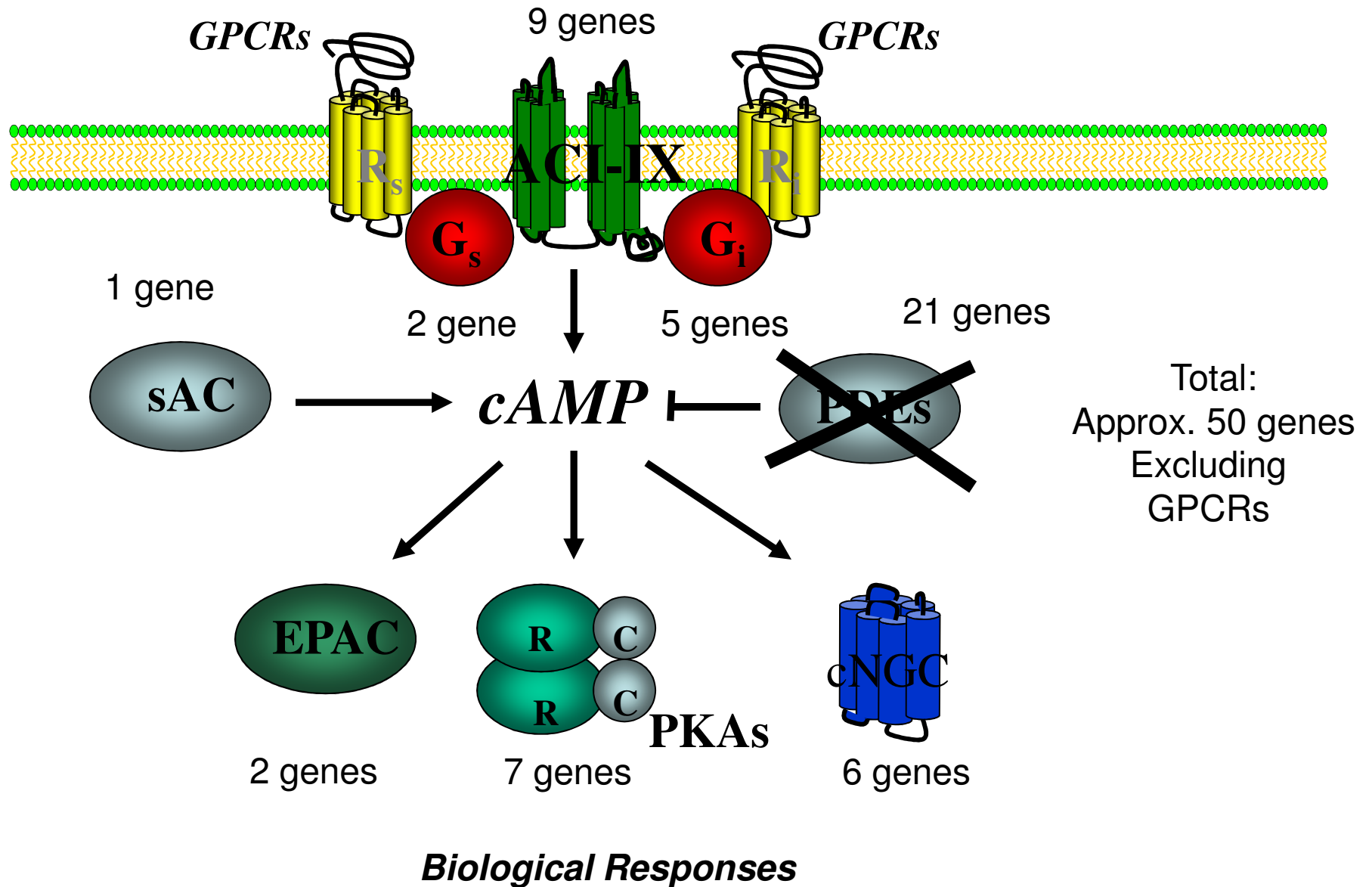


Regulatory signaling mechanisms during ovulation

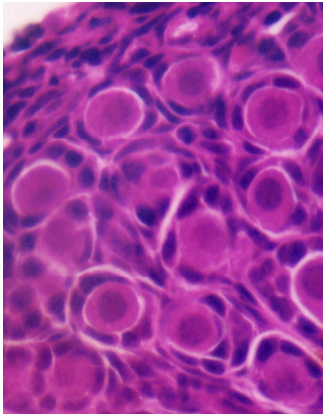
Marco Conti

Center for Reproductive Sciences
Department of Obstetrics and Gynecology
University of California at San Francisco

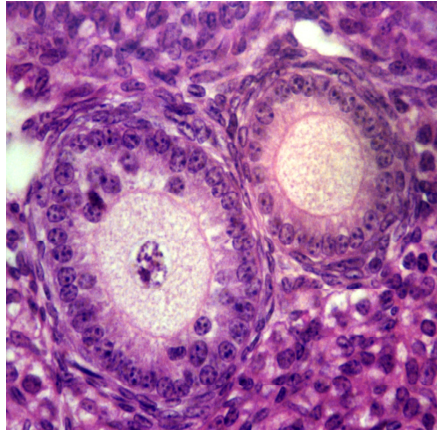
The cAMP signaling module



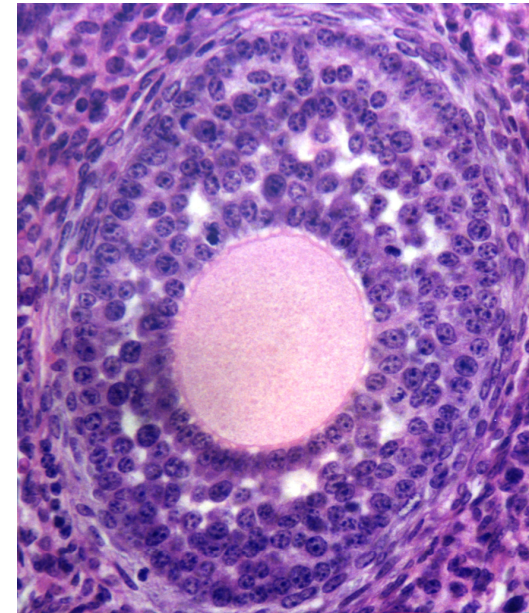
Primordial



**Primary,
Secondary**



Preamtral

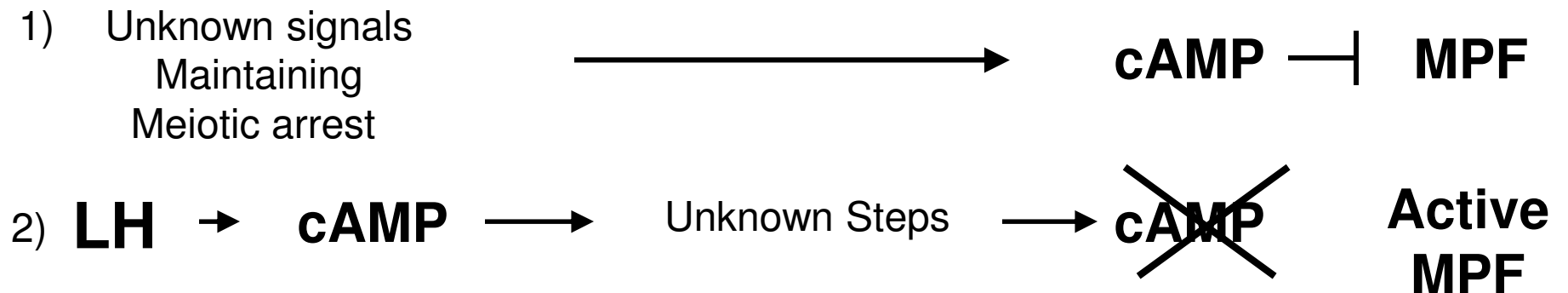
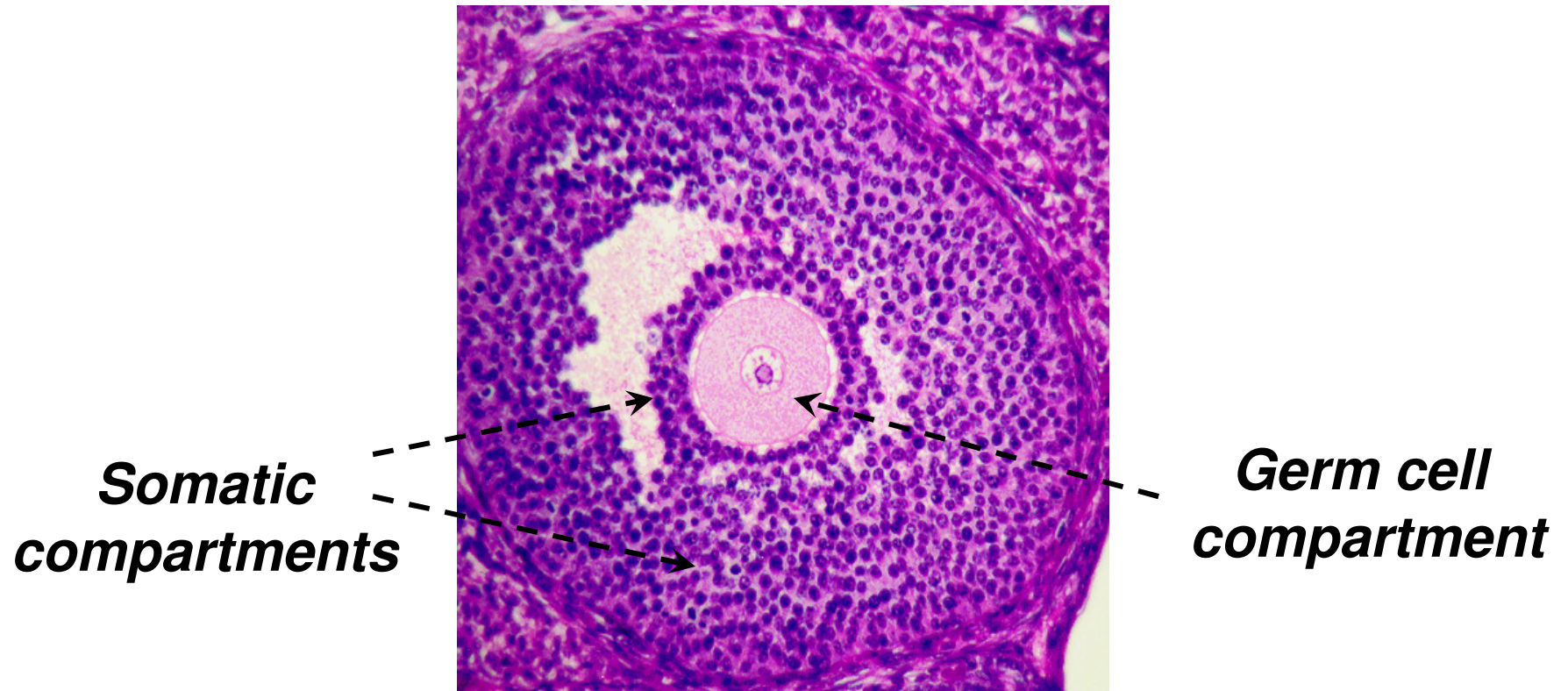


