Germ cell development and its regulation by interacting growth factors during human ovarian development

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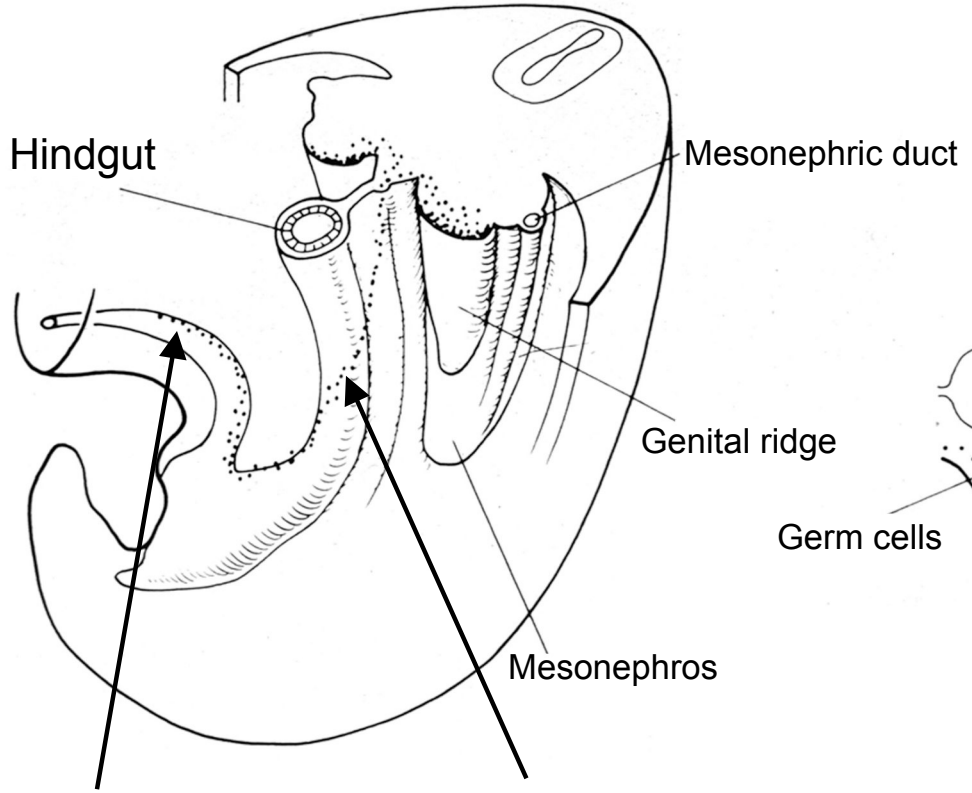
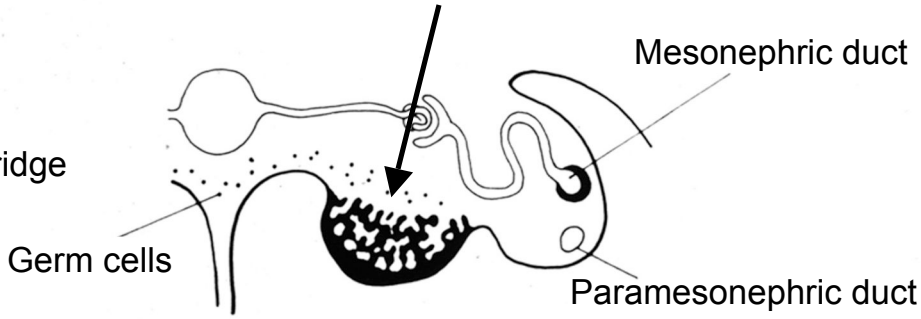
PGC formation, migration and colonisation of the gonad



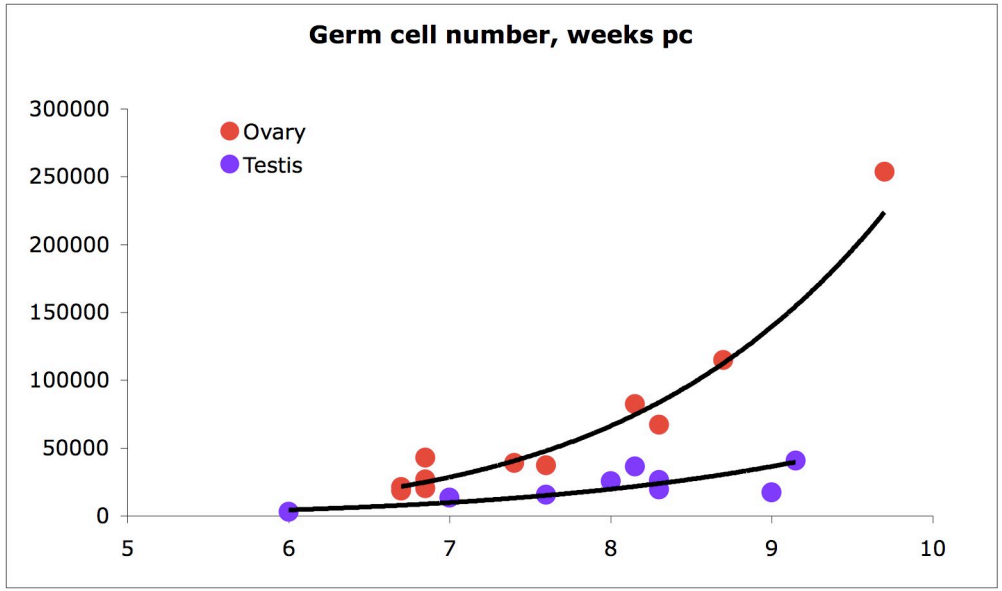
PGC specification:
BMPs2, 4, 8b

Migration/proliferation
Kit ligand/c-kit
SDF/CXCR4

Within the gonad
- **Proliferation**
- **Selection/escape from apoptosis**
- **Interaction with somatic cells**

