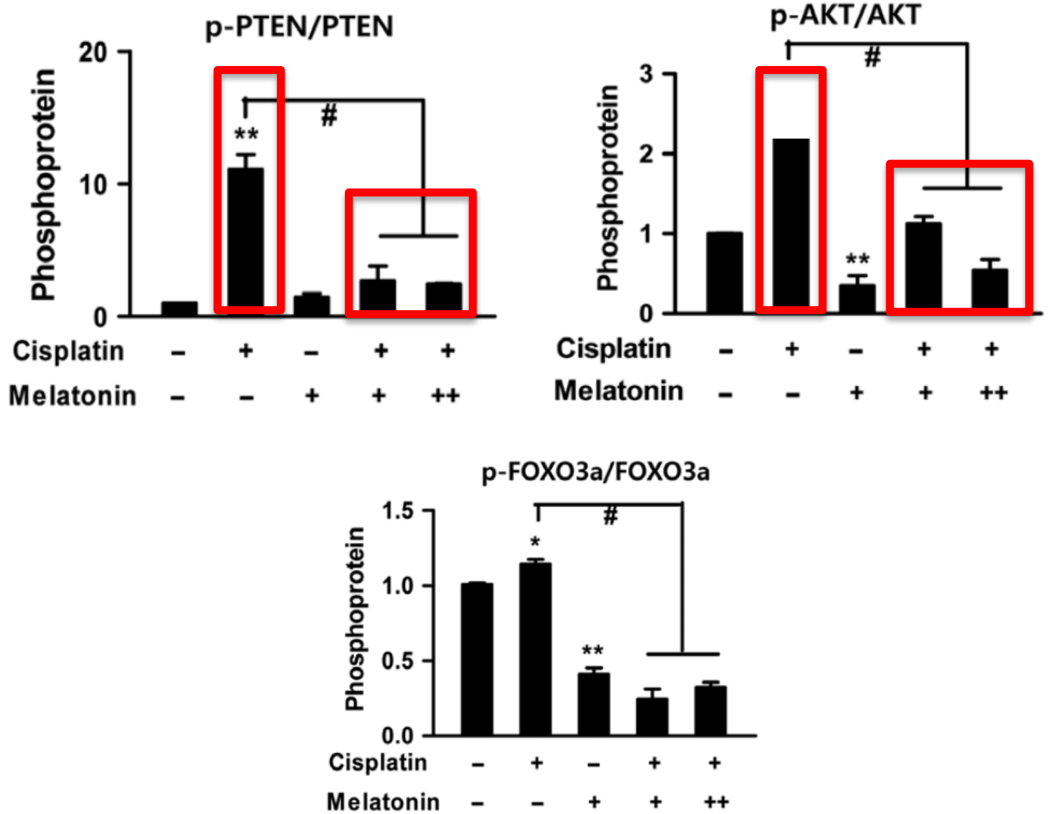




J. Pineal Res. 2016; 60:336–347
Doi:10.1111/jpi.12316

Journal of Pineal Research

Melatonin prevents cisplatin-induced primordial follicle loss via suppression of PTEN/AKT/FOXO3a pathway activation in the mouse ovary



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Jang H et al. J Pineal Research 2016

J. Pineal Res. 2016; 60:336–347
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Journal of Pineal Research

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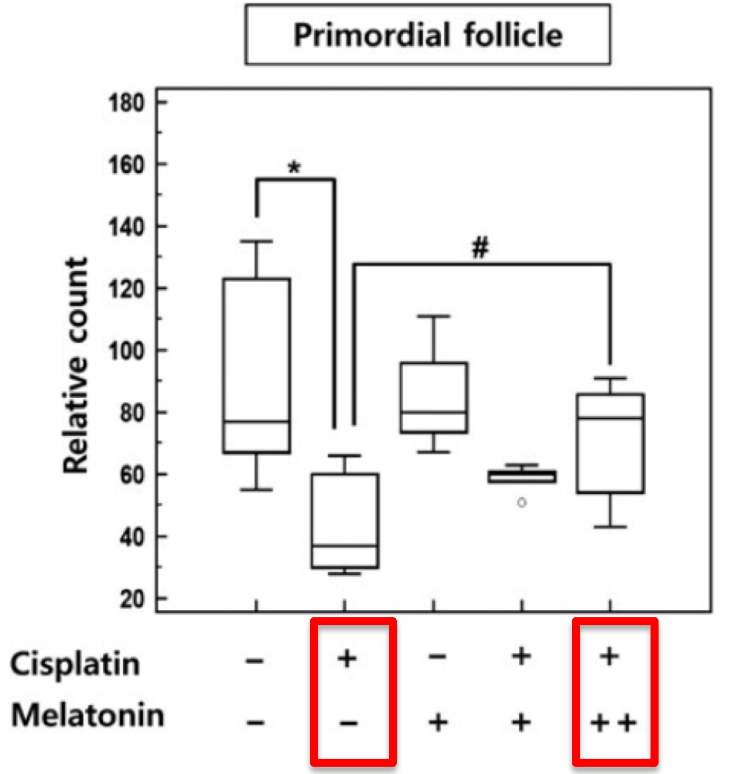

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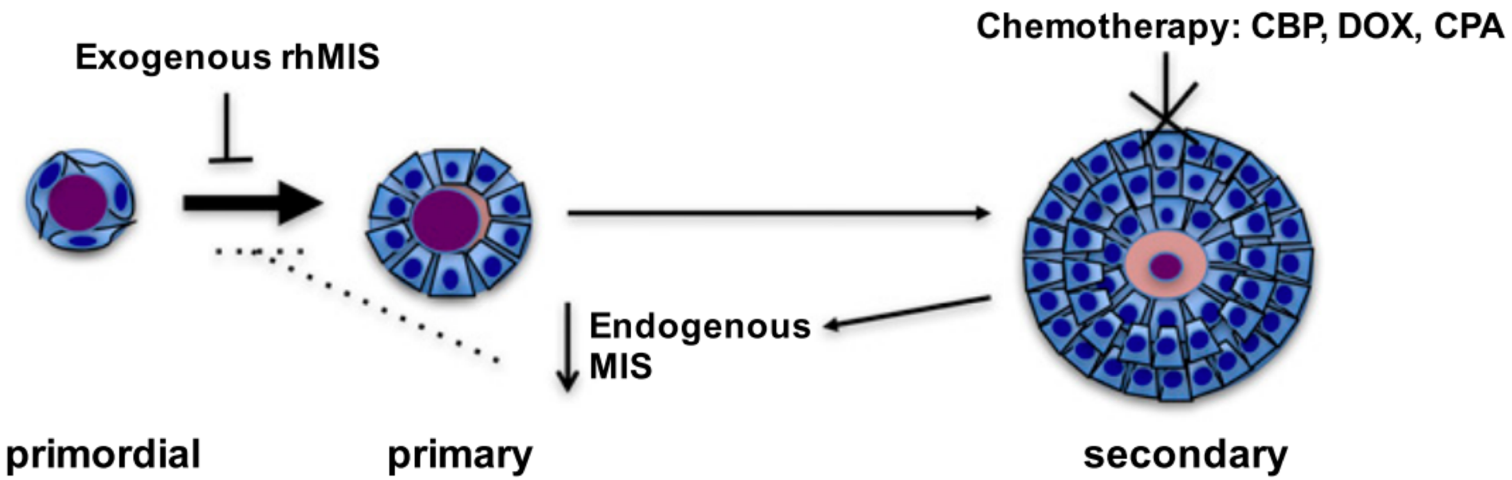
AMH/MIS as a contraceptive that protects the ovarian reserve during chemotherapy