Antral follicle

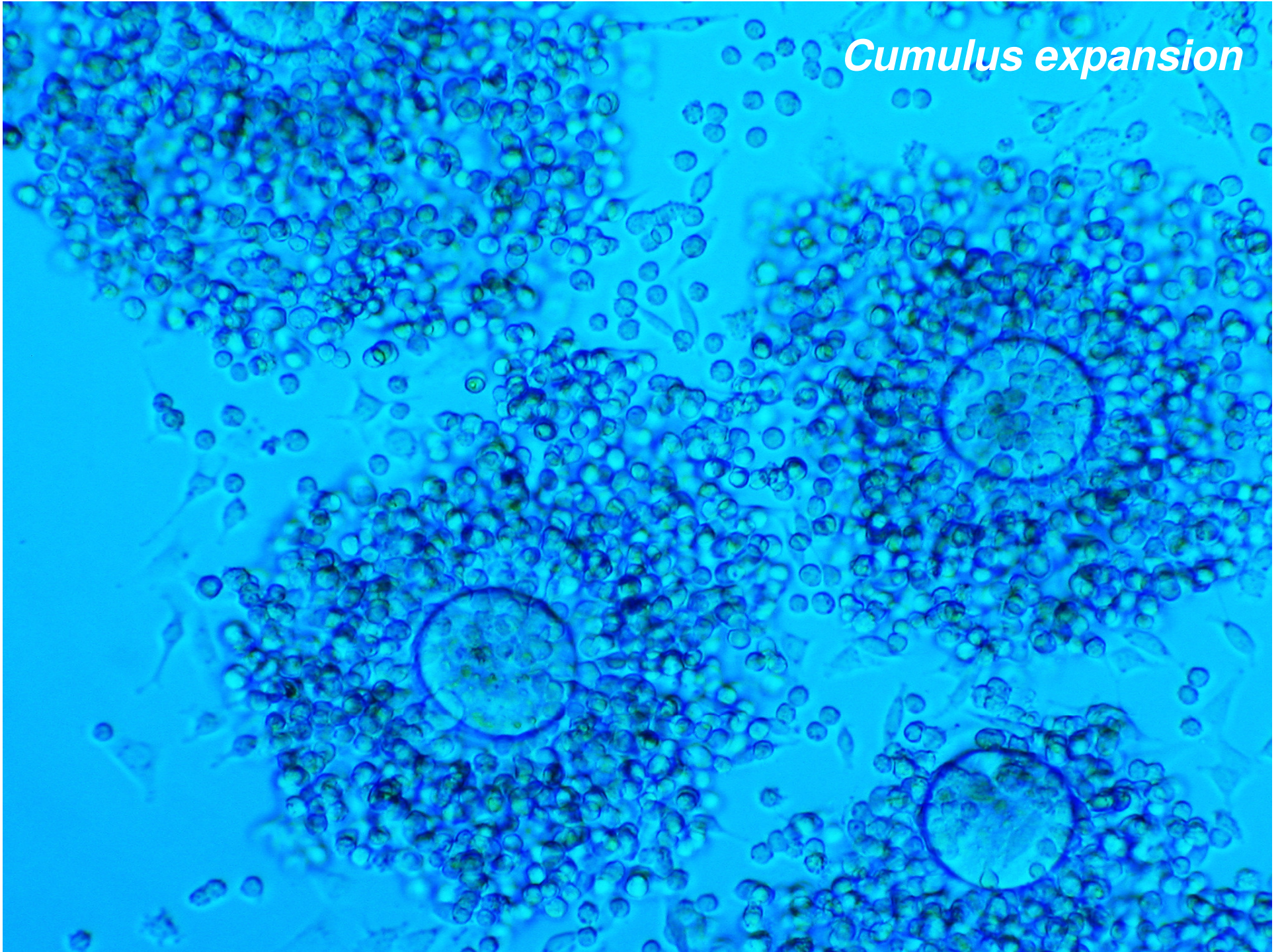


***The life cycle
of the ovarian
follicle***

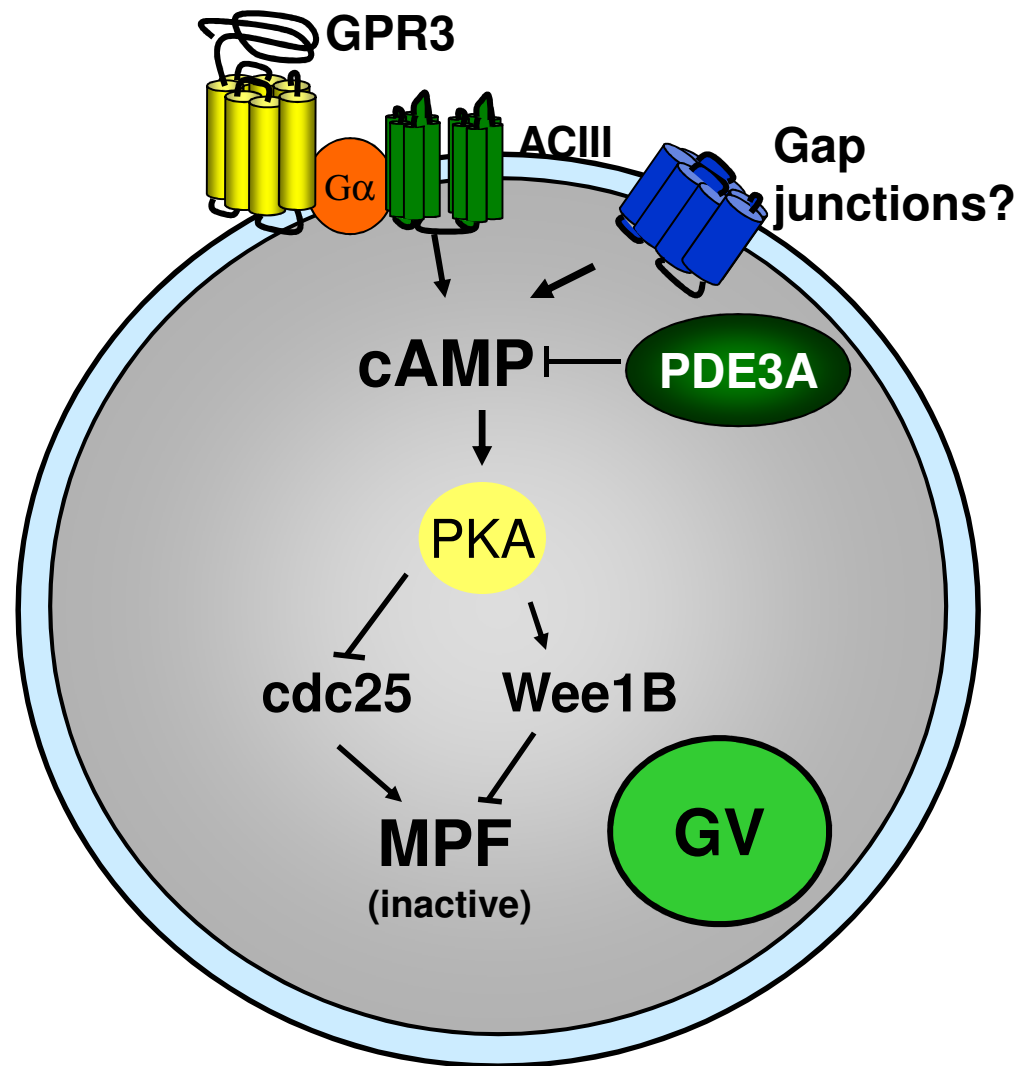
Signaling pathways involved in oocyte maturation and ovulation



Cumulus expansion

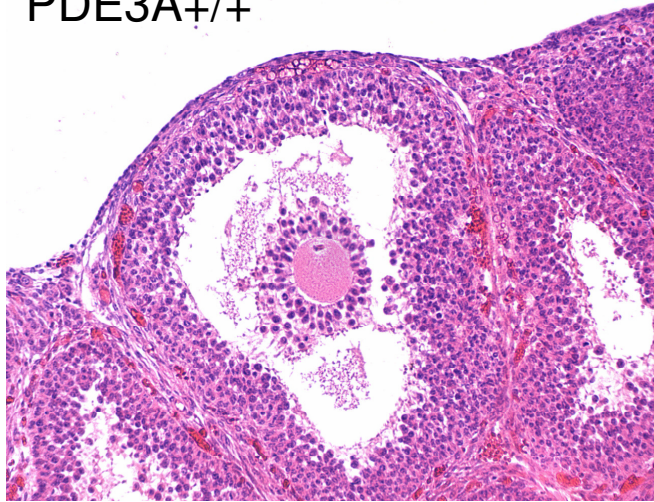


The signaling cascade controlling meiotic arrest in mammalian oocytes

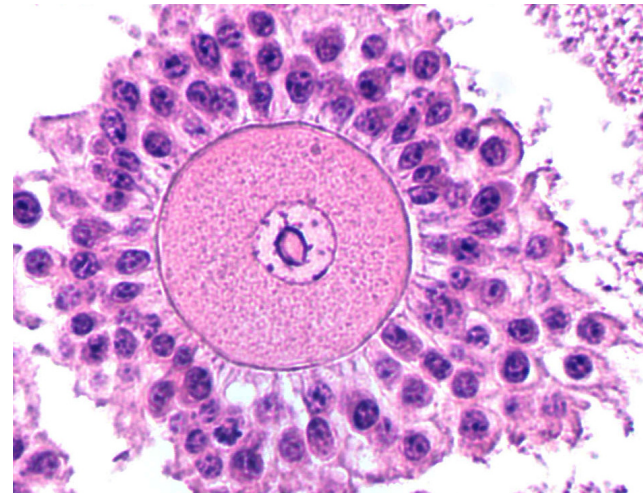
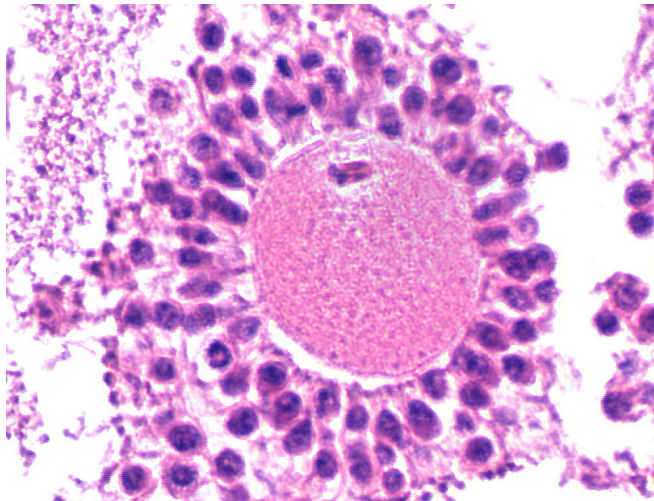
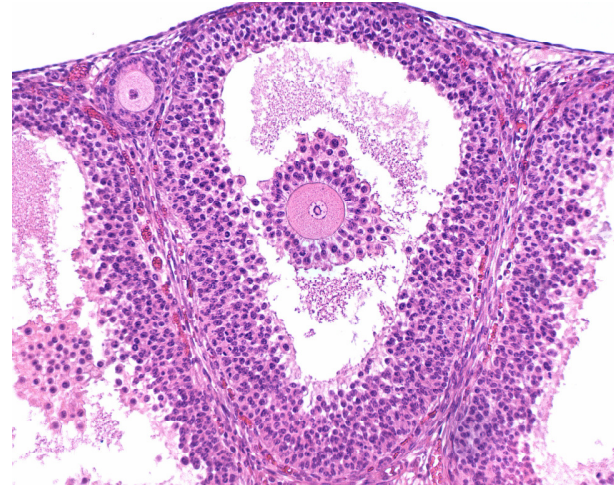