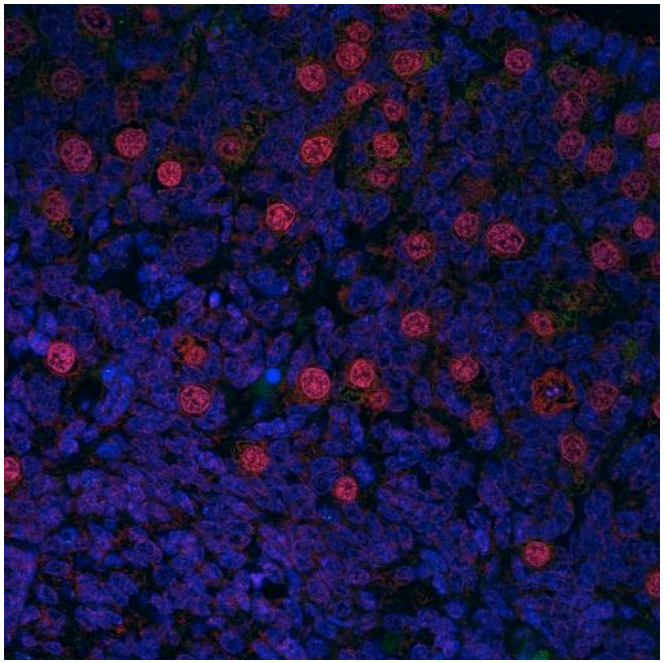


Male/female commonalities and differences

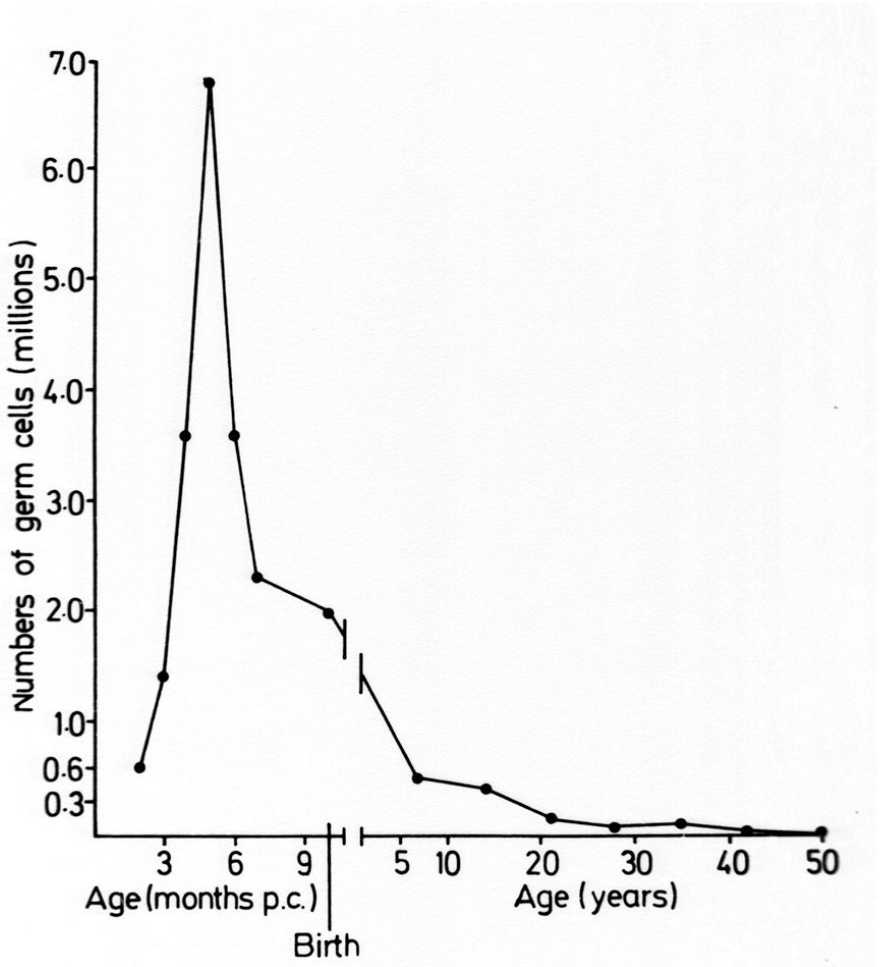


Data from Bendsen et al 2003, 2006

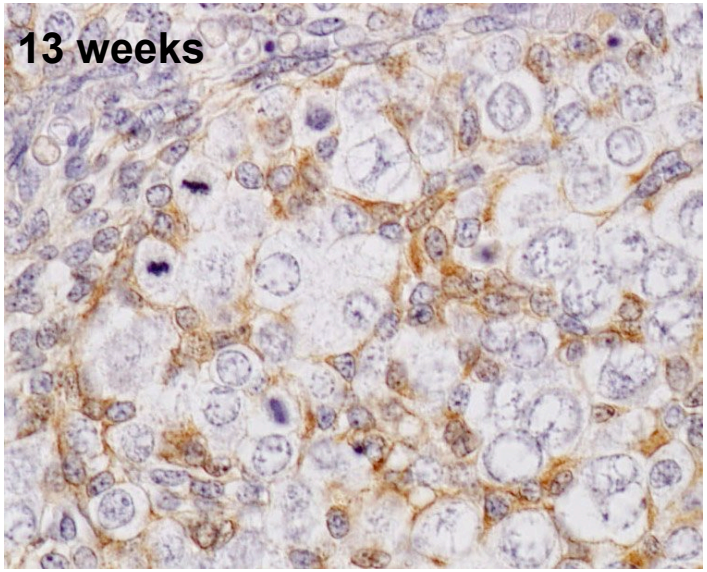
Germ cells: Oct4 at 7 wk pc

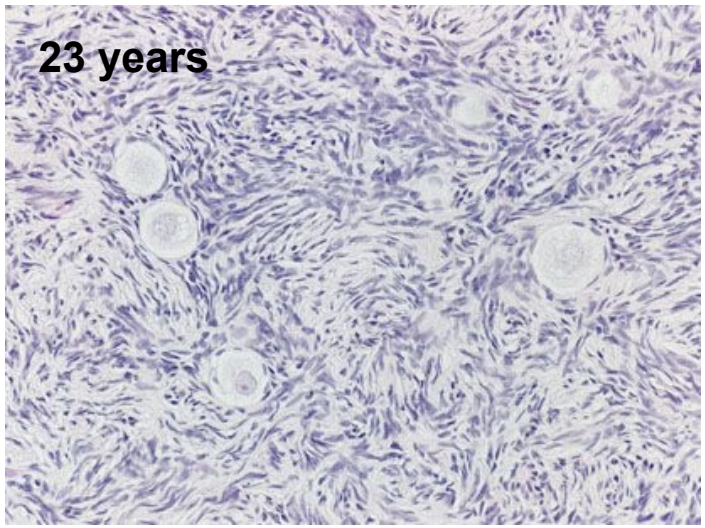


Human oocyte dynamics

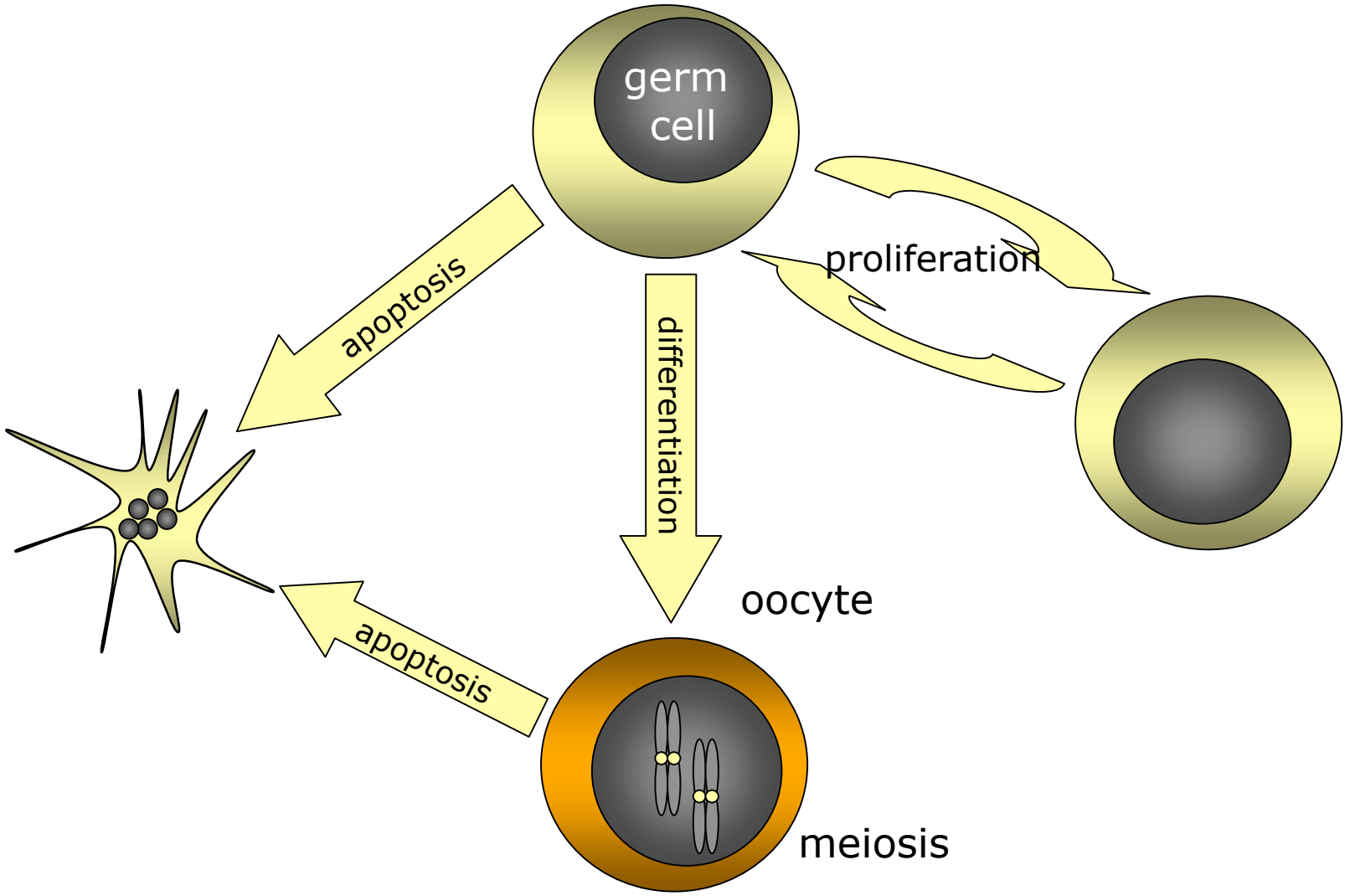


Data from Block 1952; Baker 1963