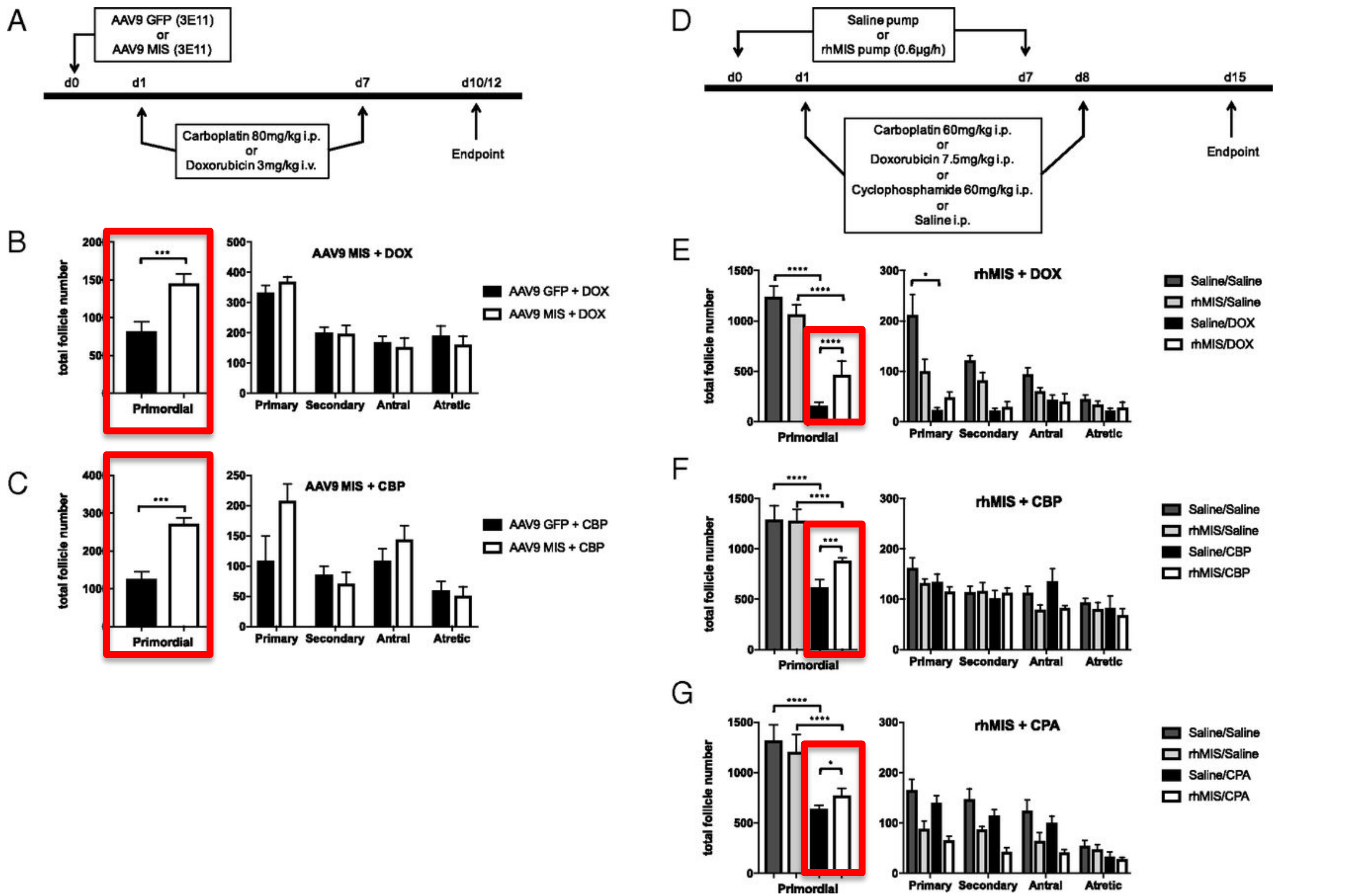
Motohiro Kano[a,b], Amanda E. Sosulski[a,b], LiHua Zhang[a,b], Hatice D. Saatcioglu[a,b], Dan Wang[c], Nicholas Nagykery[a,b], Mary E. Sabatini[d], Guangping Gao[c], Patricia K. Donahoe[a,b,1], and David Pépin[a,b,1]

[a]Pediatric Surgical Research Laboratories, Massachusetts General Hospital, Boston, MA 02114; [b]Department of Surgery, Harvard Medical School, Boston, MA 02115; [c]Horae Gene Therapy Center, University of Massachusetts Medical School, Worcester, MA 01655; and [d]Department of Obstetrics and Gynecology, Harvard Medical School and Massachusetts General Hospital, Boston, MA 02114

Contributed by Patricia K. Donahoe, December 29, 2016 (sent for review December 16, 2016; reviewed by Richard N. Freiman, Bruce D. Murphy, and Teresa K. Woodruff)