Dissociation of Cumulus Expansion and Oocyte Maturation in the PDE3A^{-/-} Mice

PDE3A^{+/+}



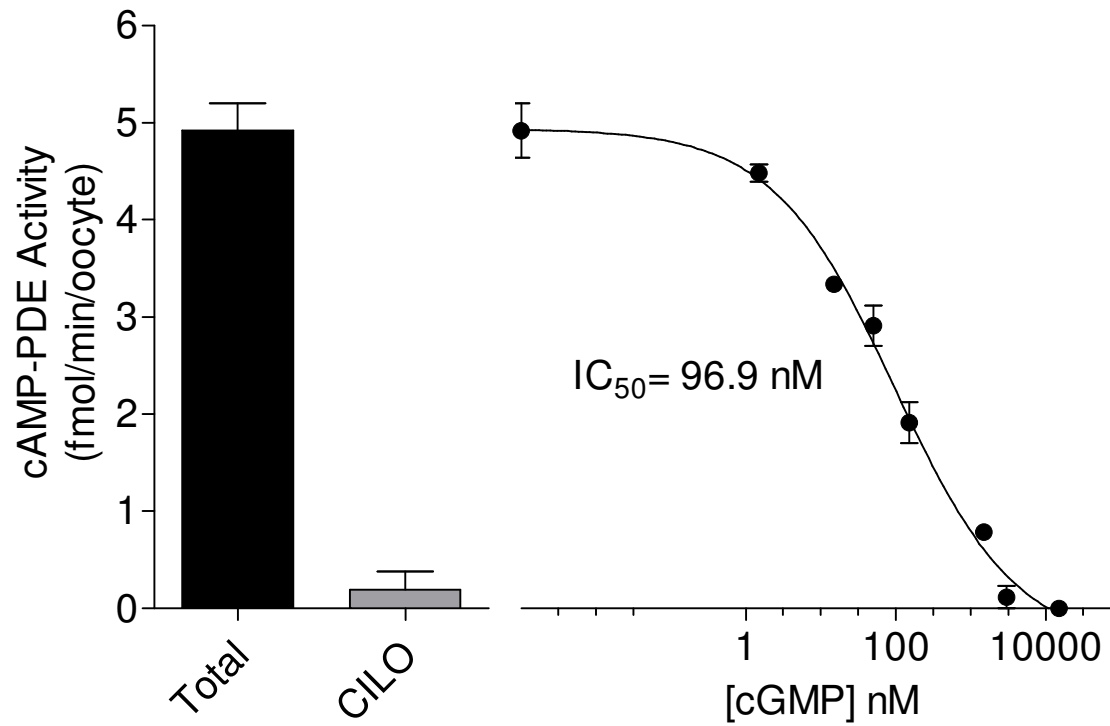
PDE3A^{-/-}



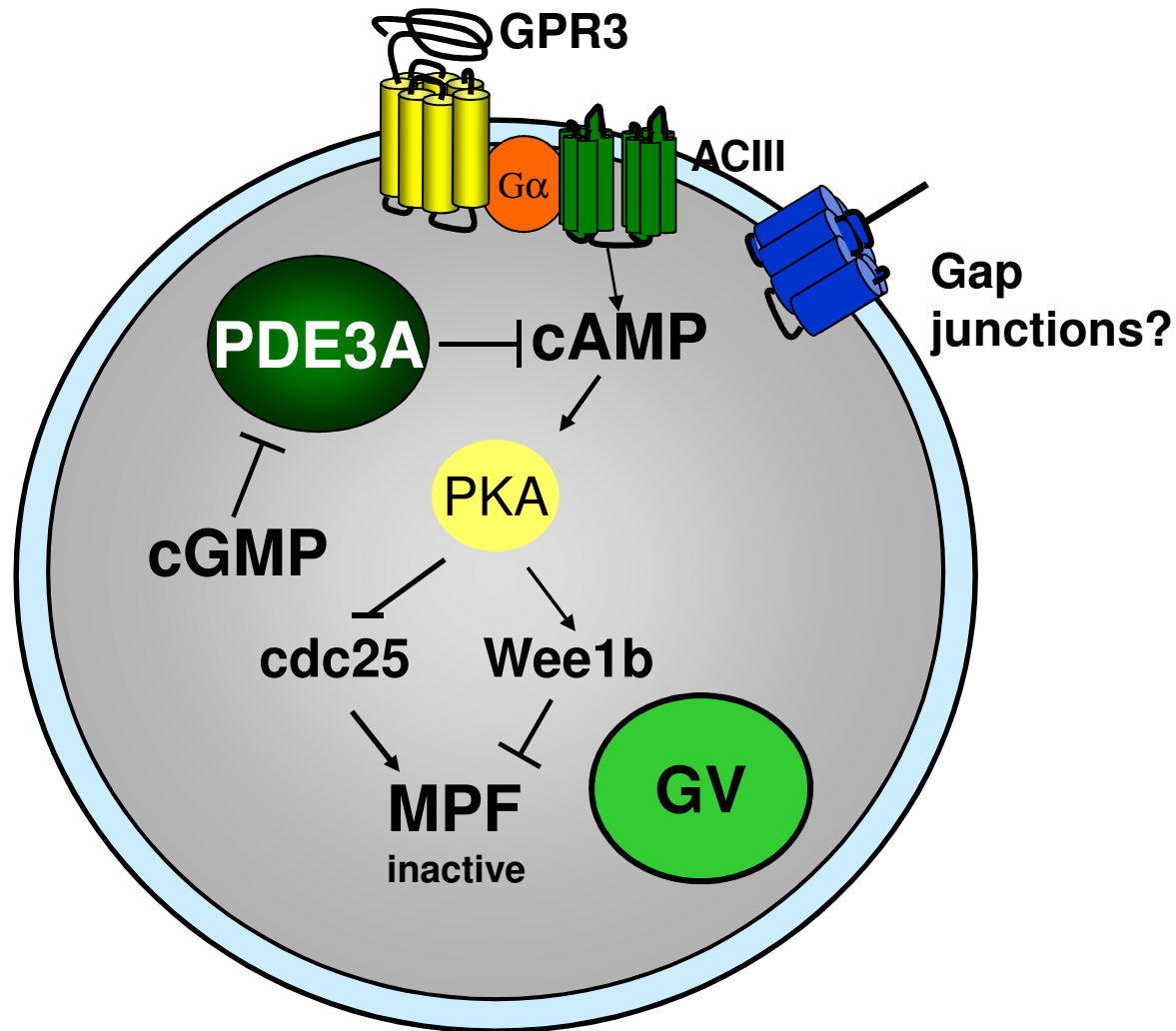
PDE3A and oocyte maturation

- PDE3A null female mice are sterile
- PDE3A null oocytes fail to undergo meiotic maturation
- Maturation of PDE3A null oocytes can be rescued by expression of PDE3A, downregulation of GPR3, blockade of PKA or overexpression of CDC25.

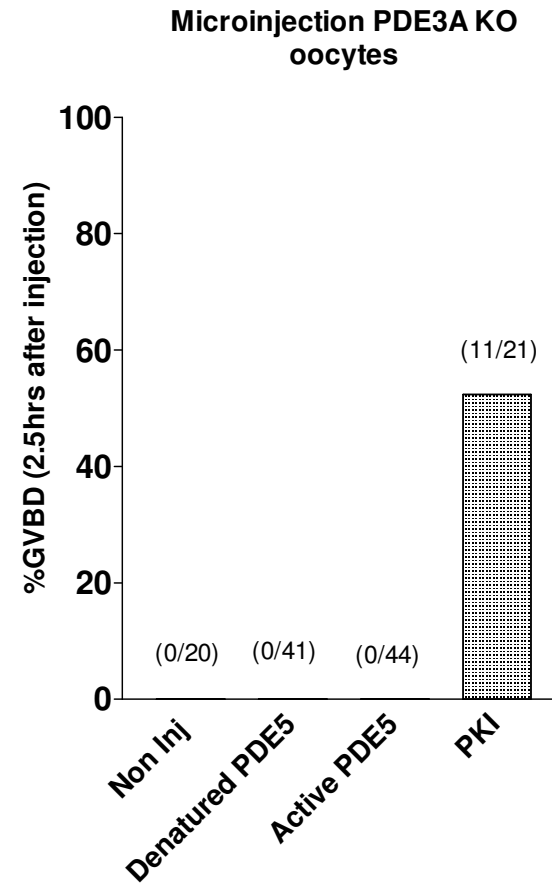
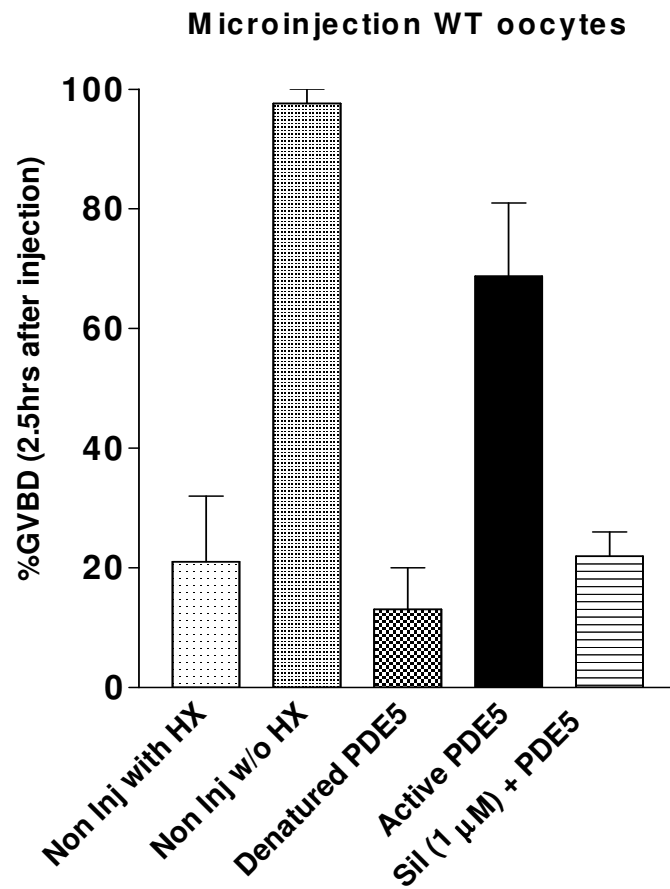
The oocyte cAMP PDE activity is inhibited by cGMP