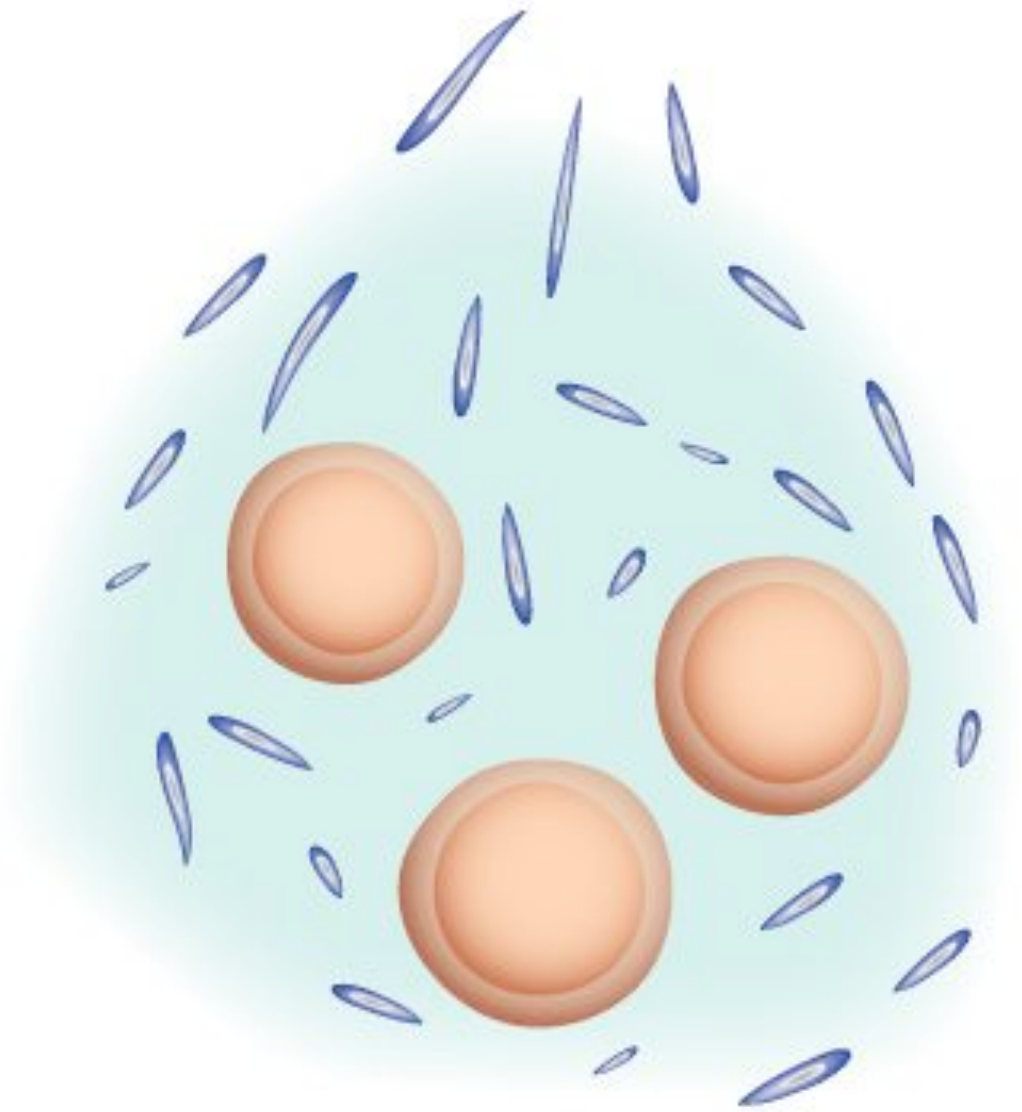


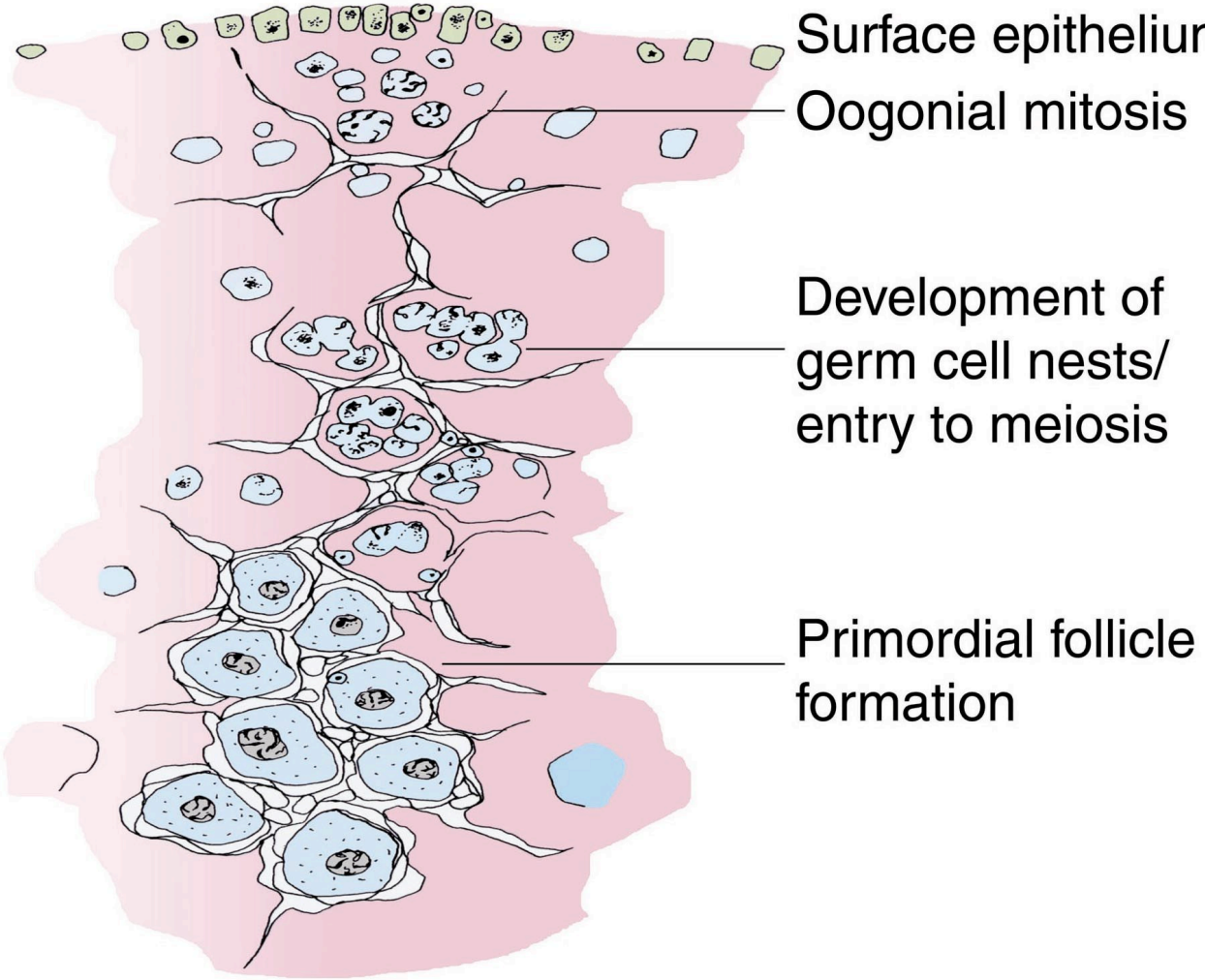


Intrinsic and extrinsic factors regulate germ cell fate decisions



Ovarian development: oogonial cluster to primordial follicle



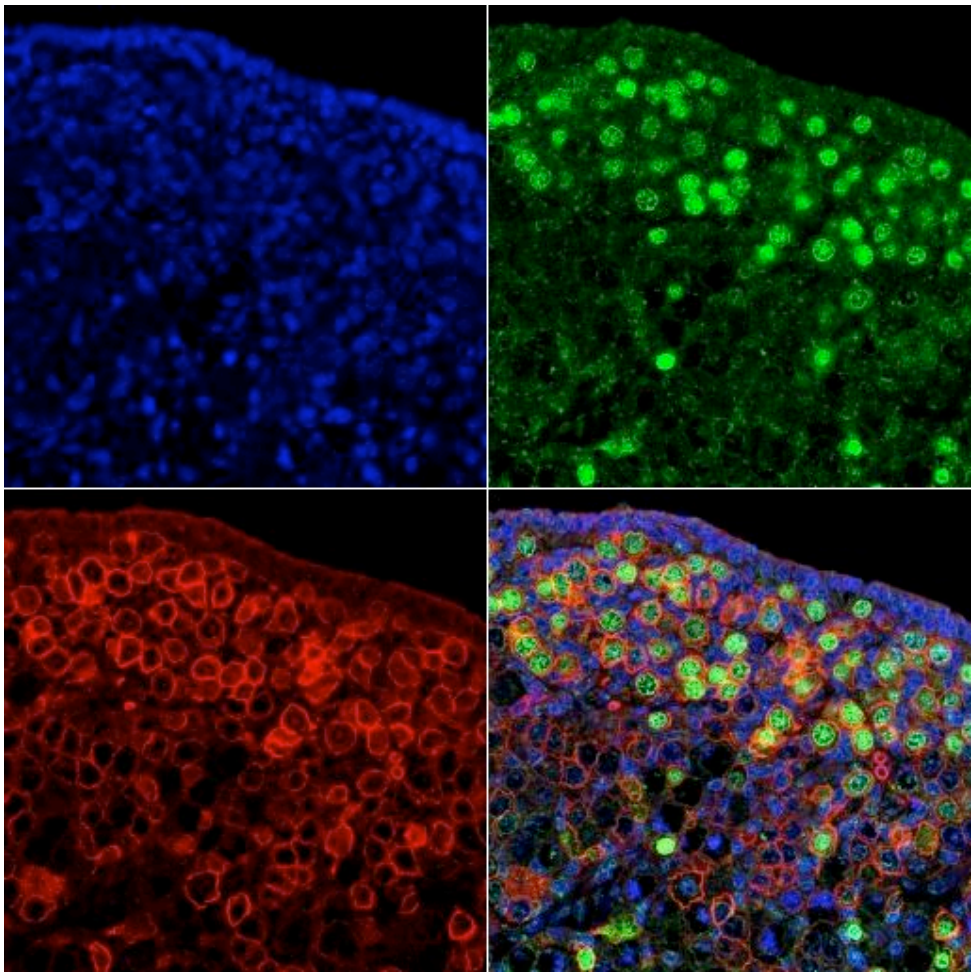


Drawing by Paul Hartley

PGC to primordial follicle

- Germ cell maturation
- Activin A, Neurotrophins, Prostaglandins in germ/somatic interactions