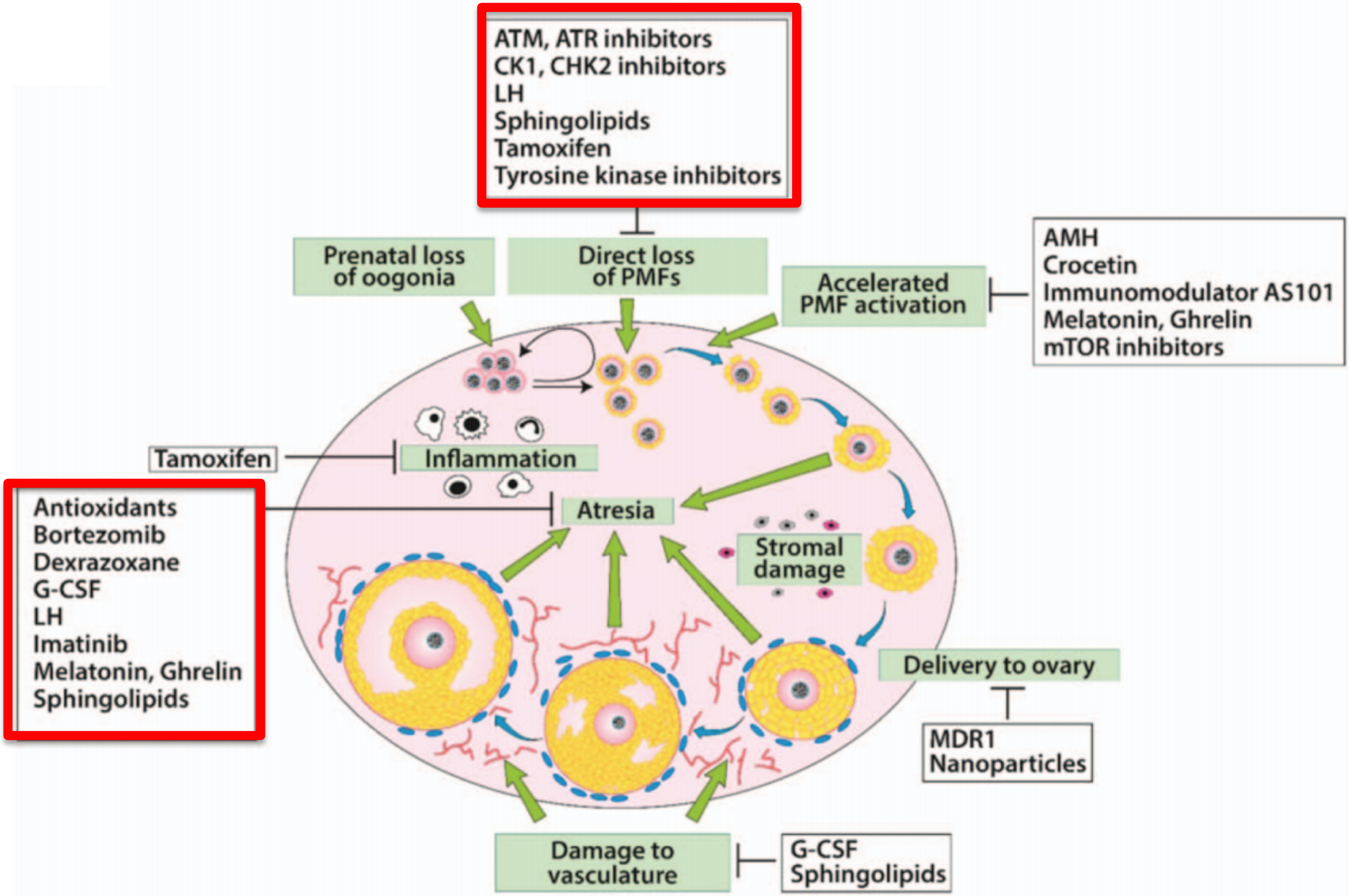


Treatment with MIS protects the ovarian reserve from the primordial follicle depletion induced by chemotherapy



Motohiro Kano et al. PNAS 2017;114:9:E1688-E1697

Growing landscape of pharmacologic fertoprotection

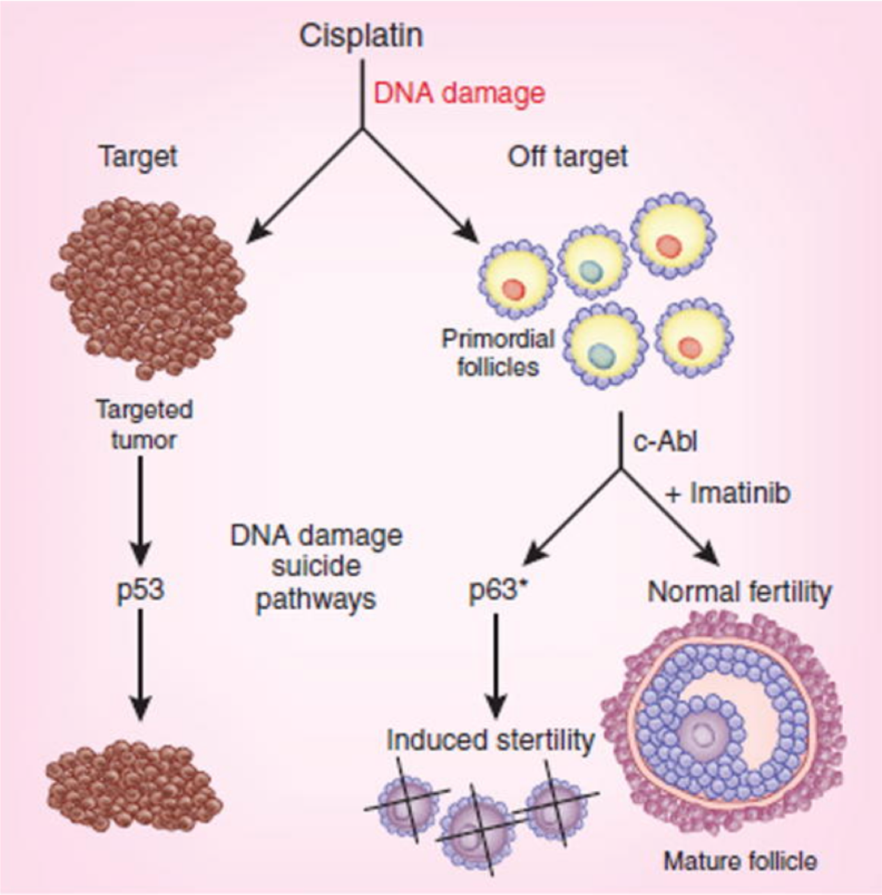


Spears et al. Hum Reprod Update 2019

Inhibition of the c-Abl–TAp63 pathway protects mouse oocytes from chemotherapy-induced death

Stefania Gonfloni, Lucia Di Tella, Sara Caldarola, Stefano M Cannata, Francesca G Klinger, Claudia Di Bartolomeo, Maurizio Mattei, Eleonora Candi, Massimo De Felici, Gerry Melino & Gianni Cesareni