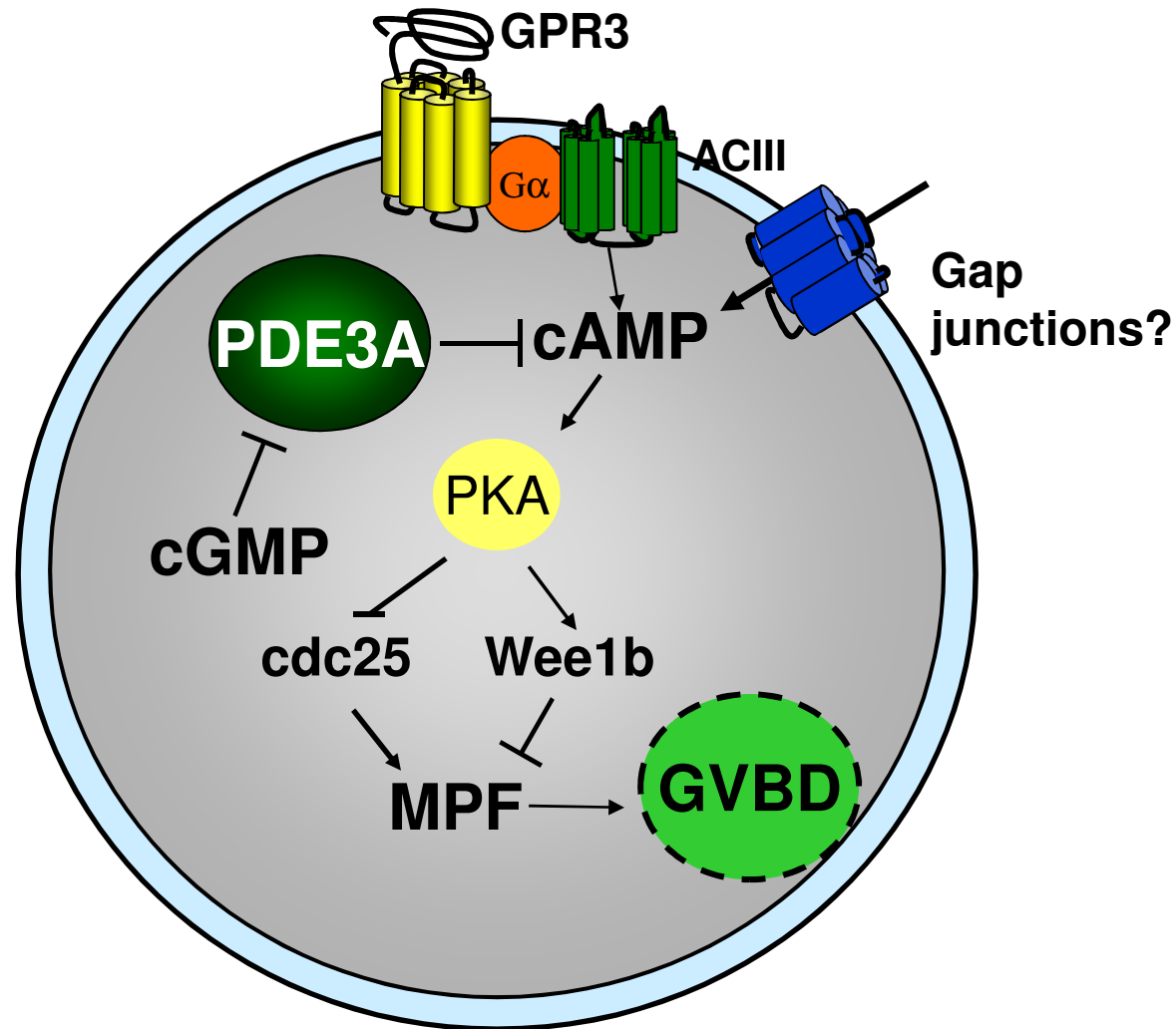
Is a pool of cGMP also involved in maintenance of meiotic arrest?



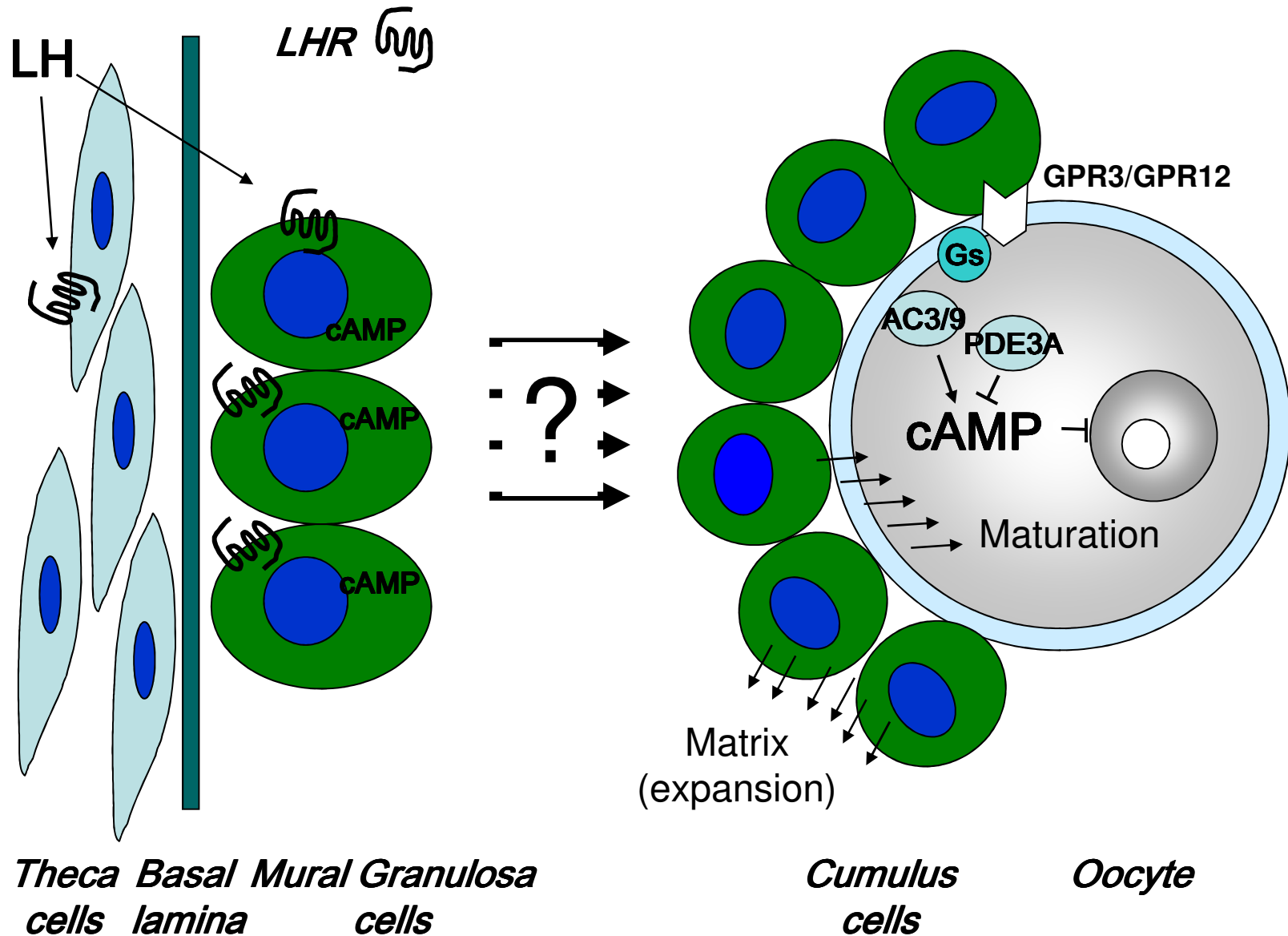
cGMP in the oocyte contributes to meiotic arrest and the effect requires PDE3A



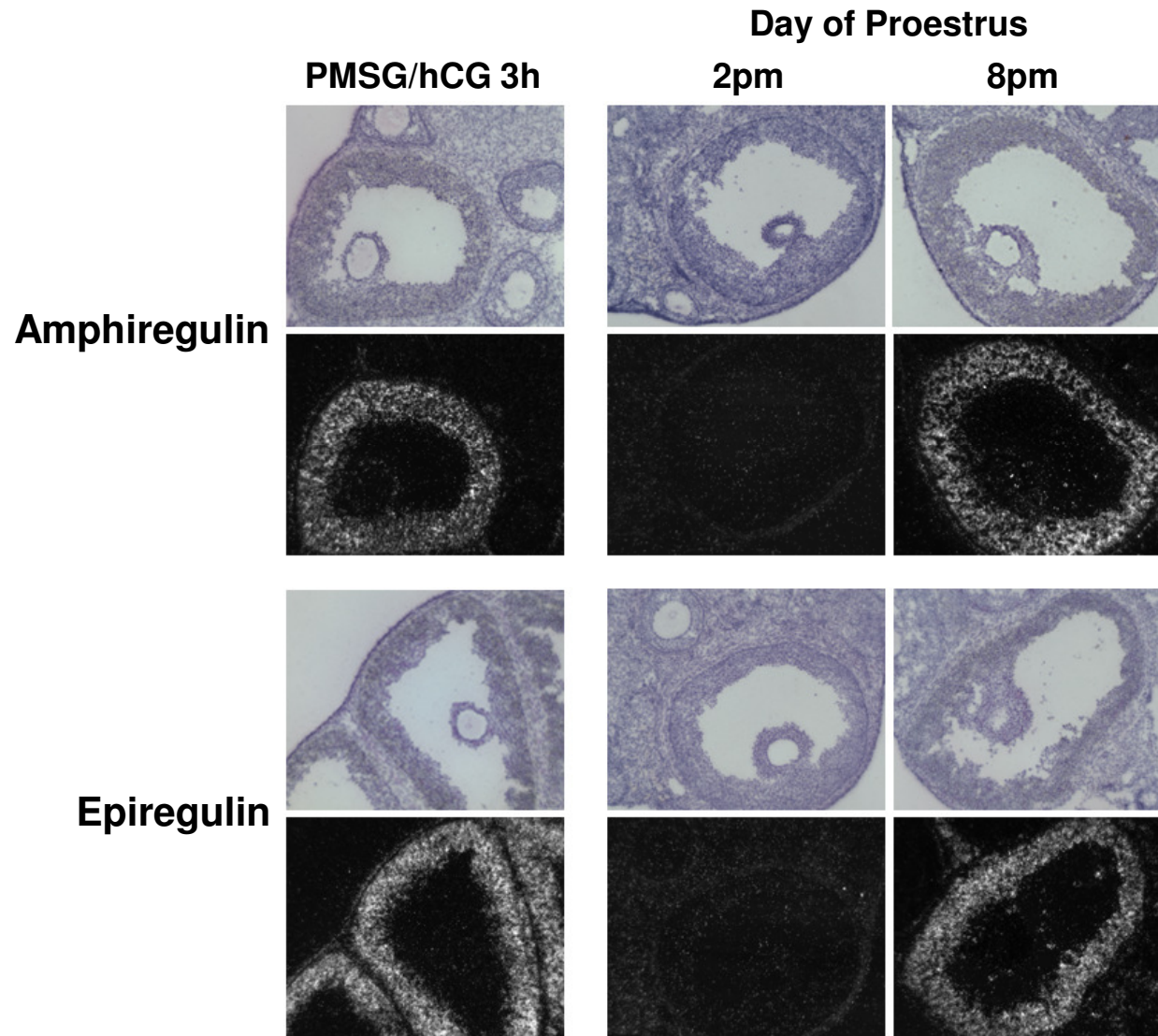
Are changes in cGMP involved in promoting meiotic maturation?