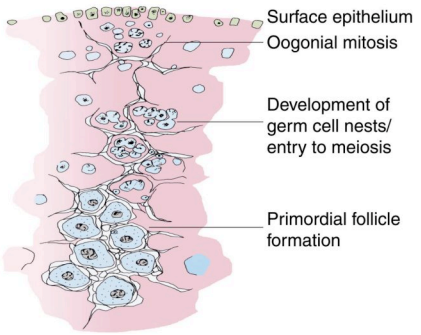
Germ cell maturation



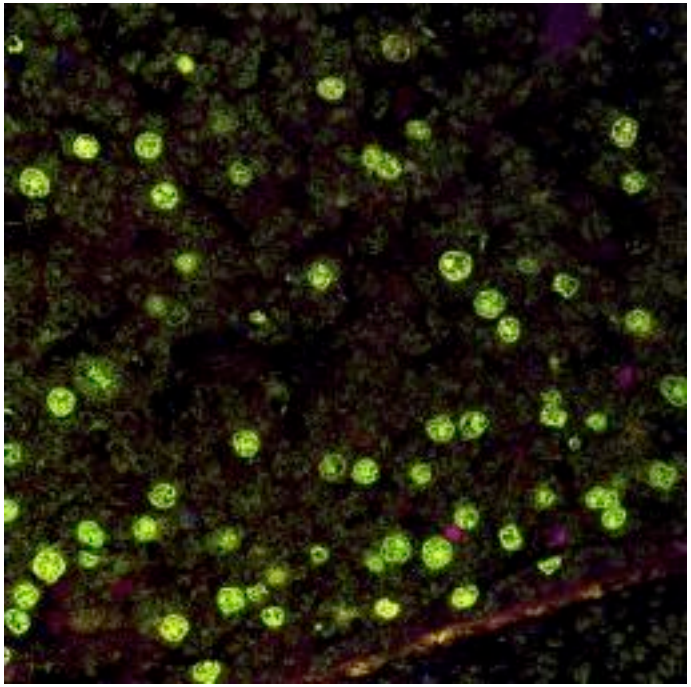
Oct 4

c-Kit

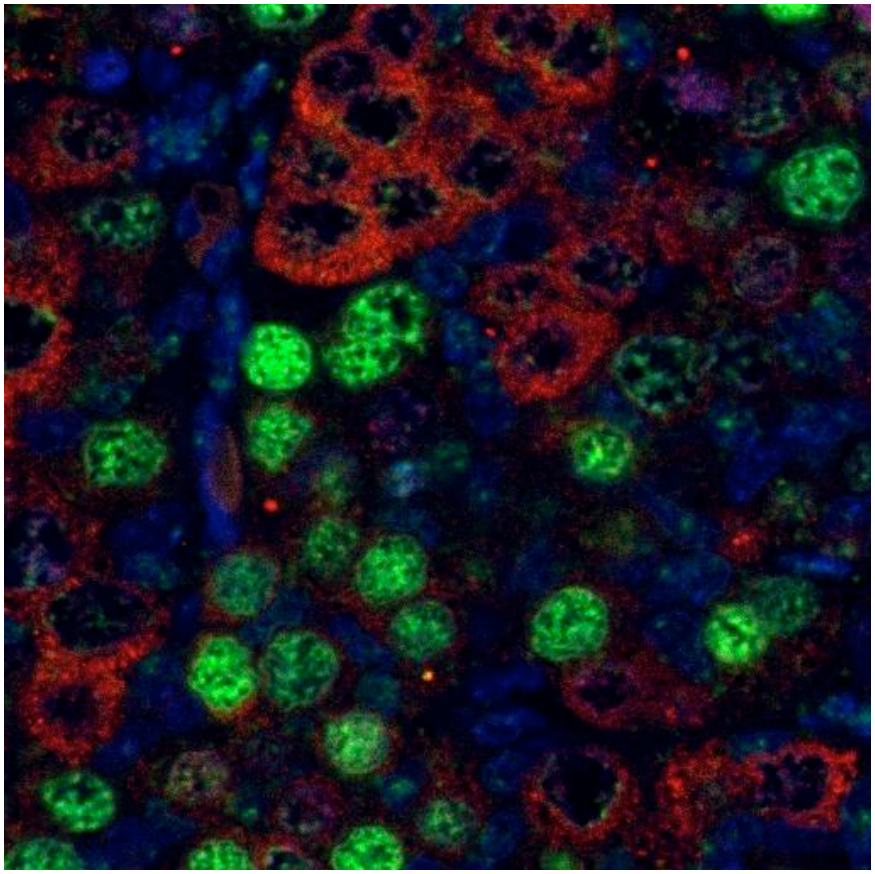
15 weeks



OCT 4 and DAZL



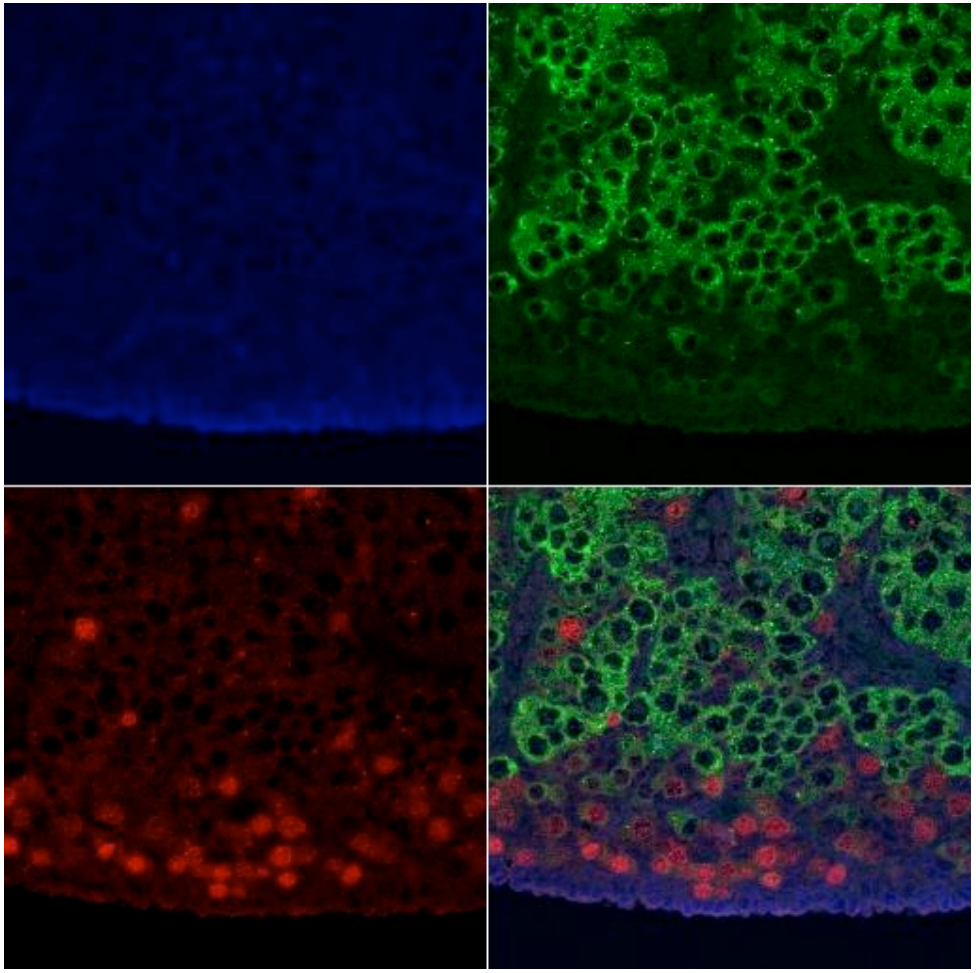
61d



14 weeks

Anderson et al BMC Dev Biol 2007

Oct4 and VASA



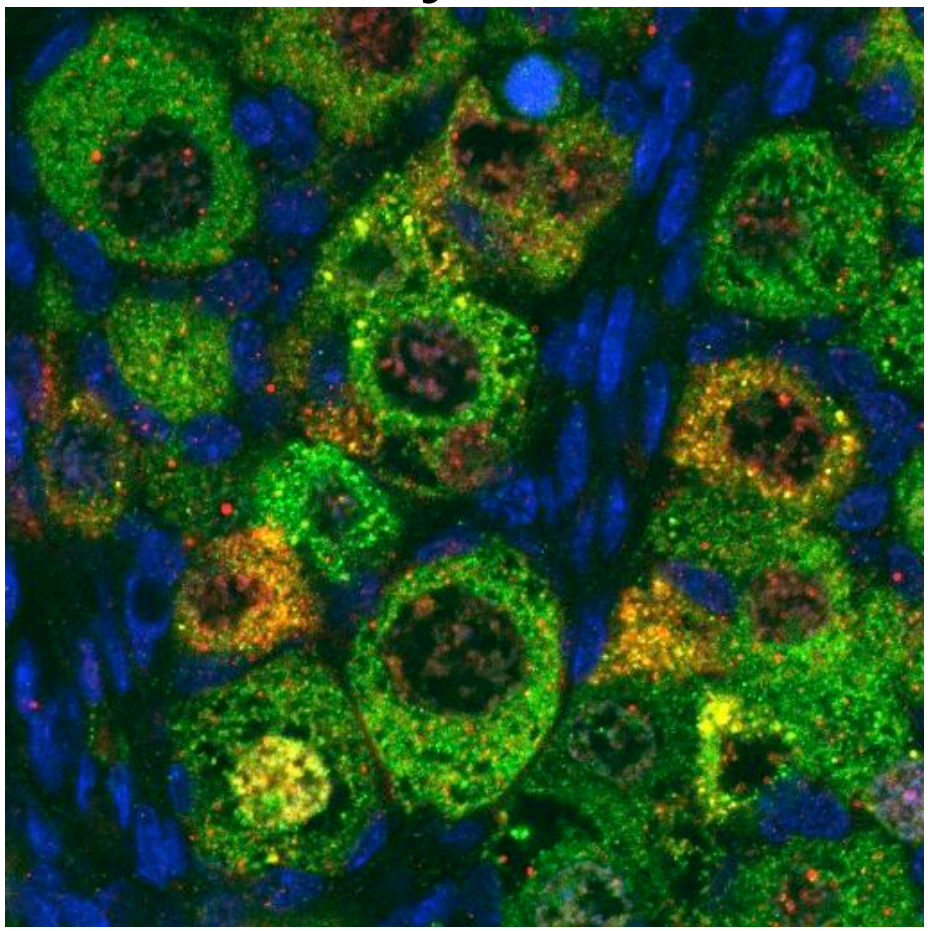
VASA

OCT 4

16 weeks

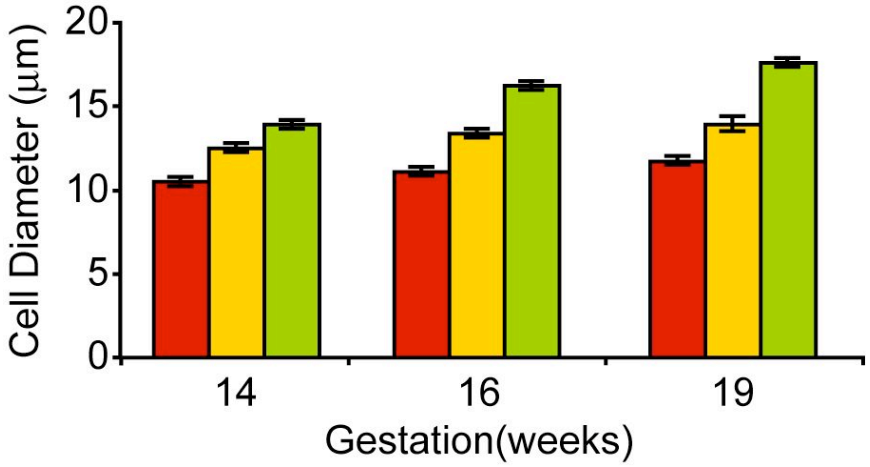
Anderson et al BMC Dev Biol 2007