Nature Medicine **15**, 1179–1185(2009) | Cite this article



Northwestern

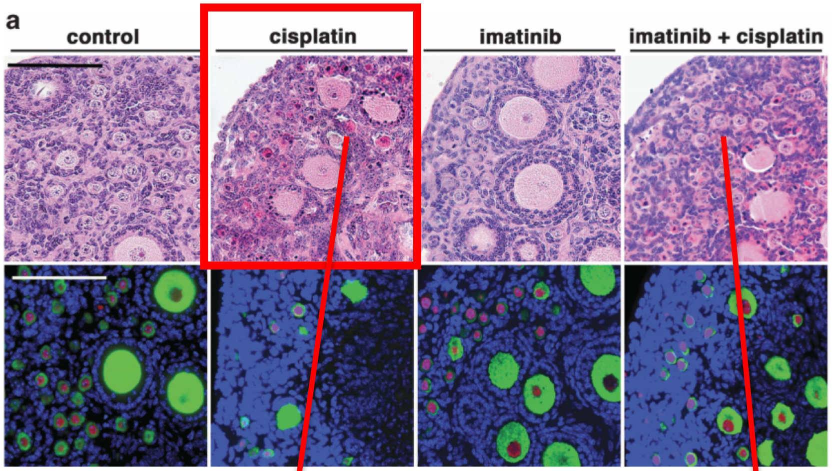
Gonfloni S et al. Nat Med 2009
Woodruff TK Nat Med 2009

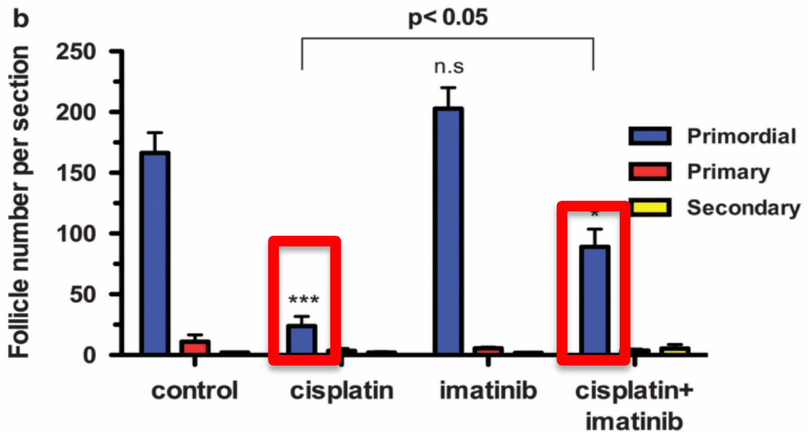
Cell Death and Differentiation (2013) 20, 987–997

1350-9047/13
www.nature.com/cdd

Rescue of platinum-damaged oocytes from programmed cell death through inactivation of the p53 family signaling network

S-Y Kim[1], MH Cordeiro[1], VA Serna[2], K Ebbert[1], LM Butler[2], S Sinha[3], AA Mills[4], TK Woodruff*[,1,5] and T Kurita*[,2,5]





Cisplatin-treated ovaries with damaged follicles (pink cytoplasm, condensed nuclei)

Co-treated mice with healthy appearing PMFs

Northwestern
Kim SY….Woodruff et al. Cell Death Differ 2013

J Endocrinol. 2019 Feb 1;240(2):243-256. doi: 10.1530/JOE-18-0370.

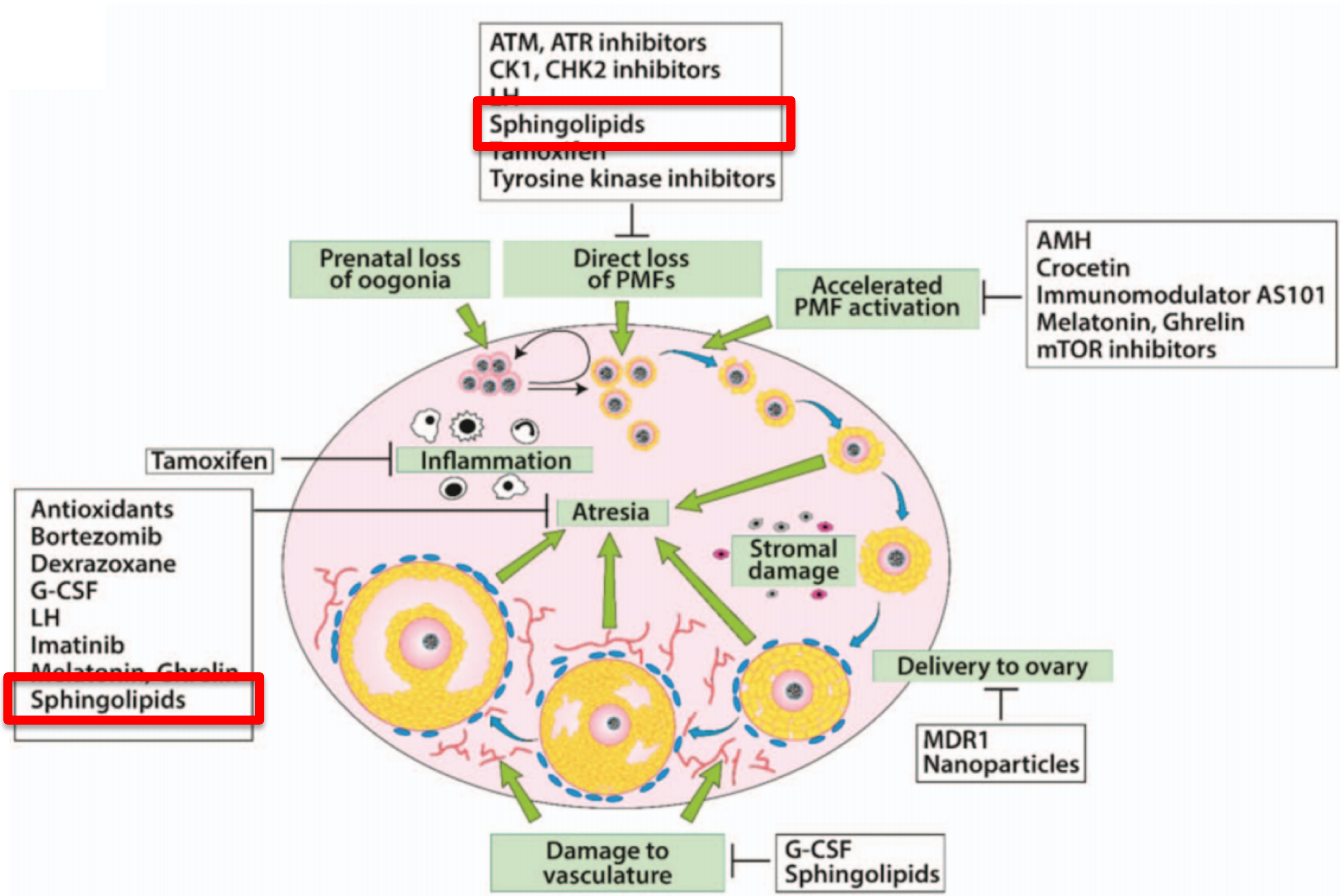
Inhibitors of apoptosis protect the ovarian reserve from cyclophosphamide.

Luan Y[1], Edmonds ME[1], Woodruff TK[1], Kim SY[1,2].