LH Action in the Follicle

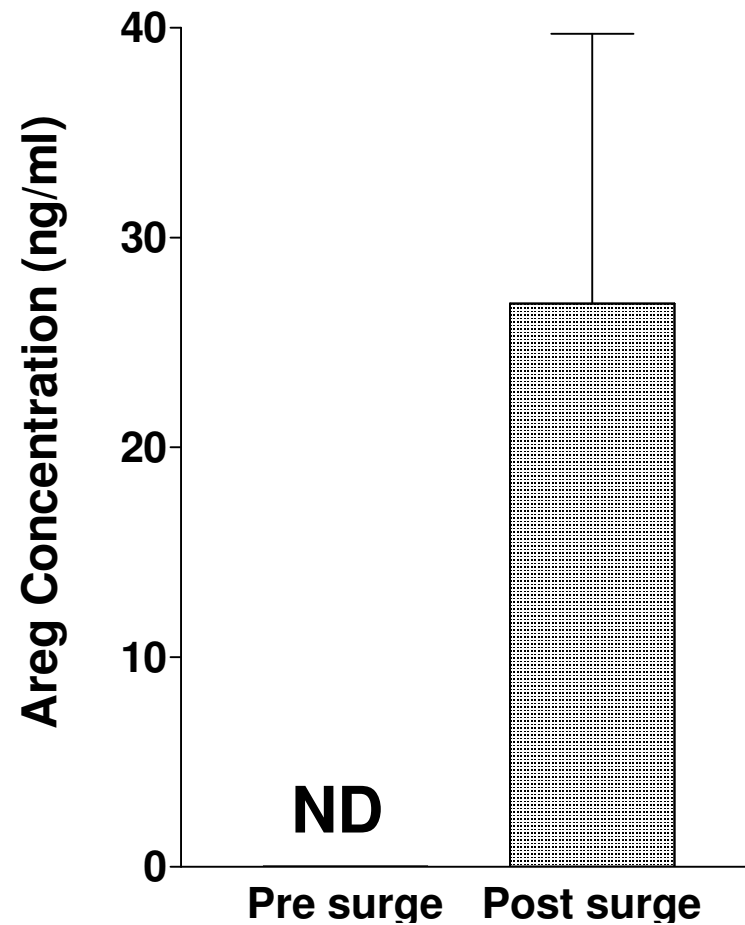
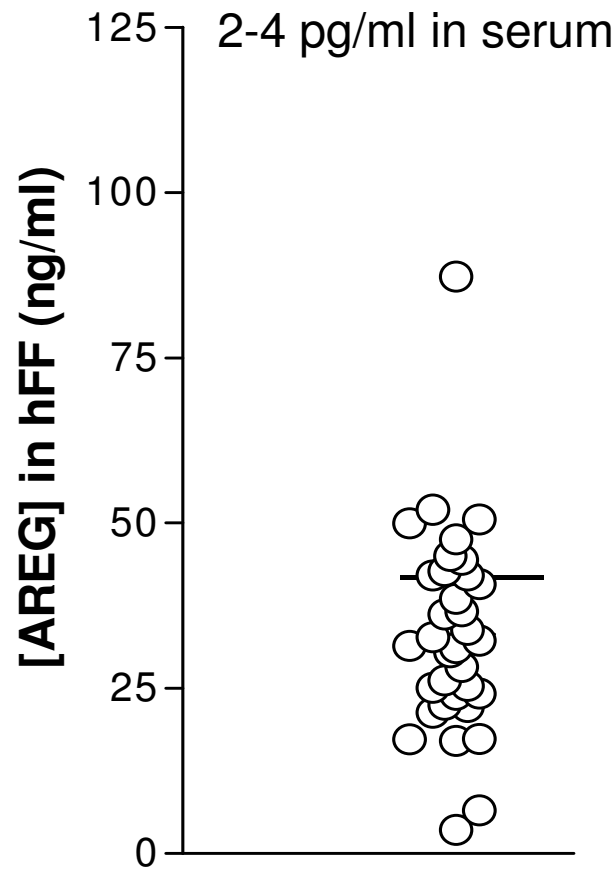


Amphiregulin and Epiregulin are Expressed in the Adult Mouse Ovary During the Normal Estrous Cycle

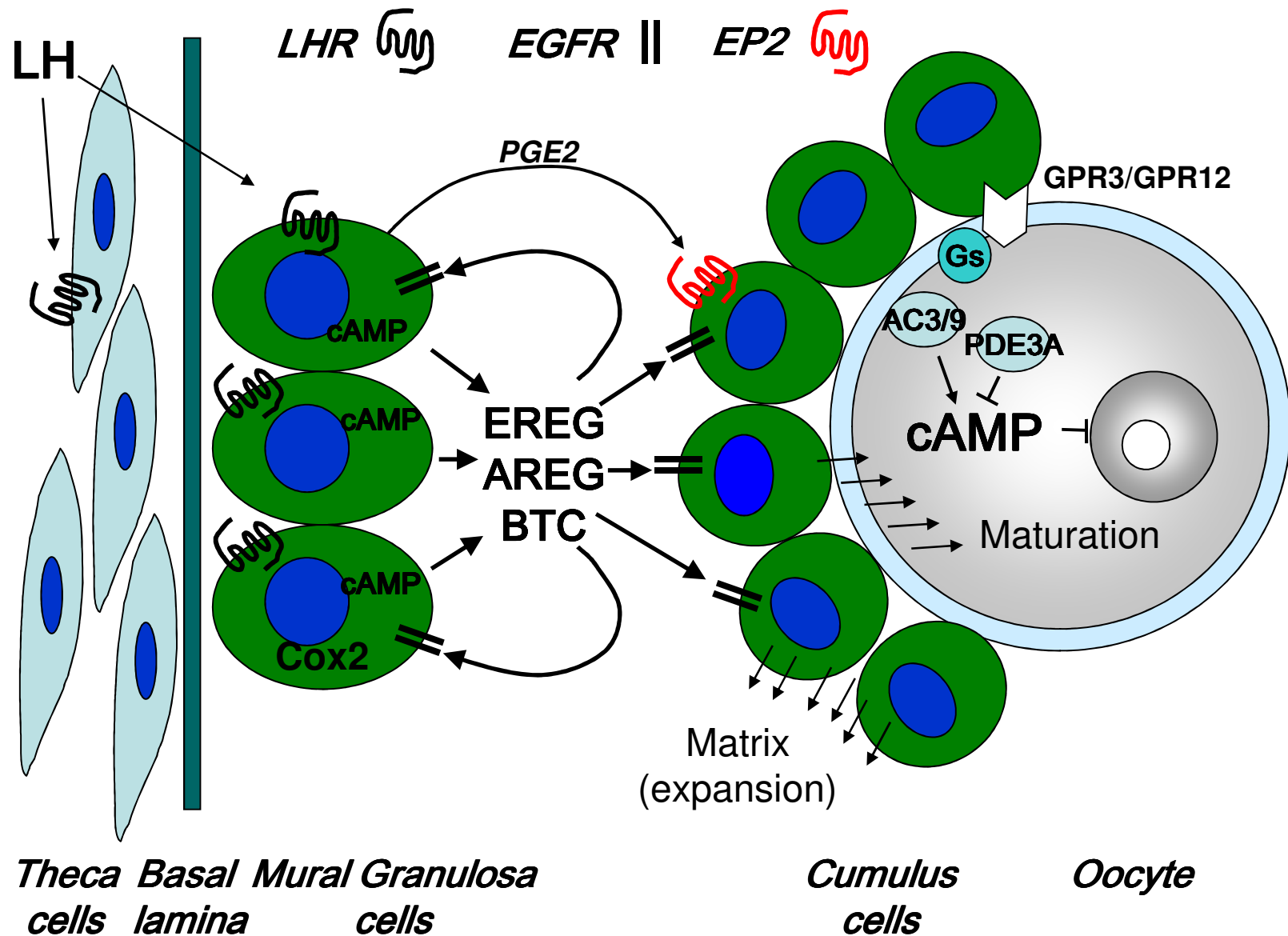


Amphiregulin accumulates at high levels in the follicular fluid of human ovulatory follicles

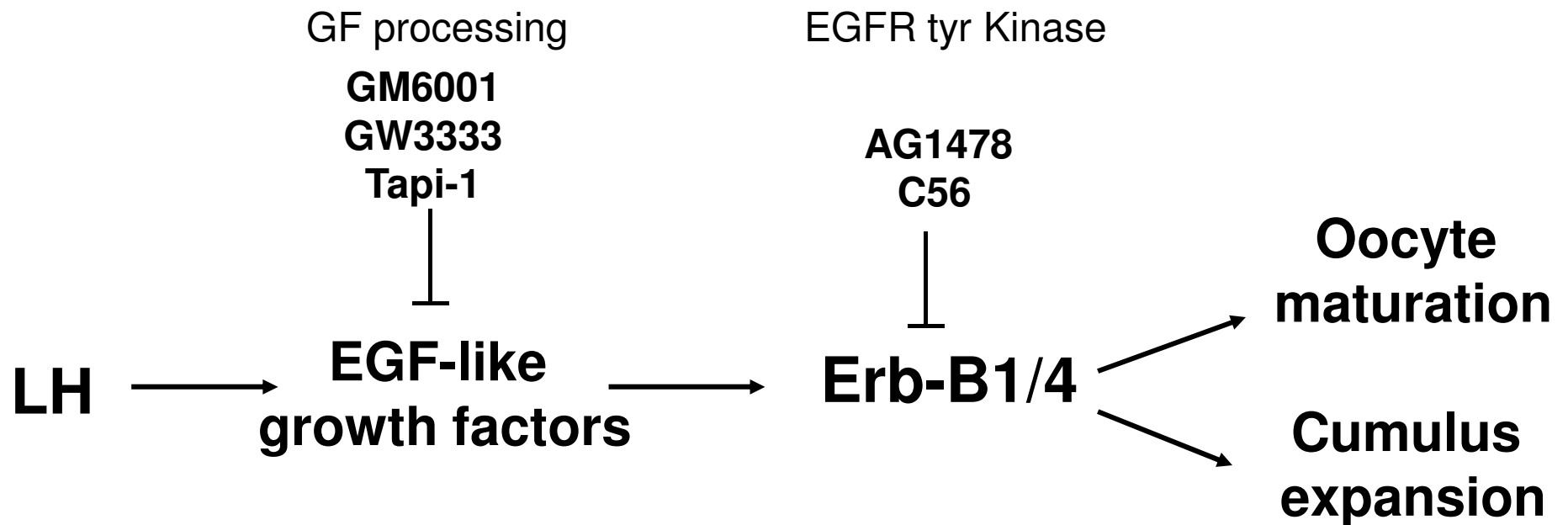
Average conc. = 33.17 ± 2.6 ng/ml



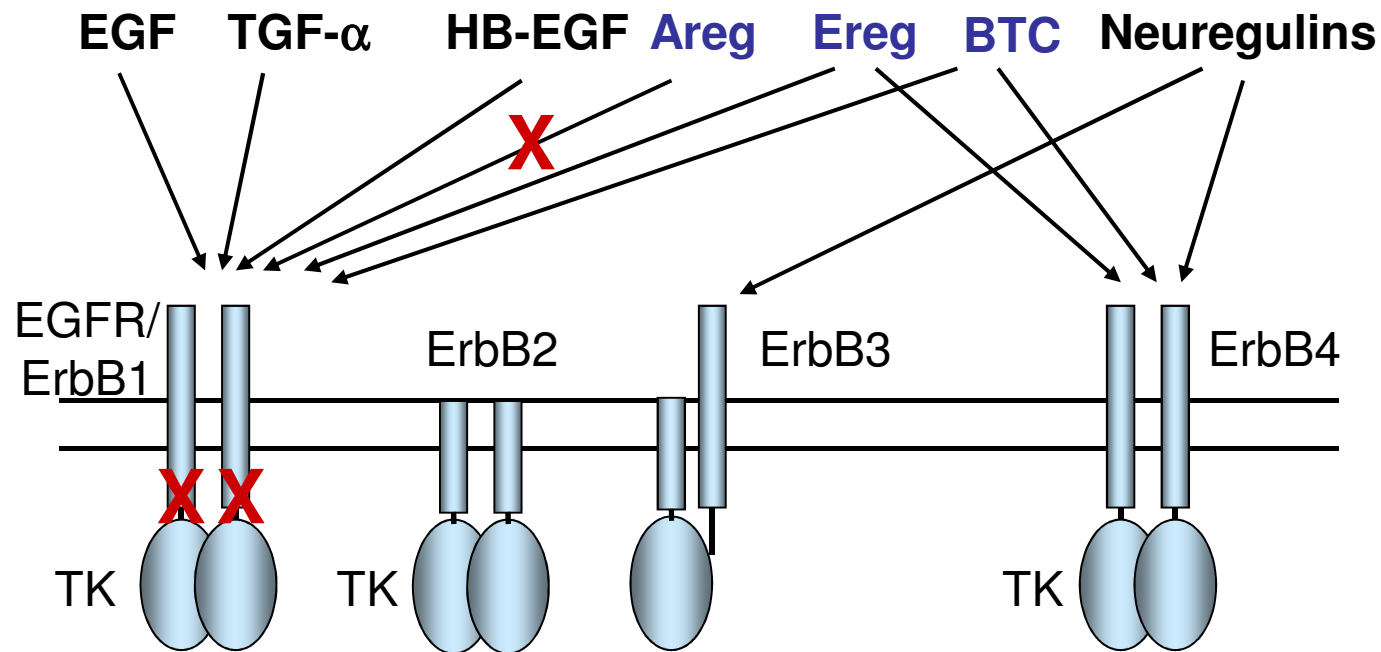
LH Action in the Follicle



LH action in the follicle is dependent on EGFR signaling: pharmacological evidence