Progressive development from PGC to oocyte: OCT4 to DAZL to VASA



DAZL VASA

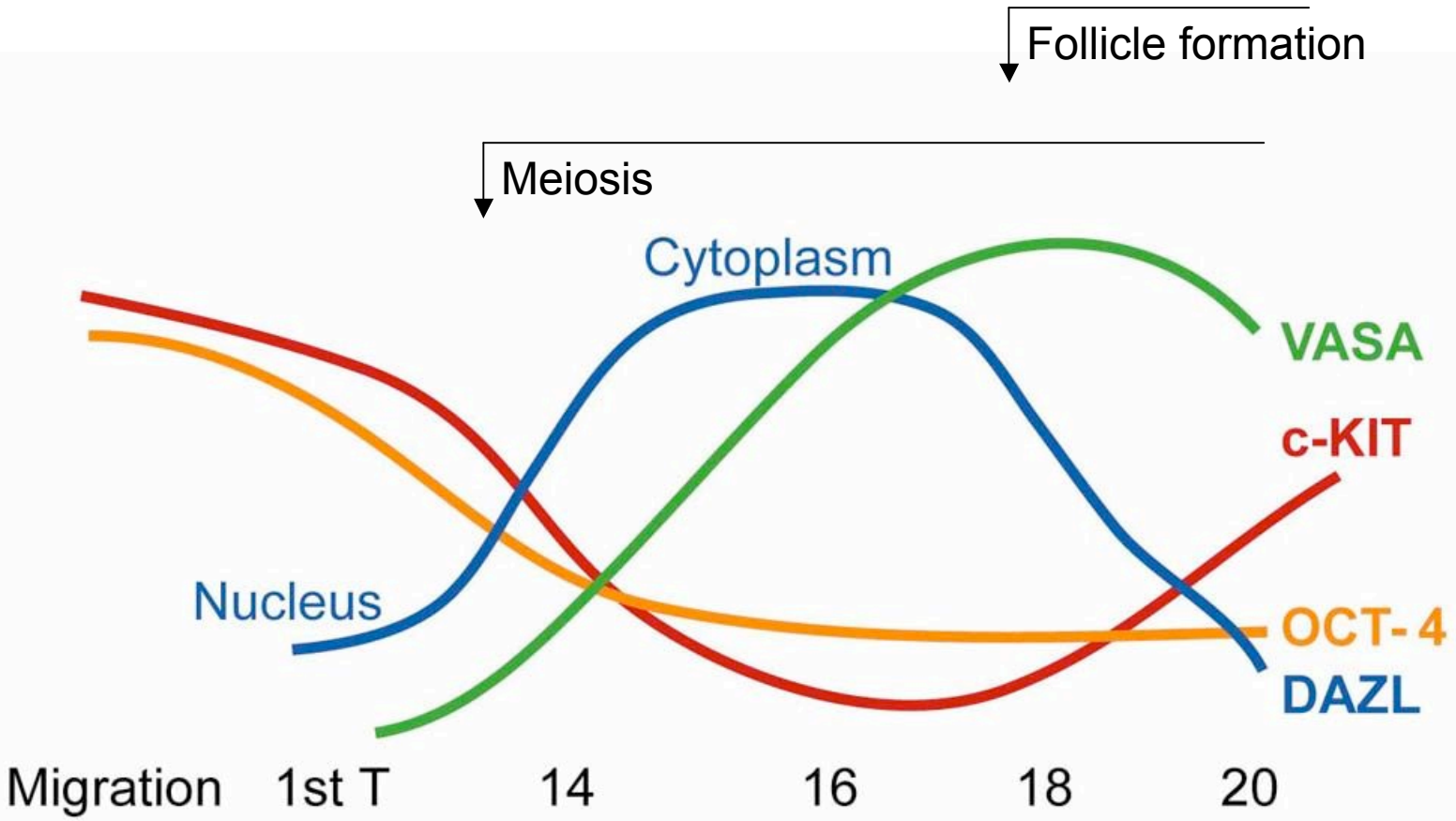
19 weeks



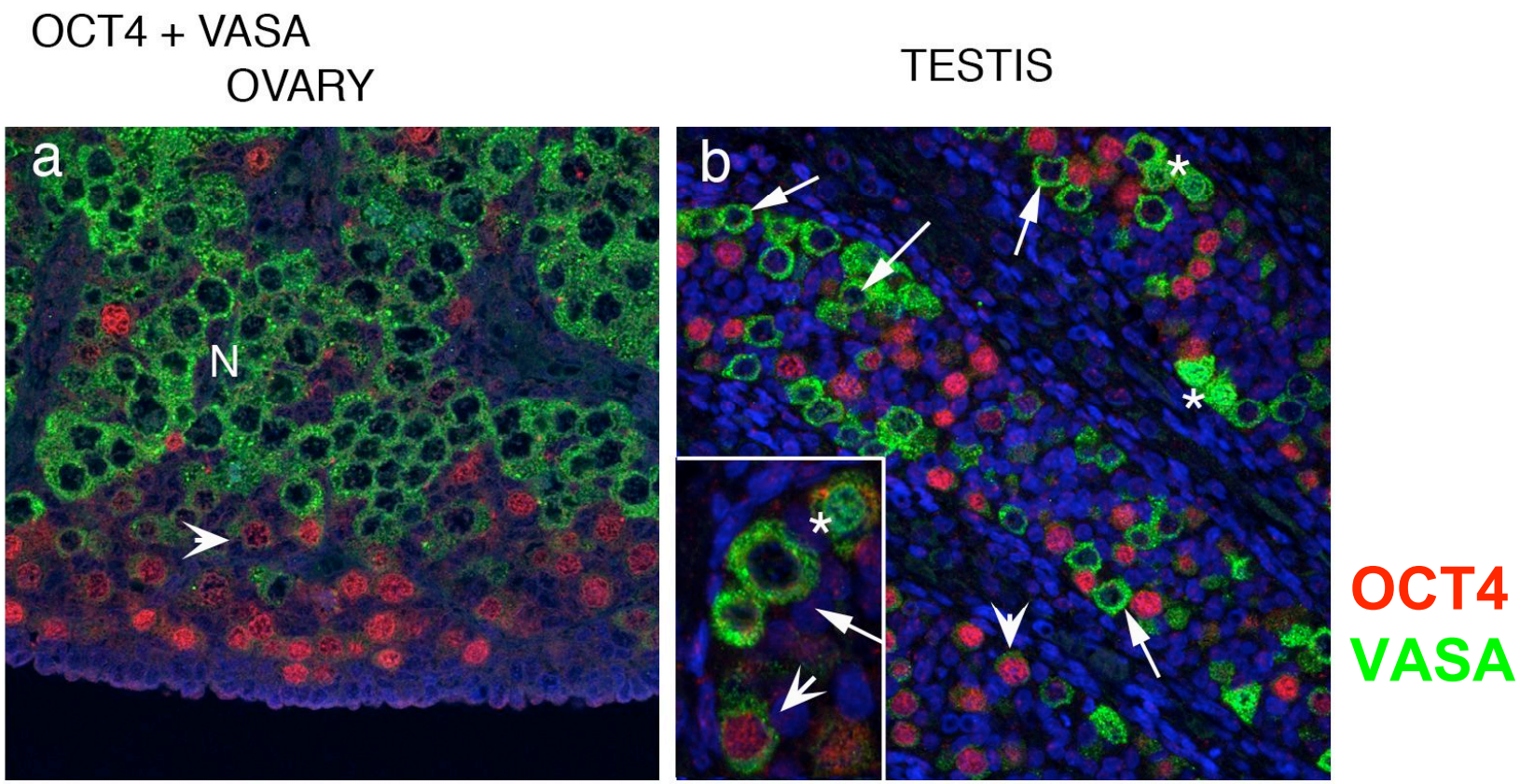
Oct4
DAZL
VASA

Anderson et al BMC Dev Biol 2007

Germ cell maturation

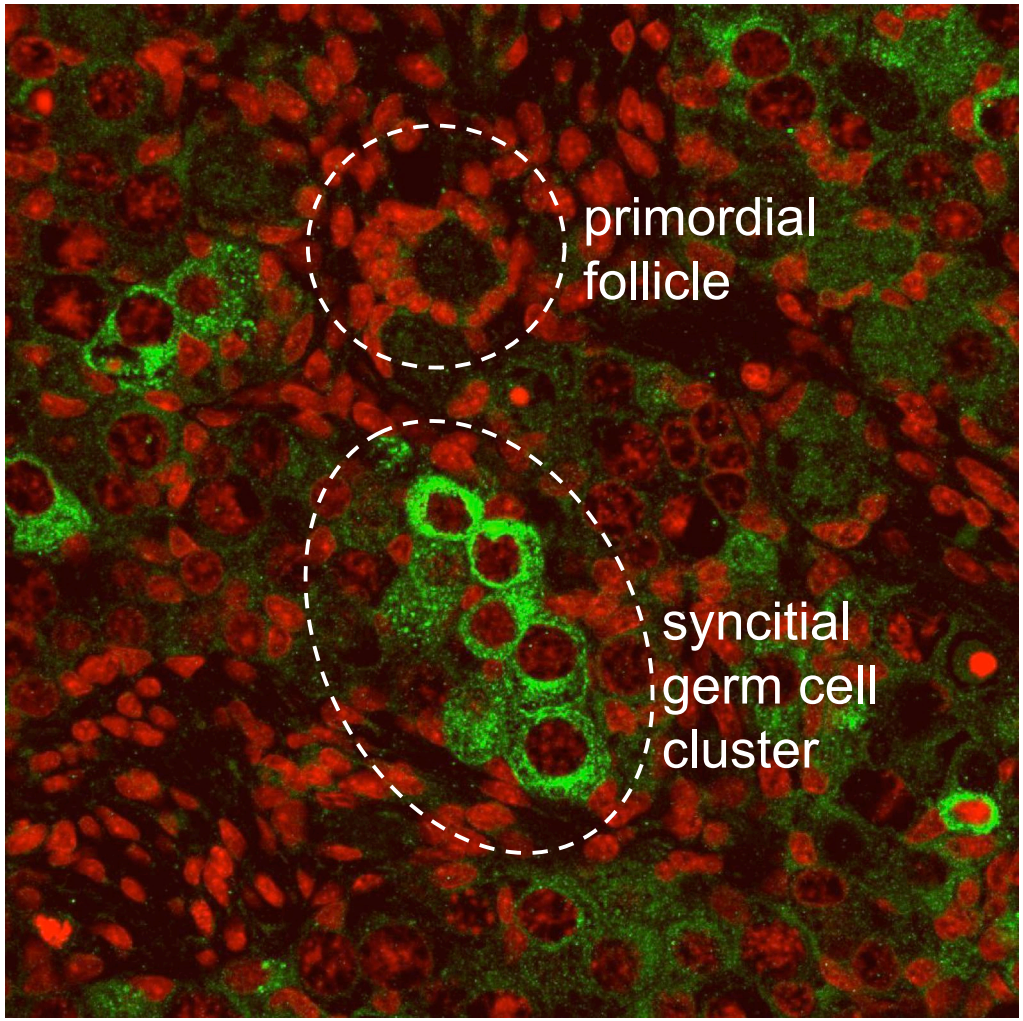


Parallel changes in the male

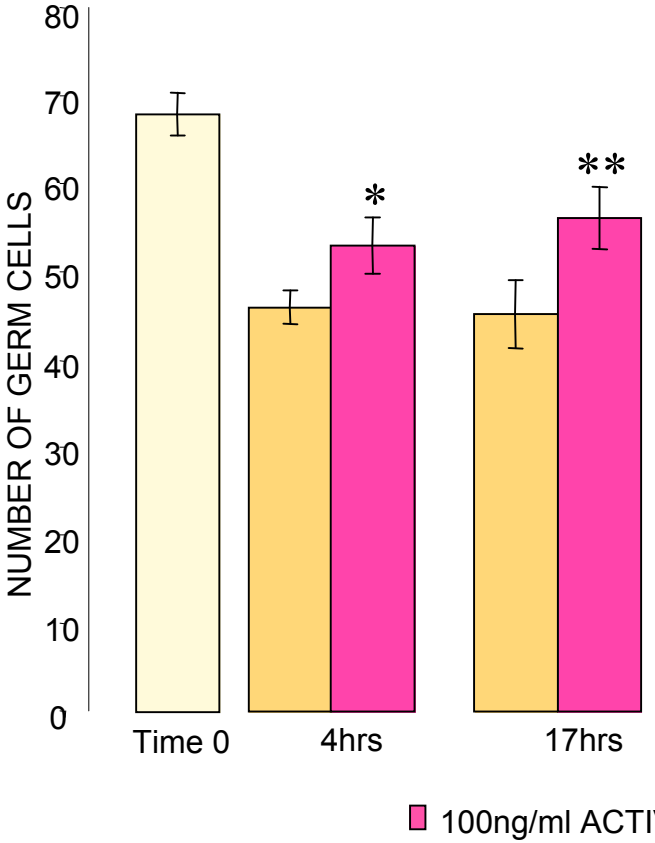


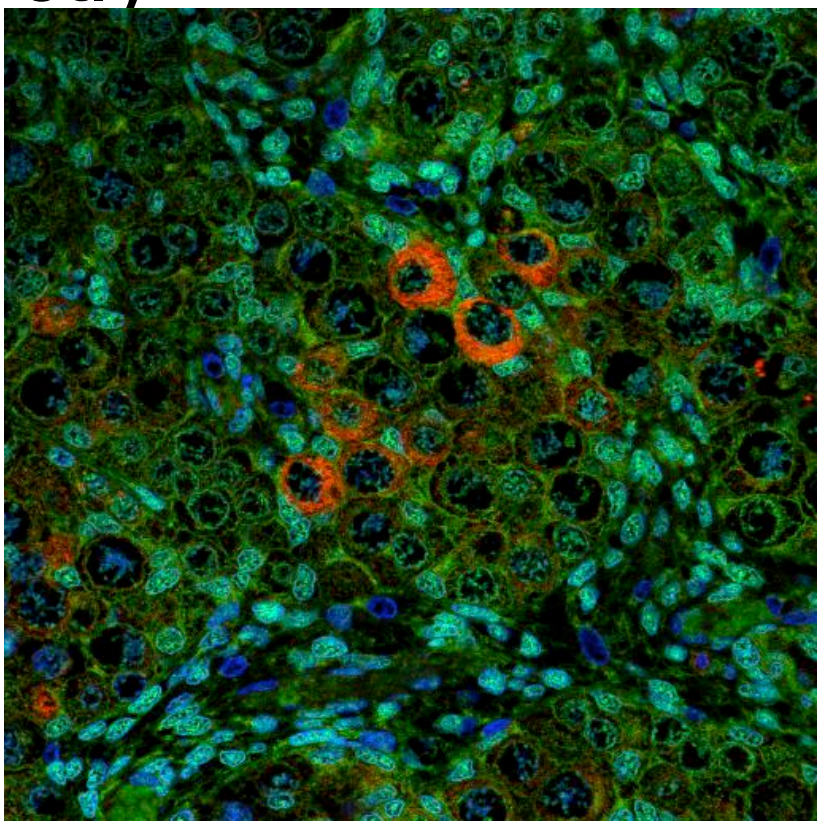
Anderson et al BMC Dev Biol 2007

Differential expression of activin βA in clustered and follicular germ cells