- In vitro evaluation of the effect of CY metabolites in 3 murine strains
  - identified primordial follicle apoptosis
  - Identified phospho-AKT and cleaved PARP within primordial oocytes 3 days after CY injection

Luan Y et al. J Endocrinol 2019

Growing landscape of pharmacologic fertoprotection



Spears et al. Hum Reprod Update 2019

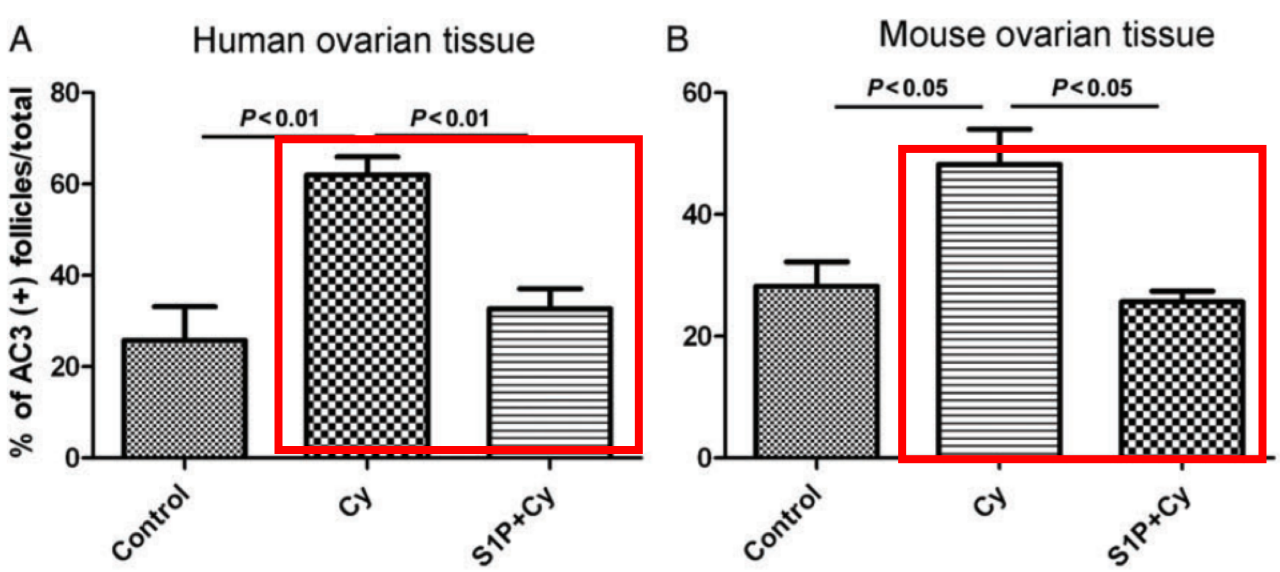
Northwestern

Human Reproduction, Vol.29, No.1 pp. 107–113, 2014
Advanced Access publication on November 12, 2013 doi:10.1093/humrep/det391

human reproduction **ORIGINAL ARTICLE** ***Reproductive biology***

Sphingosine-1-phosphate prevents chemotherapy-induced human primordial follicle death

Fang Li[1,2], Volkan Turan[1,2], Sylvie Lierman[3], Claude Cuvelier[4], Petra De Sutter[3,†], and Kutluk Oktay[1,2,†*]



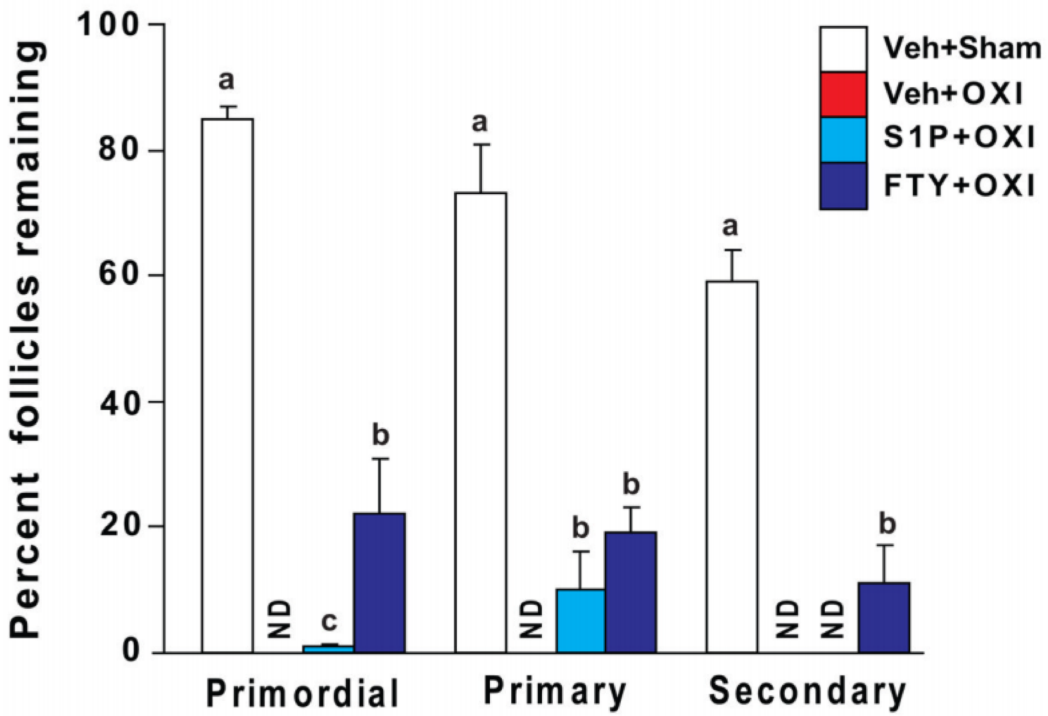
S1P mediated CY-induced apoptosis

Li F et al. Hum Reprod 2014

In-vivo delivery of FTY720 prevents radiation-induced ovarian failure and infertility in adult female non-human primates

Mary B. Zelinski, Ph.D.[a], Mark K. Murphy, M.S.[b], Maralee S. Lawson, B.S.[a], Andrea Jurisicova, Ph.D.[c], K. Y. Francis Pau, Ph.D.[a], Natalia P. Toscano, B.S.[a], Darla S. Jacob, B.S.[d], John K. Fanton, D.V.M.[d], Robert F. Casper, M.D.[c], Stephen D. Dertinger, Ph.D.[e], and Jonathan L. Tilly, Ph.D.[f]

- Intra-bursal S1P and S1P mimetic FTY720 via osmotic mini-pump
  - attenuates radiation-induced oocytes loss in primates