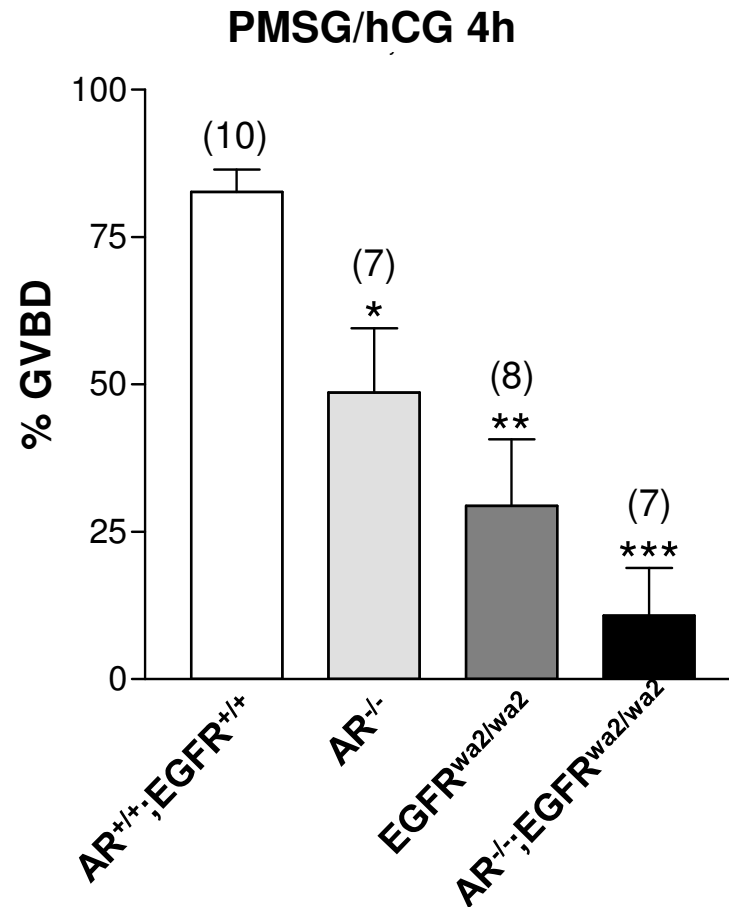
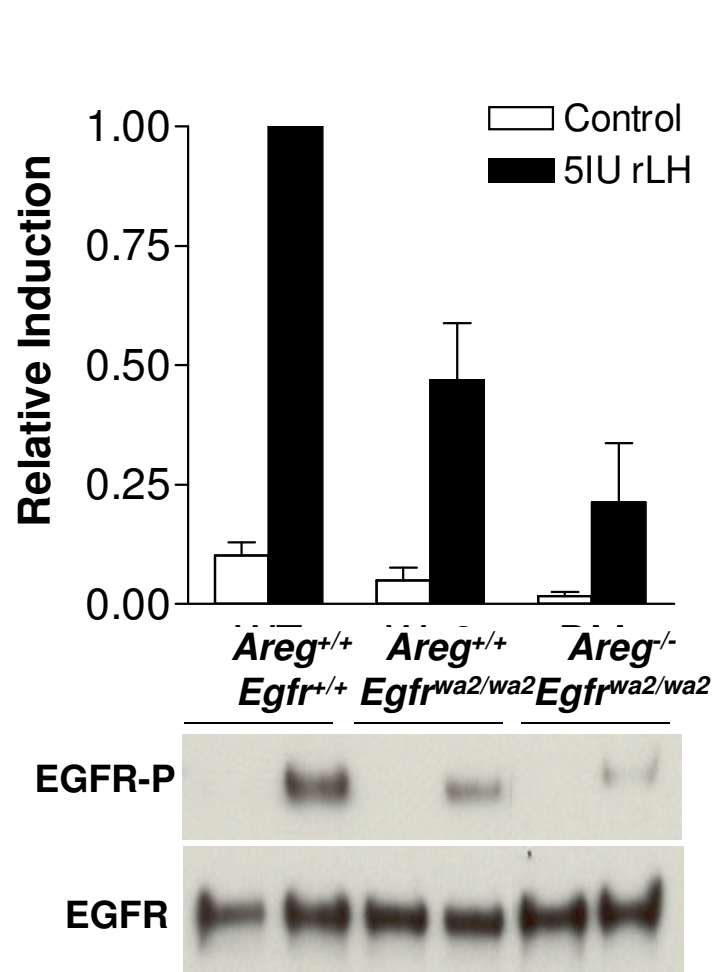


Genetic Evidence that the EGF Signaling Network Plays a Critical Role in Ovulation



waved-2 (wa-2): point mutation in the Egfr resulting in the expression of a receptor with impaired tyrosine kinase activity.

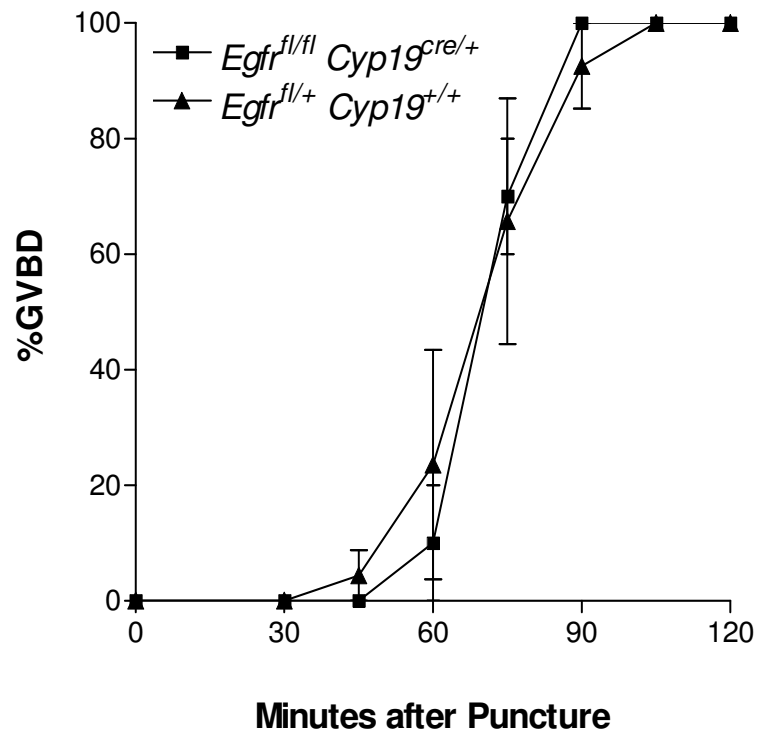
Impaired LH-dependent EGFR Transactivation and oocyte maturation in *Areg*^{-/-} *Egfr*^{wa2/wa2} Follicles



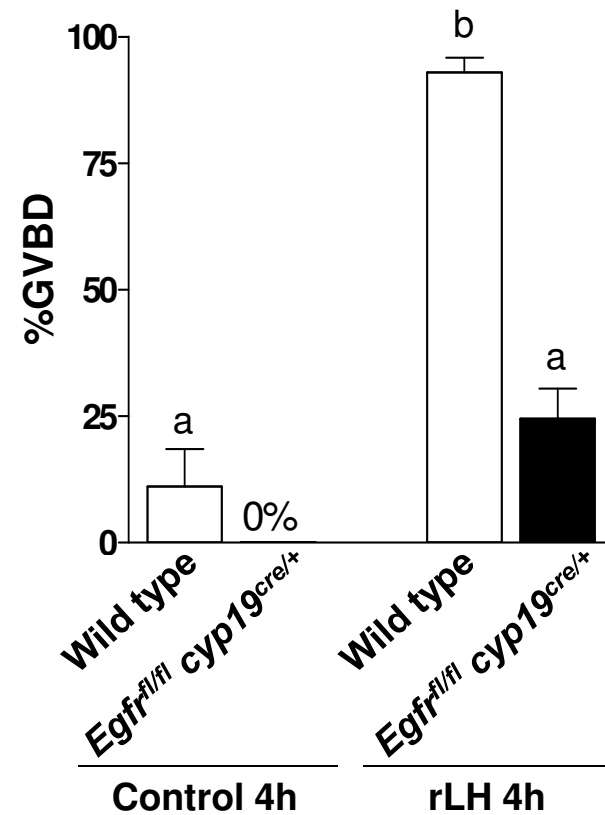
*P<0.05, **P<0.01, ***P<0.0001 compared to wild-type

LH-induced maturation is disrupted in the follicle when granulosa cells are deficient in EGFR