Activin increases germ cell number -indirectly



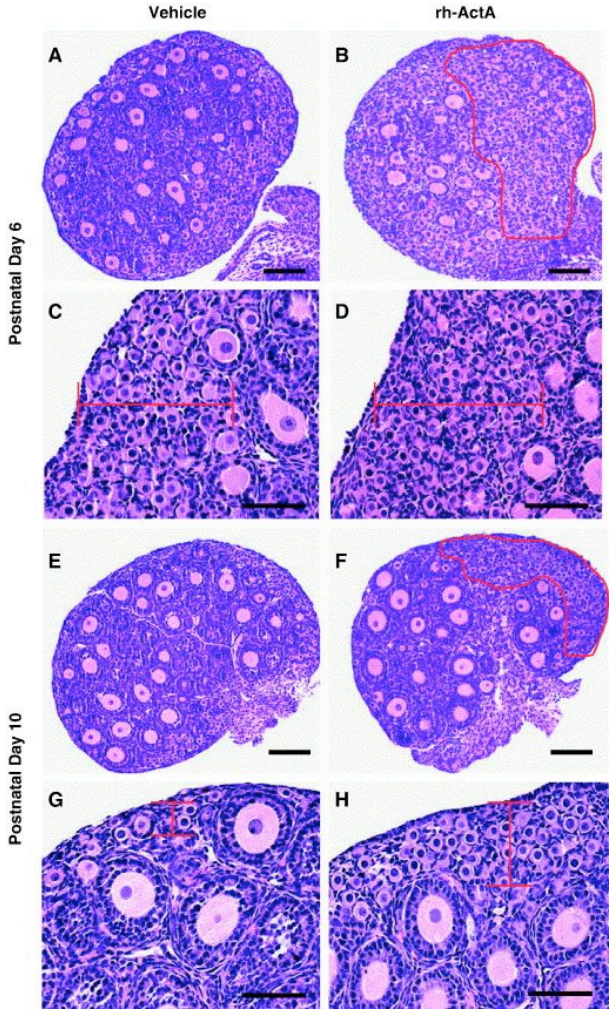


Smad 3
Activin
Counterstain
Nuclear Smad 3

18 wk fetal ovary

Martins da Silva et al 2004 Dev Biol 266, 334; Coutts et al 2008 Dev Biol 314, 189

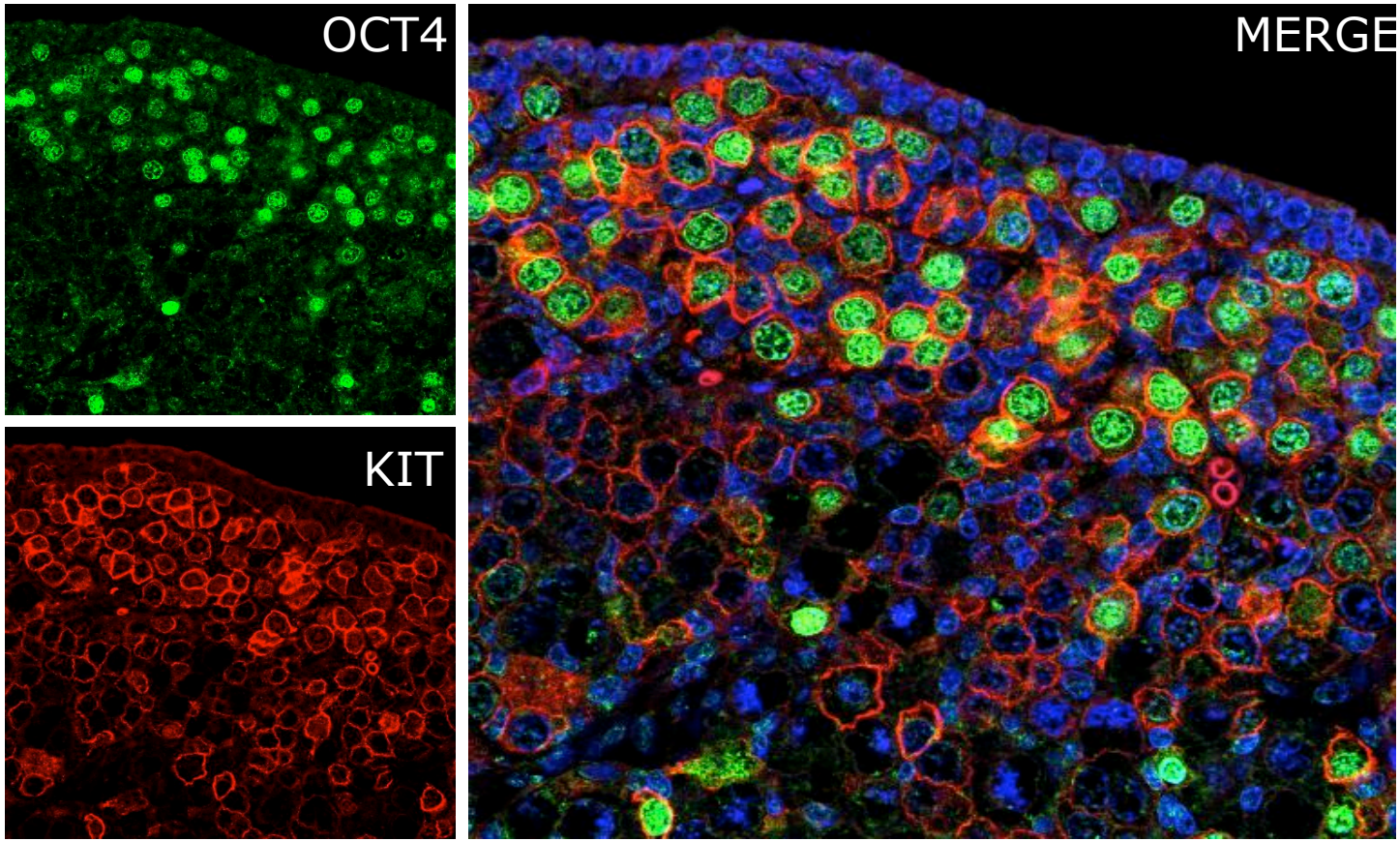
Activin increases follicle pool in mouse



'On pn days 6 and 10, there were more primordial follicles (27% and 35% more respectively) in ovaries from rh-ActA-treated mice'