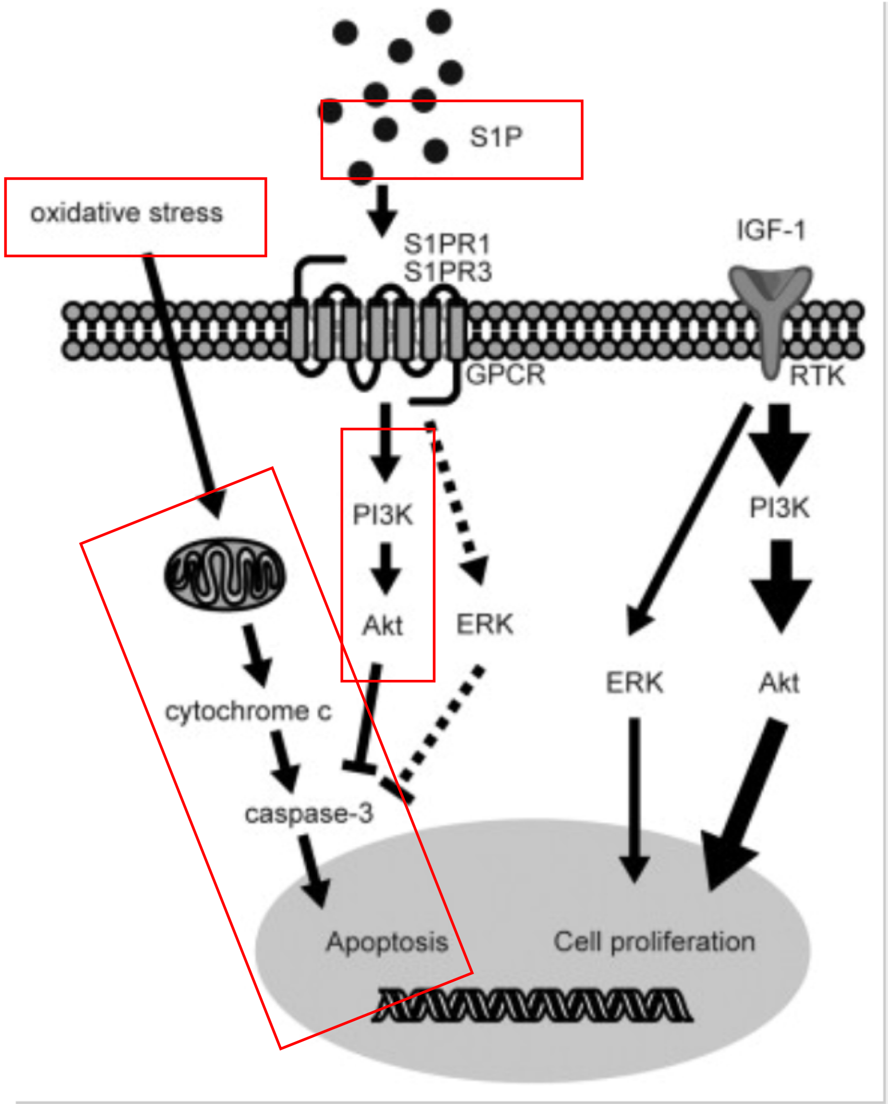


Northwestern

Zelinski et al. Fertil Steril 2011

Oxidative stress, apoptosis, and mTOR

- Oxidative stress induces mitochondrial dysfunction; leads to activation of caspase-3
- S1P may inhibit oxidative stress-induced granulosa cell apoptosis
    - suppressing caspase-3 release via PI3K/AKT signaling pathway



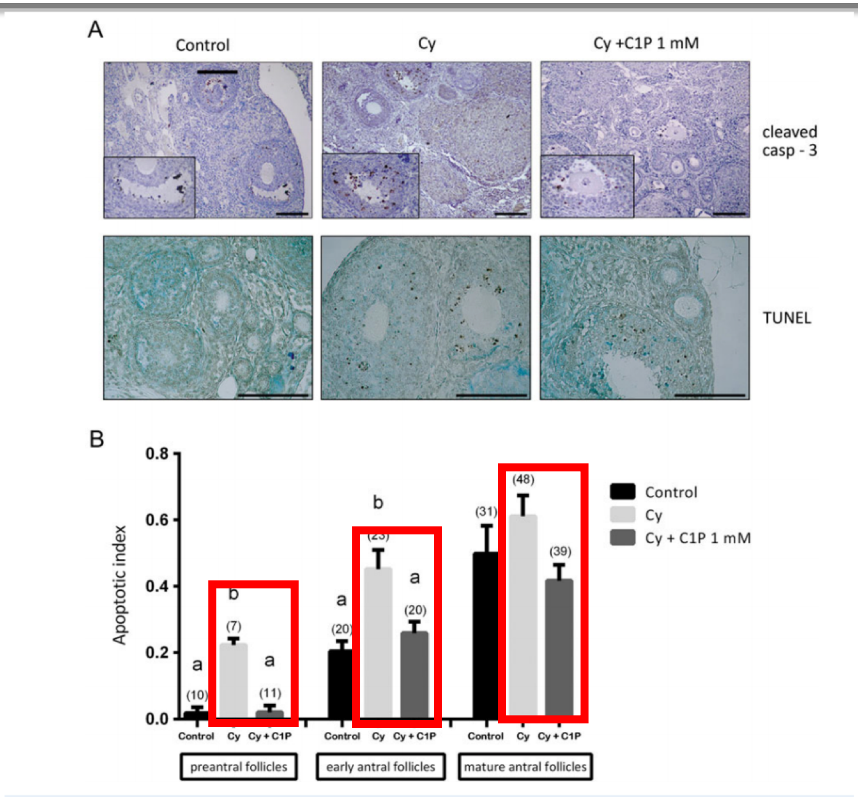
Nakahara 2012 Fertil Steril

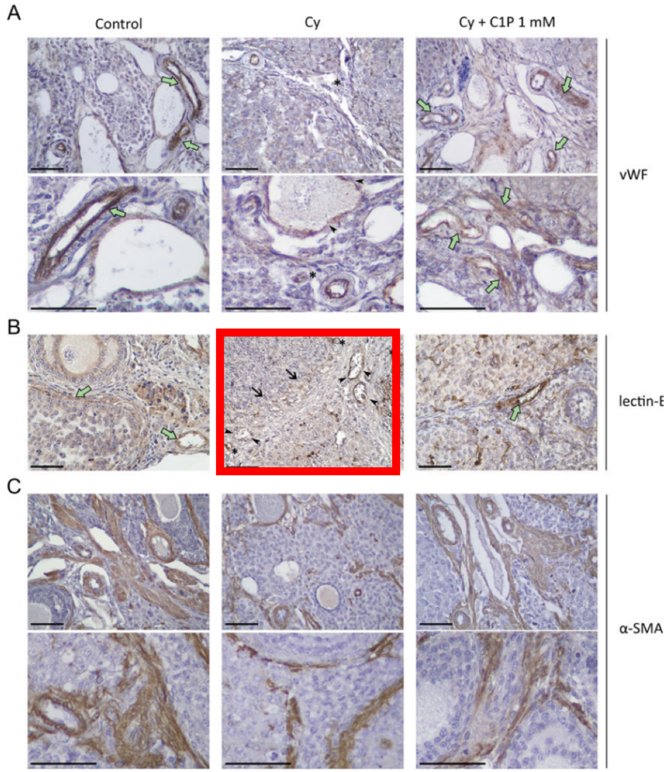
Human Reproduction, Vol.33, No.5 pp. 844–859, 2018
Advanced Access publication on March 9, 2018 doi:10.1093/humrep/dey045

human reproduction ORIGINAL ARTICLE *Infertility*

Ceramide-1-phosphate has protective properties against cyclophosphamide-induced ovarian damage in a mice model of premature ovarian failure