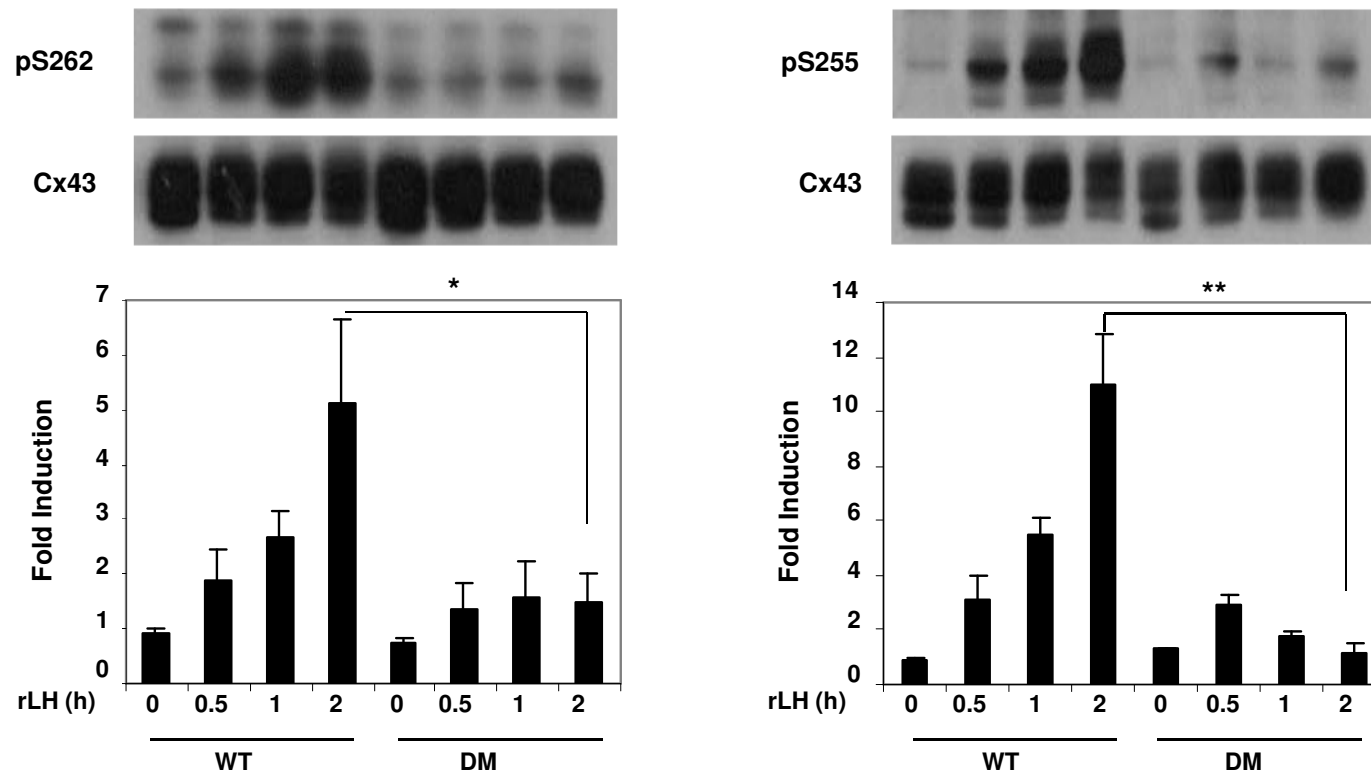
Spontaneous maturation



LH-induced maturation

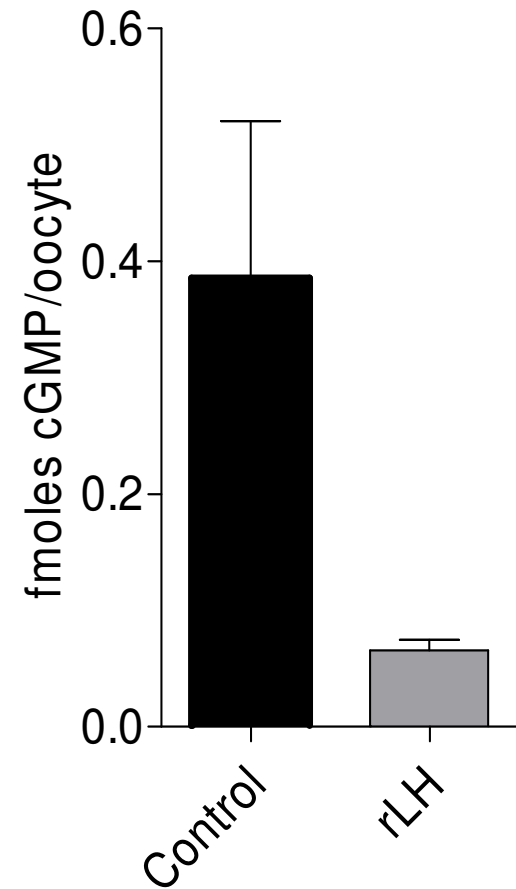
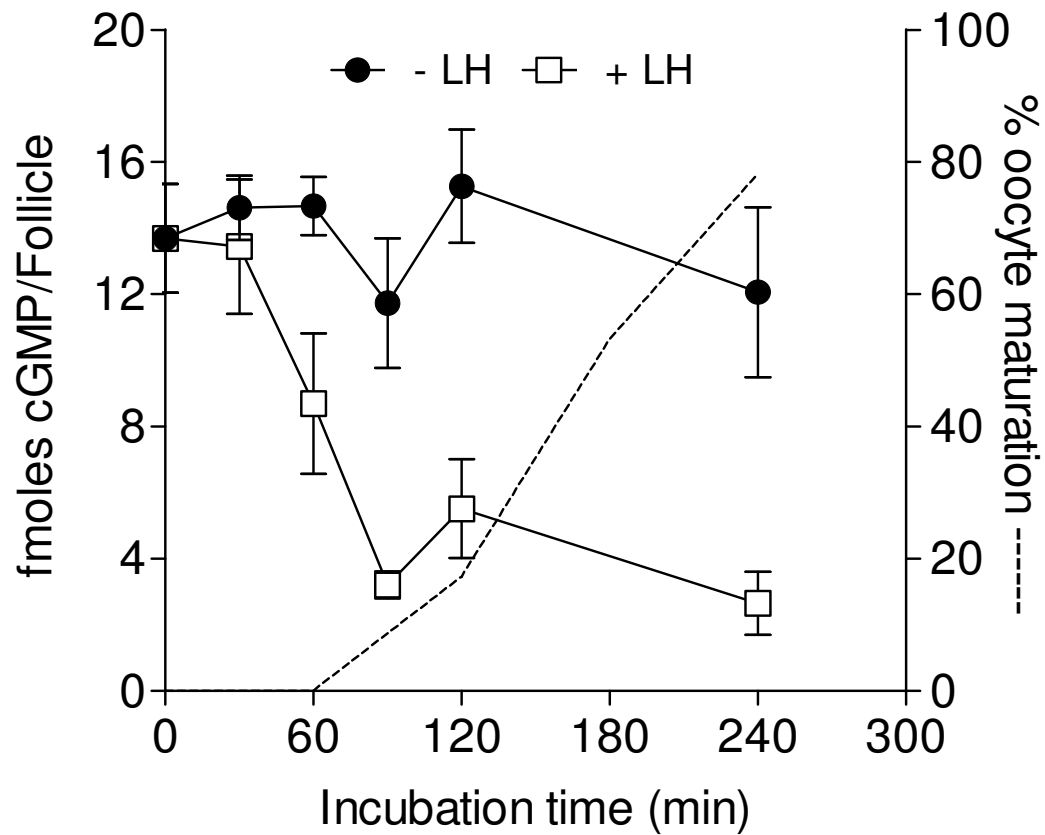


Disruption of the EGF network affects the LH regulation of gap junctions

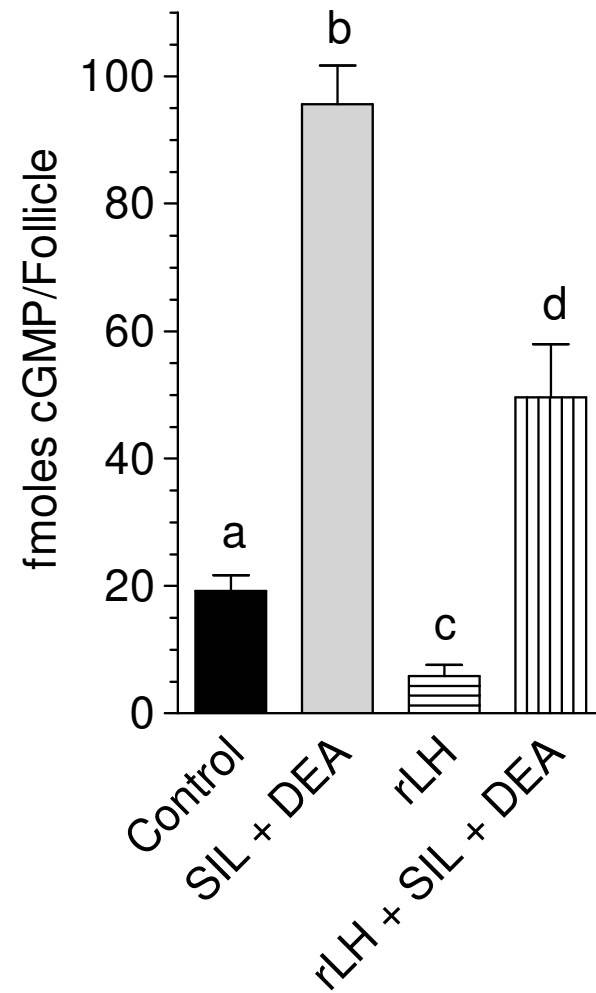
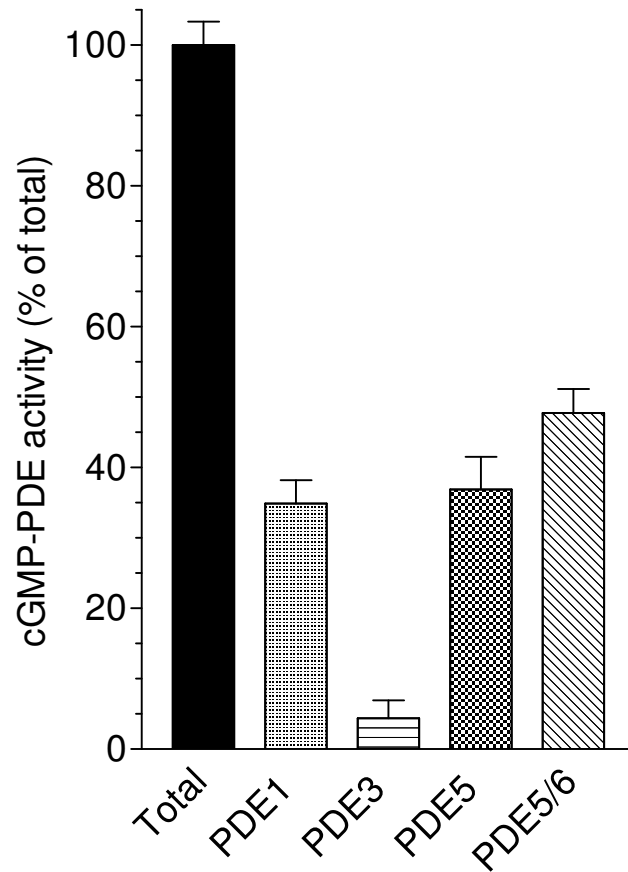


connexin 43 phosphorylation state

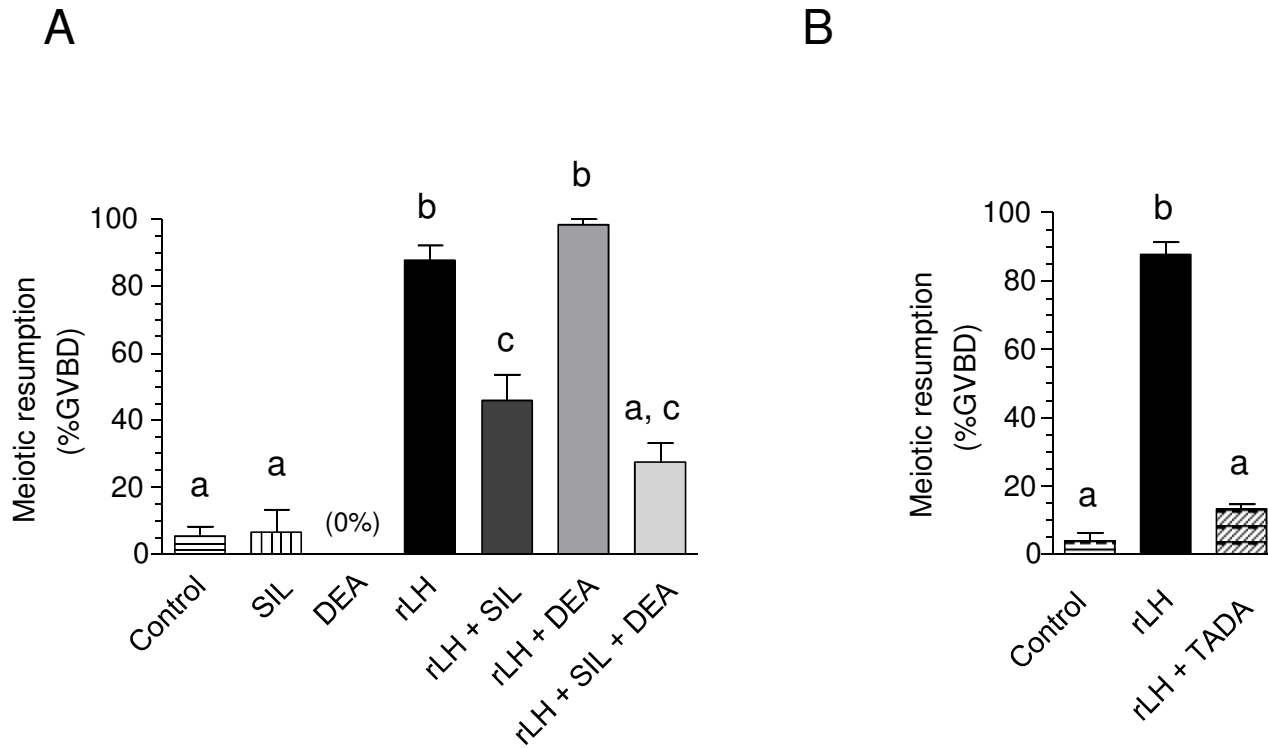
LH induces a marked decrease in cGMP content of the ovulatory follicle