Bristol-Gould SK et al., 2006 Dev Biol 298, 132

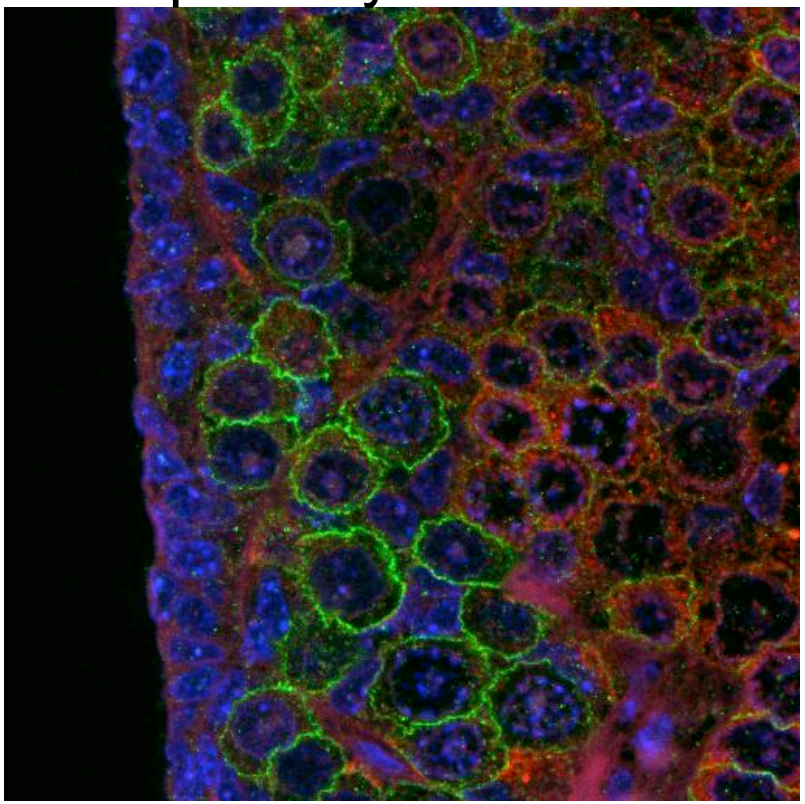
Germ cell differentiation: downregulation of OCT4 and KIT



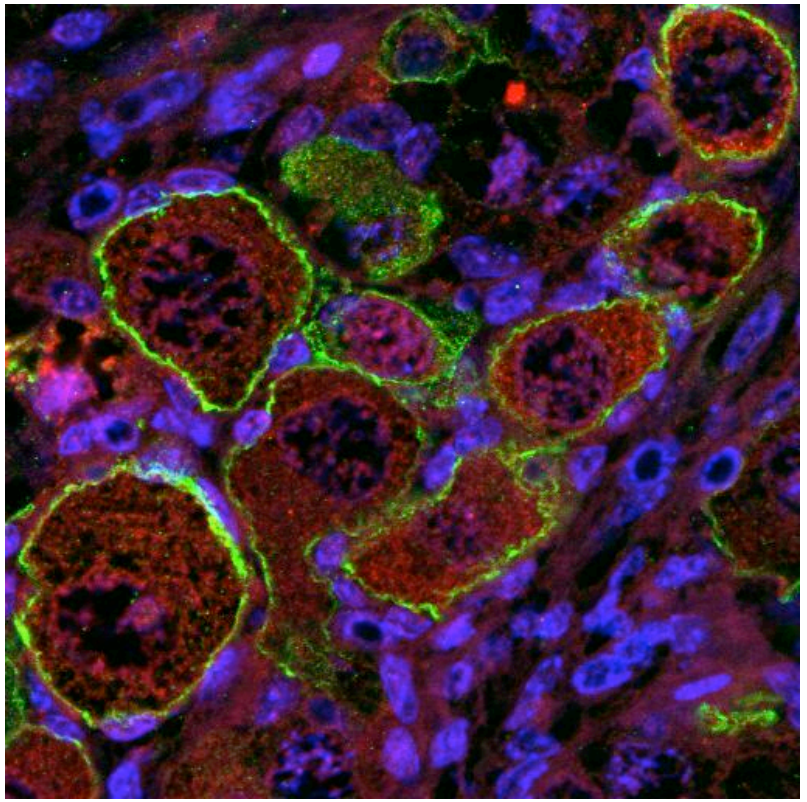
15 weeks

Germ cell differentiation

Peripherally….



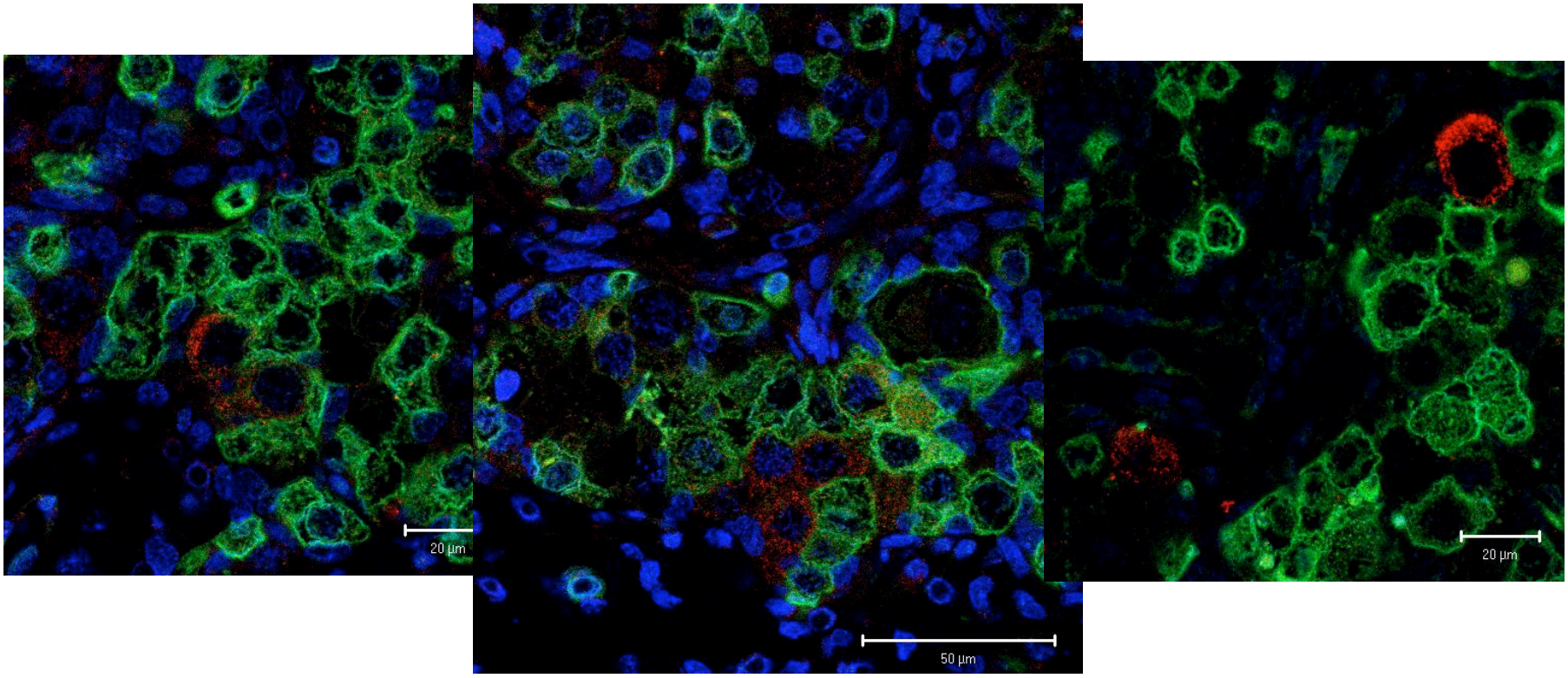
Centrally….



KIT DAZL

Same section of 20 week ovary

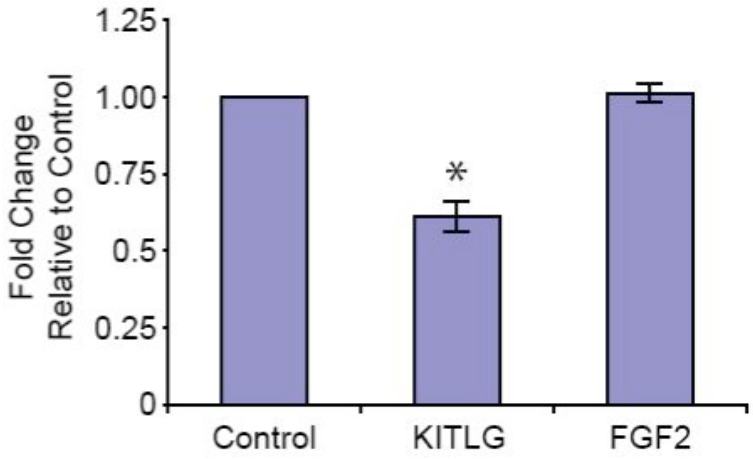
Absence of co-expression of activin with c-Kit