Natalia Pascuali[1], Leopoldina Scotti[1], Mariana Di Pietro[1], Gonzalo Oubiña[1], Diana Bas[1], María May[2], Antonio Gómez Muñoz[3], Patricia S. Cuasnicú[1], Débora J. Cohen[1], Marta Tesone[1], Dalhia Abramovich[1], and Fernanda Parborell[1,*]





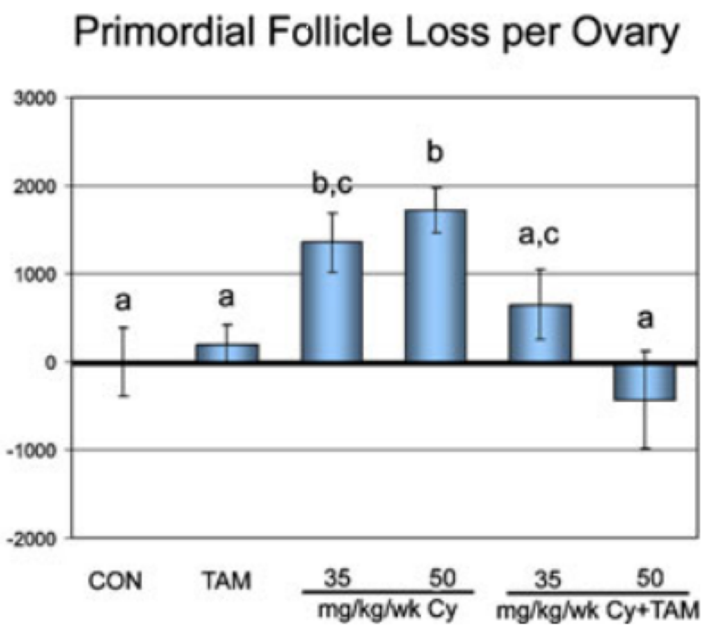
C1P decreased CY-induced apoptosis and reduced CY-induced stromal vascular damage

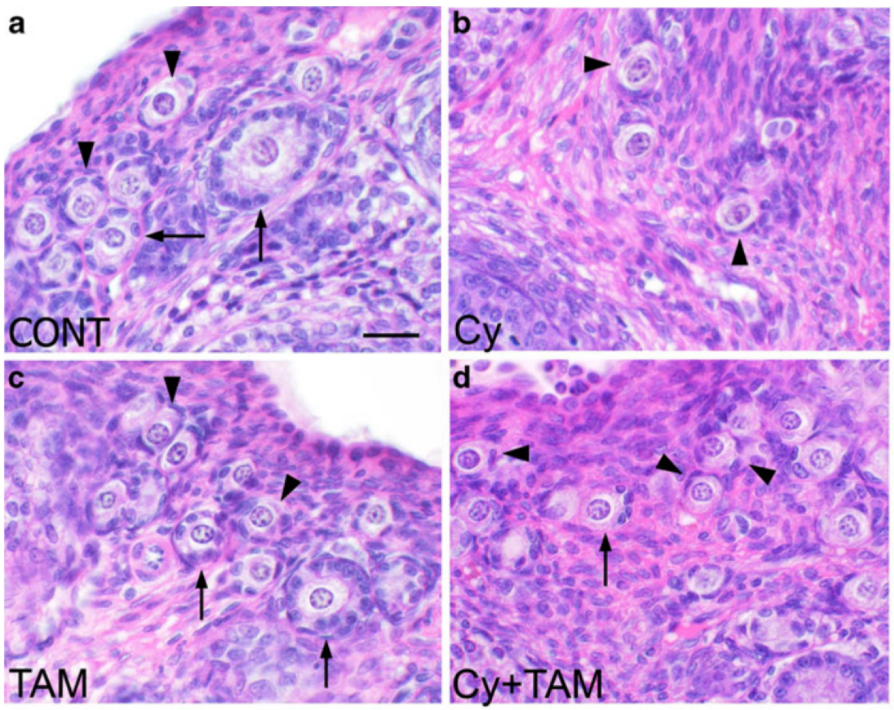
J Assist Reprod Genet (2010) 27:591–597
DOI 10.1007/s10815-010-9463-y

FERTILITY PRESERVATION

Tamoxifen decreases ovarian follicular loss from experimental toxicant DMBA and chemotherapy agents cyclophosphamide and doxorubicin in the rat

Alison Y. Ting · Brian K. Petroff





Ting and Petroff. JARG 2010

Table II Agents used to protect ovaries from chemotherapy-induced damage.