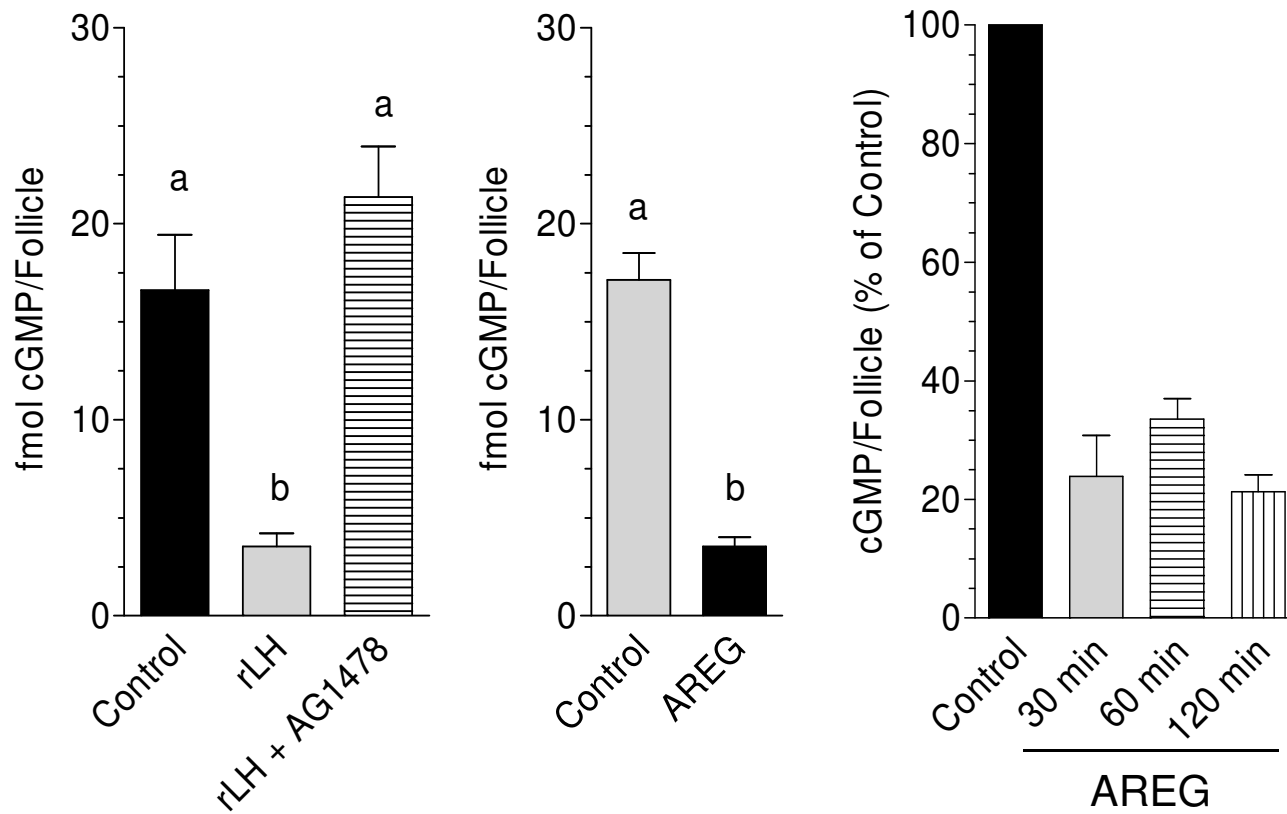
***Inhibition of PDE5 activity in the follicle
increases cGMP accumulation***



Increasing cGMP in the follicle blocks LH-mediated oocyte maturation



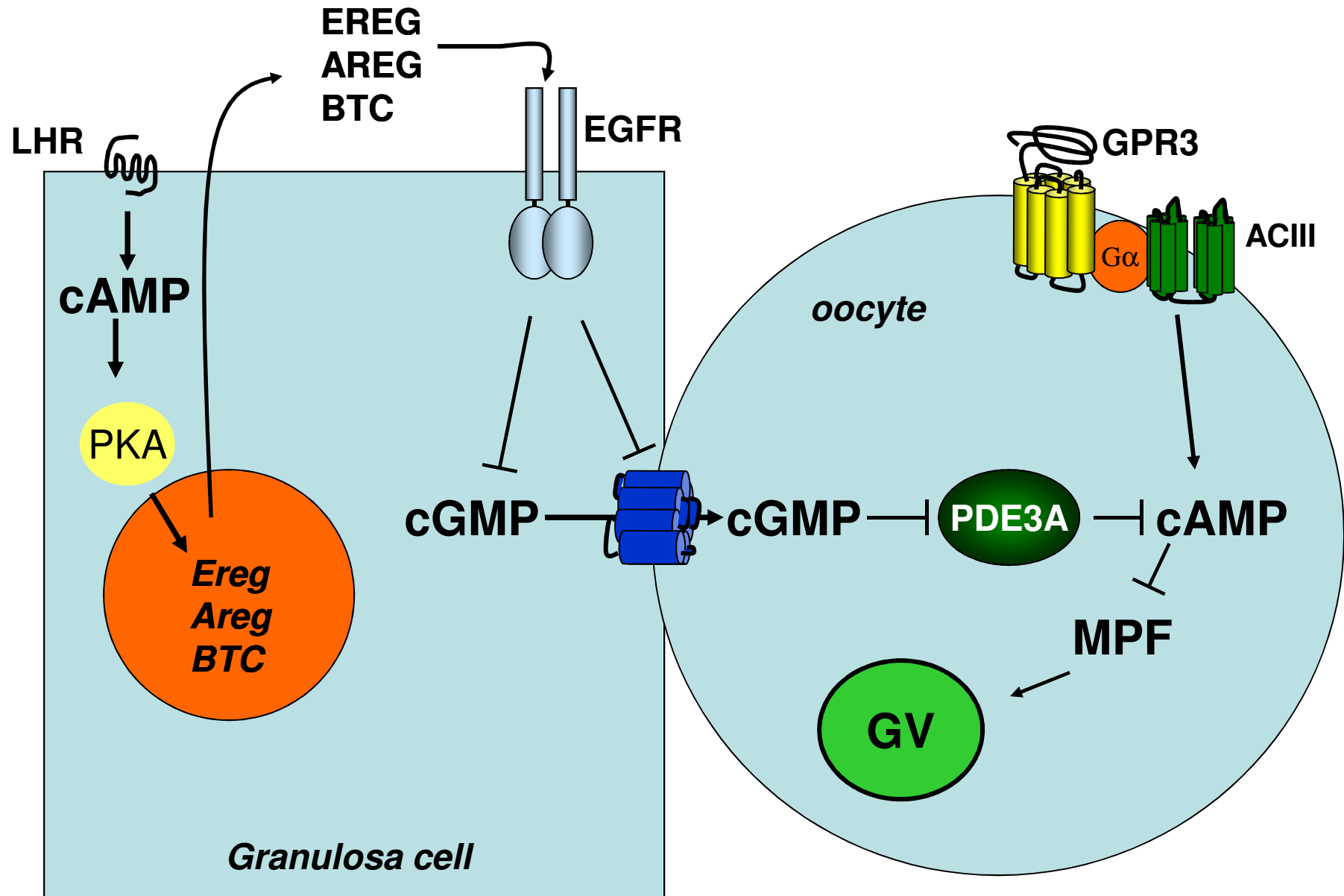
The LH-induced decrease in cGMP in the follicle requires EGFR signaling



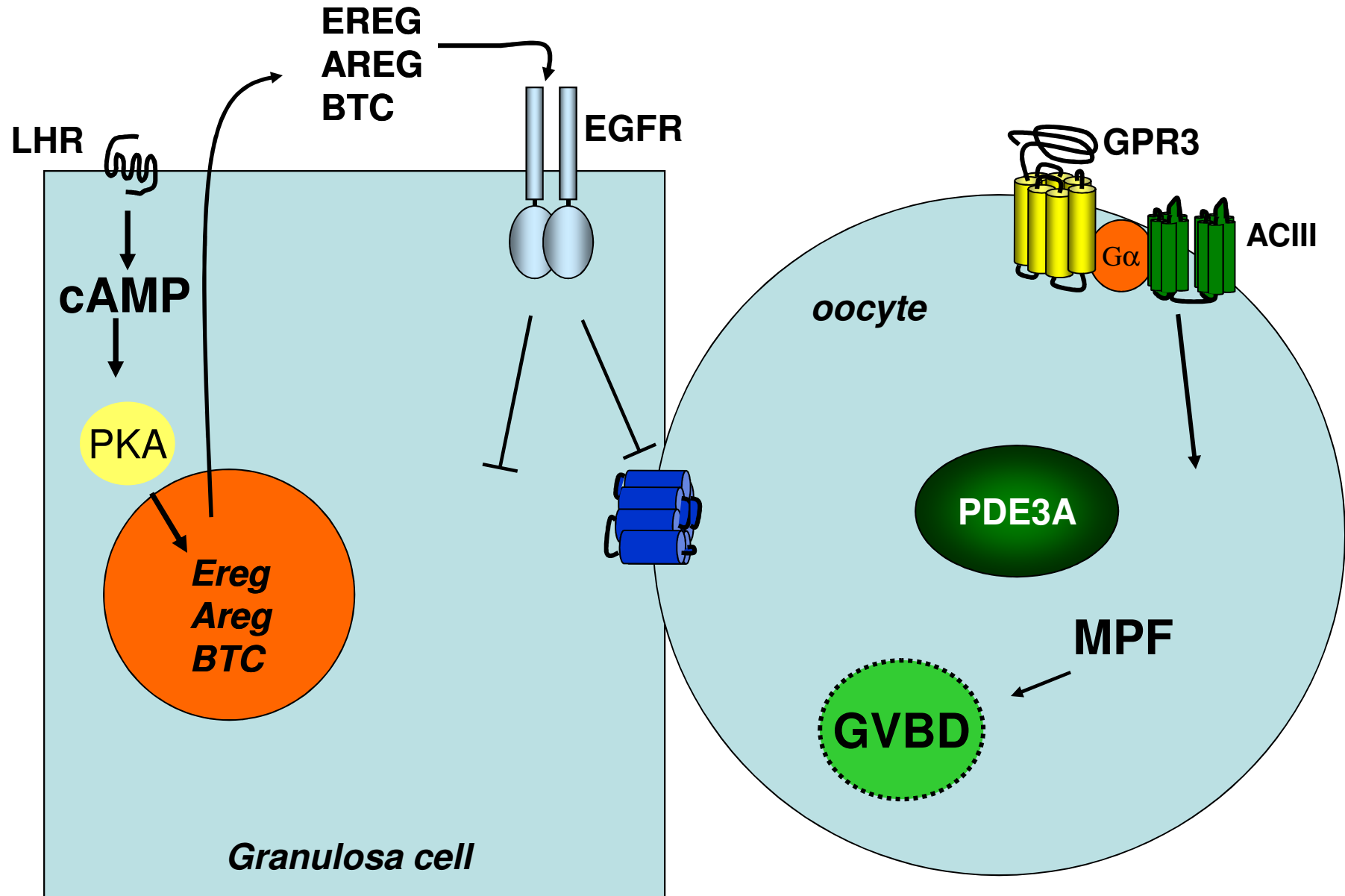
Summary

- Both cAMP and cGMP are involved in maintaining meiotic arrest of the mouse oocyte
- Transactivation of the EGF network is an essential component of the signaling machinery at triggered by LH ovulation
- LH induces a marked decrease in cGMP in the follicle prior to GVBD
- cGMP dependent regulation of PDE3A may be the olecaurl switch requiried for oocyte maturation

Signaling involved in meiotic arrest and maturation of the mouse oocyte



Signaling involved in meiotic arrest and maturation of the mouse oocyte



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