Protectant	Drug	Target action	Species	Reference
AMH/MIS	CPM	Accelerated PMF activation	Mouse	Kano et al. 2016
	DOX			Sonigo et a.l 2018
	Carboplatin			
ATM inhibitors:	CIS	Direct loss of PMFs	Mouse	Tuppi et al. 2018
ETP-46464	DOX			Kim et al. 2018
KU55399				
ATR inhibitors:	CIS	Direct loss of PMFs	Mouse	Kim et al. 2018
ETP-46464	DOX			Luan et al. 2019
AZD6738	CPM			
AS101	CPM	Accelerated PMF activation	Mouse	Kalich-Philosoph et al. 2013
				Di Emidio et al. 2017
Bortezomib	DOX	Atresia	Mouse	Roti Roti et al. 2014
Ceramide-1-phosphate	CPM	Direct loss of PMFs	Mouse	Pascuali et al. 2018
		Atresia		
		Vascularization		
CHK2 inhibitors:	CIS	Direct loss of PMFs	Mouse	Rinaldi et al. 2017
BML277	DOX			Tuppi et al. 2018
LY2603618	CPM			Luan et al. 2019
LY2606368				
CK1 inhibitors:	CIS	Direct loss of PMFs	Mouse	Tuppi et al. 2018
MK-8776	DOX			
CHIR-124				
PMF670462				
PMF4800567				
PMF5006739				
Crocetin	CPM	Accelerated PMF activation	Mouse	Di Emidio et al. 2017
Dexrazoxane	DOX	Atresia	Mouse	Kropp et al. 2015
Ghrelin	CIS	Accelerated PMF activation	Mouse	Jang et al. 2017
G-CSF	CIS	Atresia	Mouse	Skaznik-Wikiel et al. 2013
		Vascularisation		Akdemir et al. 2014
Imatinib	CIS	Direct loss of PMFs	Mouse	Kim et. 2013
		Atresia		Maiani et al. 2012
				Zamah et al. 2011
				Rinaldi et al. 2017
				Tuppi et al. 2018
				Gonfloni et al. 2009
				Kim et al. 2018
Luteinizing Hormone	CIS	Direct loss of PMFs	Mouse	Rossi et al. 2017
		Atresia		Tuppi et al. 2018
MDR1	CPM	Delivery to ovary	Mouse	Brayboy et al. 2013; 2017
				Salih 2011
				Wang et al. 2018
Melatonin	CIS	Accelerated PMF activation	Mouse	Jang et al. 2016
Mesna	CIS	Atresia	Rat	Li et al. 2013
Mirtazapine	CIS	Atresia	Rat	Altuner et al. 2013
mTORC inhibitors:	CPM	Accelerated PMF activation	Mouse	Adhikari et al. 2013
Everolimus (RAD001)	CIS			Goldamn et al. 2017
INK128				Zhou et al. 2017
Rapamycin				Tanaka et al. 2018
Resveratrol	CIS	Atresia	Rat	Ozcan et al. 2015
Sphingosine-1- phospate	CPM	Direct loss of PMFs	Mouse	Morita et al.2000
			Rat	Li et al. 2017
			Human	Li et al. 2014
				Meng et al. 2014
Sildenafil Citrate	CIS	Atresia	Rat	Taskin et al. 2015
Tamoxifen	CPM	Direct loss of PMFs	Rat	Ting and Petroff 2010
		Inflammation	Human	Piasecka-Srader et al. 2015
				Sverrisdottir et al. 2009
				Sverrisdottir et al. 2011

Table II Continued

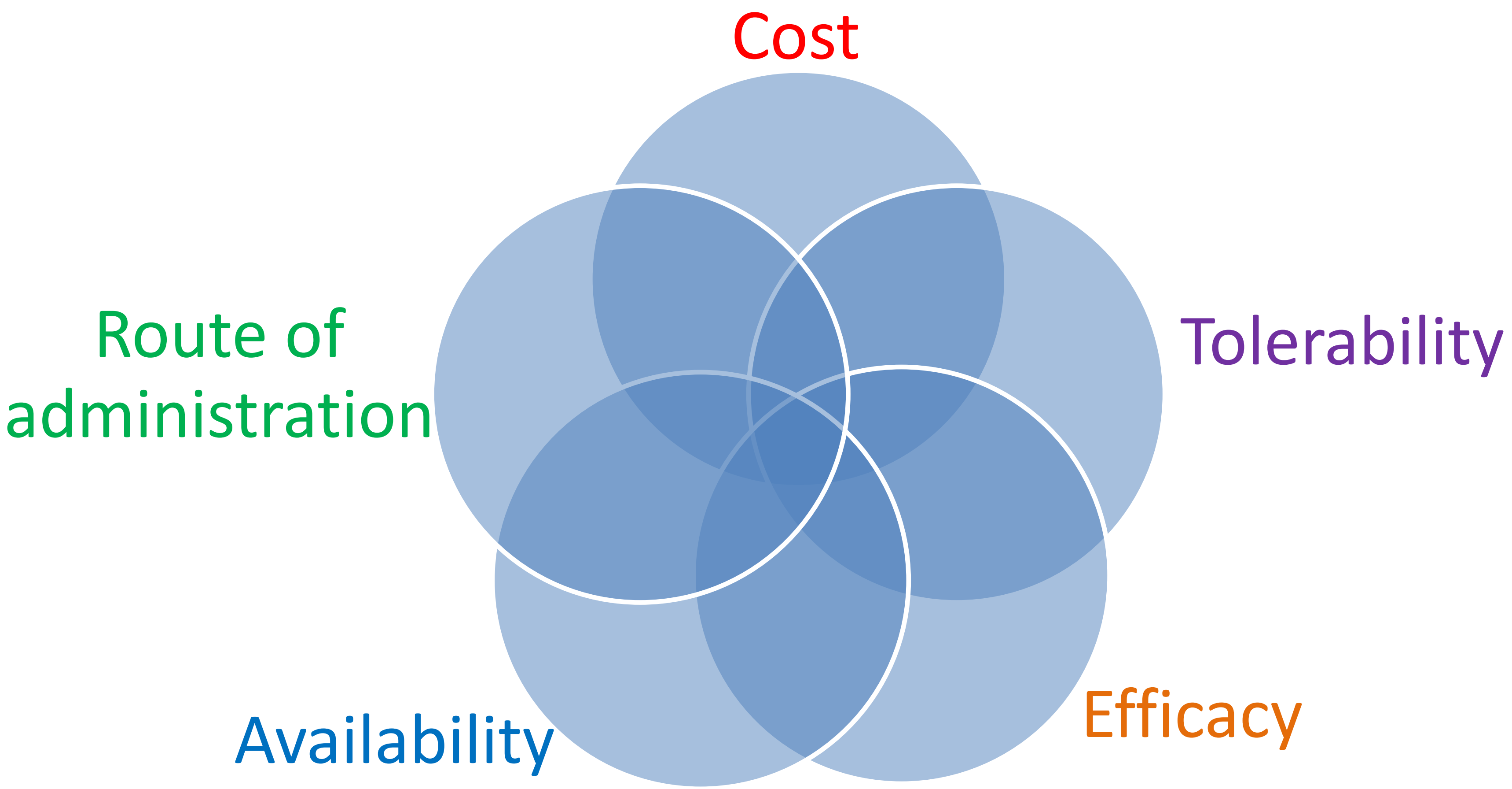
Rapidly growing field of fertoprotection

Spears et al. Hum Reprod Update 2019

Limitations of existing data

- Pre-clinical
- Highly heterogeneous studies
  - Timing of administration
  - Animal models
  - Chemotherapy regimens

Qualities important in a fertoprotective agent



Re-purposed drugs?

PNAS

A win-win for women's reproductive health: A nonsteroidal contraceptive and fertoprotective neoadjuvant

Teresa K. Woodruff[a,1]

PNAS | February 28, 2017 | vol. 114 | no. 9 | 2101–2102

(and a word of cautious optimism):

"In the case of a fertoprotective therapy… we may protect the oocyte from death but damage to the germline may persist, increasing the likelihood of birth defects."

- Teresa K. Woodruff, PhD

Thank you

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Abhi Ghilash

Alliance for Fertility Preservation

Joyce Reineke, JD

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