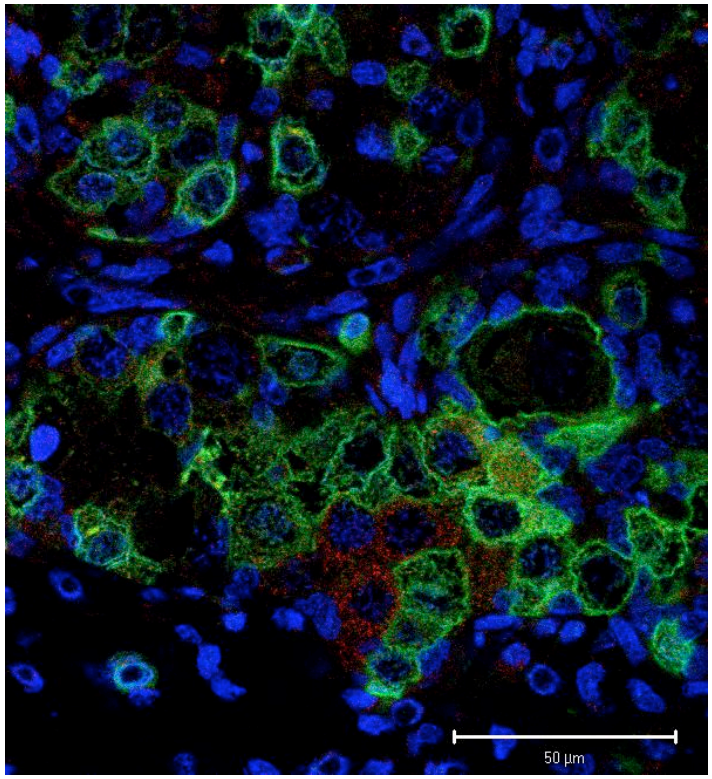
19 weeks

Activin regulates KitL/c-Kit as primordial follicles form in the human

Activin inhibits KITLG expression



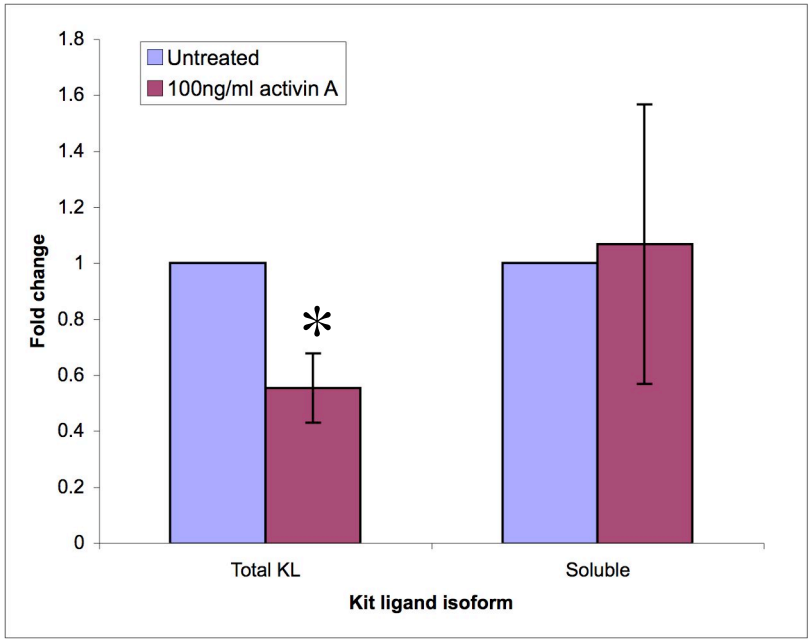
Activin and c-Kit are not co-expressed

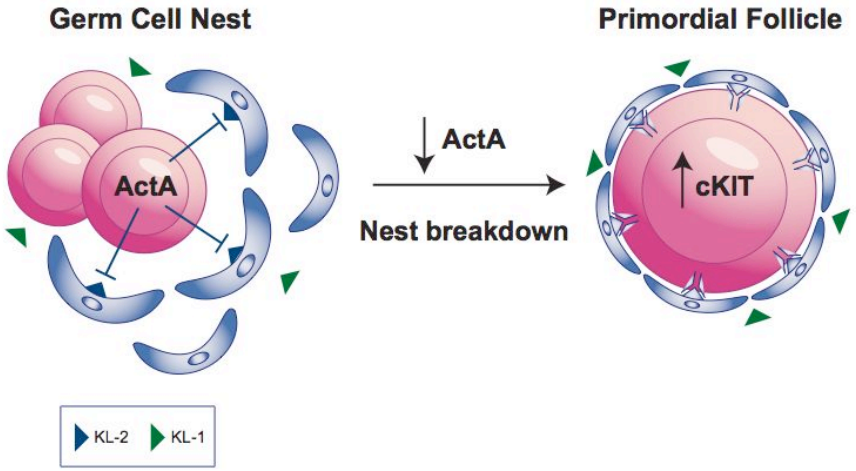


Activin **c-Kit**

Coutts et al 2007 Devel Biol 314, 189

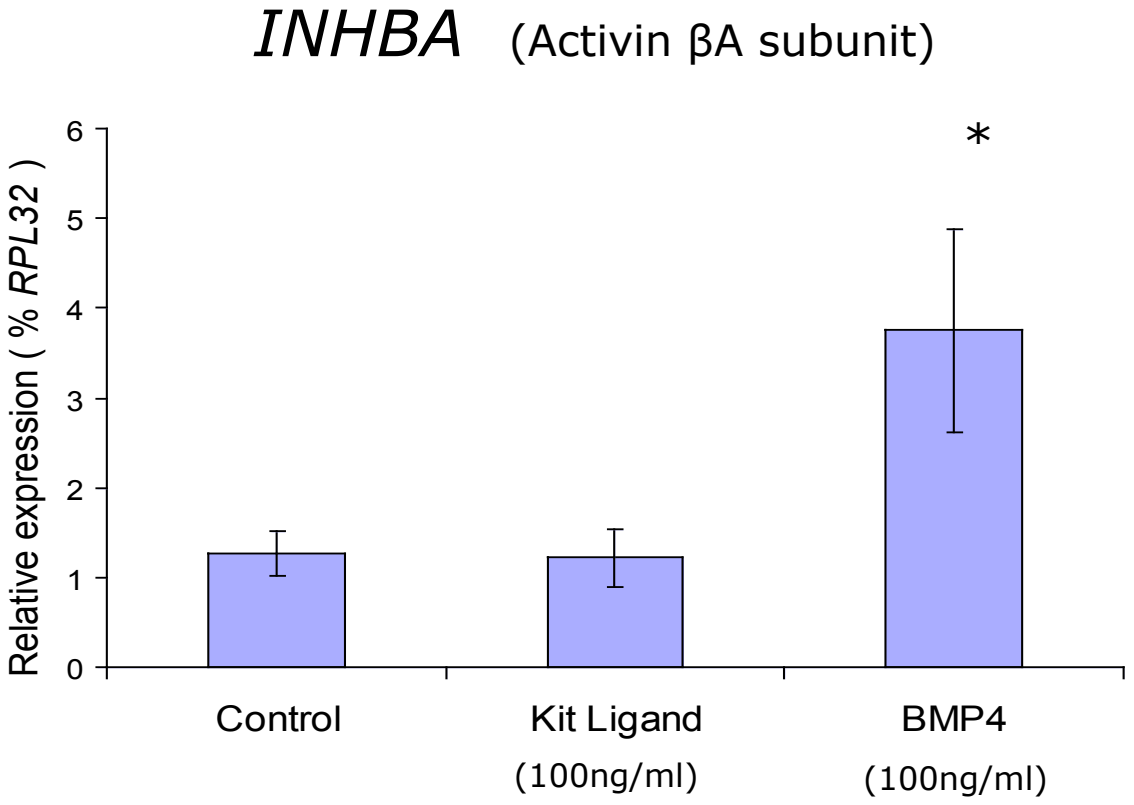
Selective effects on KL isoforms- trigger for follicle formation?





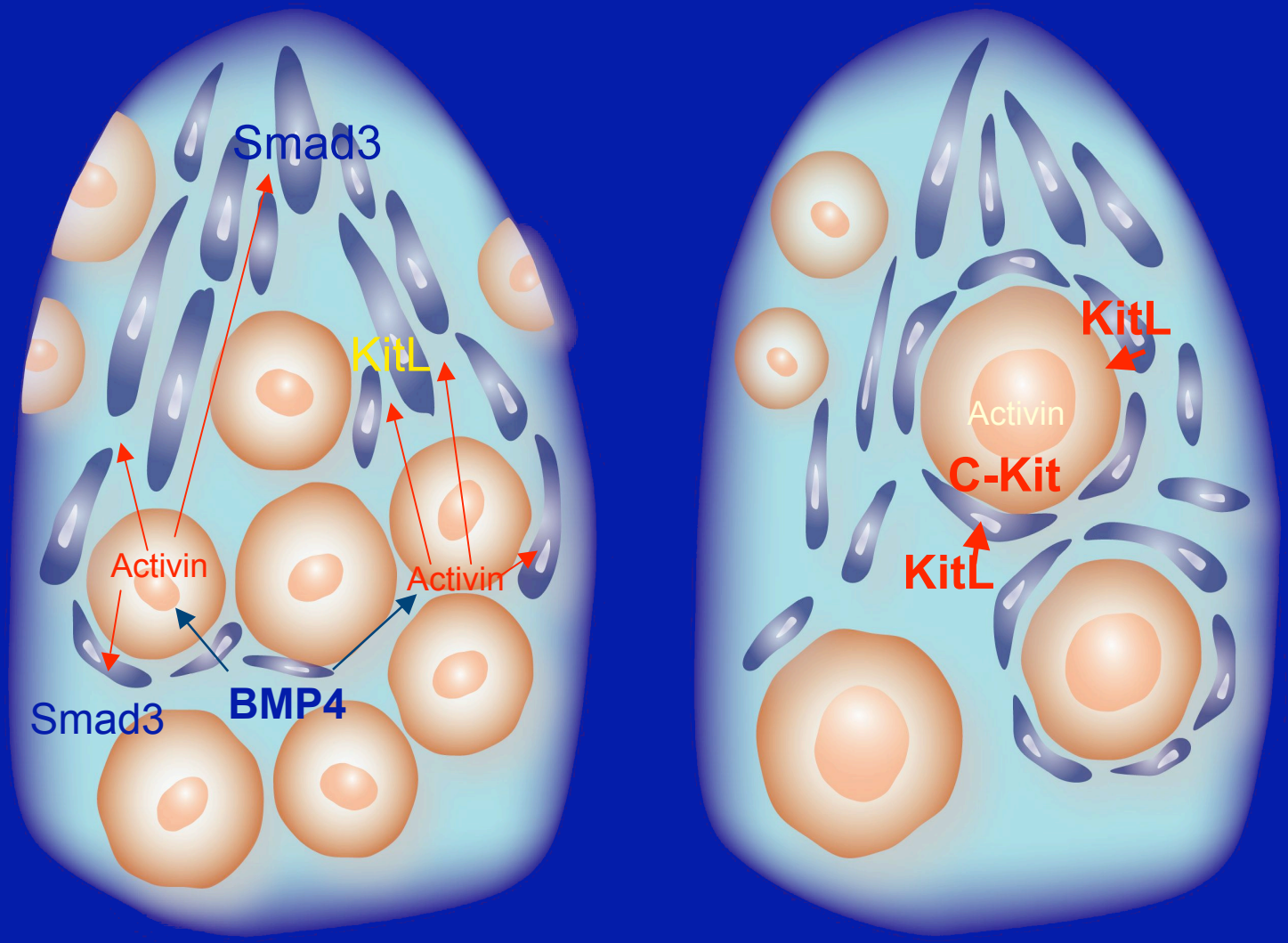
Childs and Anderson 2009 Fertil Steril in press

What regulates activin expression?



disaggregated ovaries, 24hrs, n=3 (14-15w)

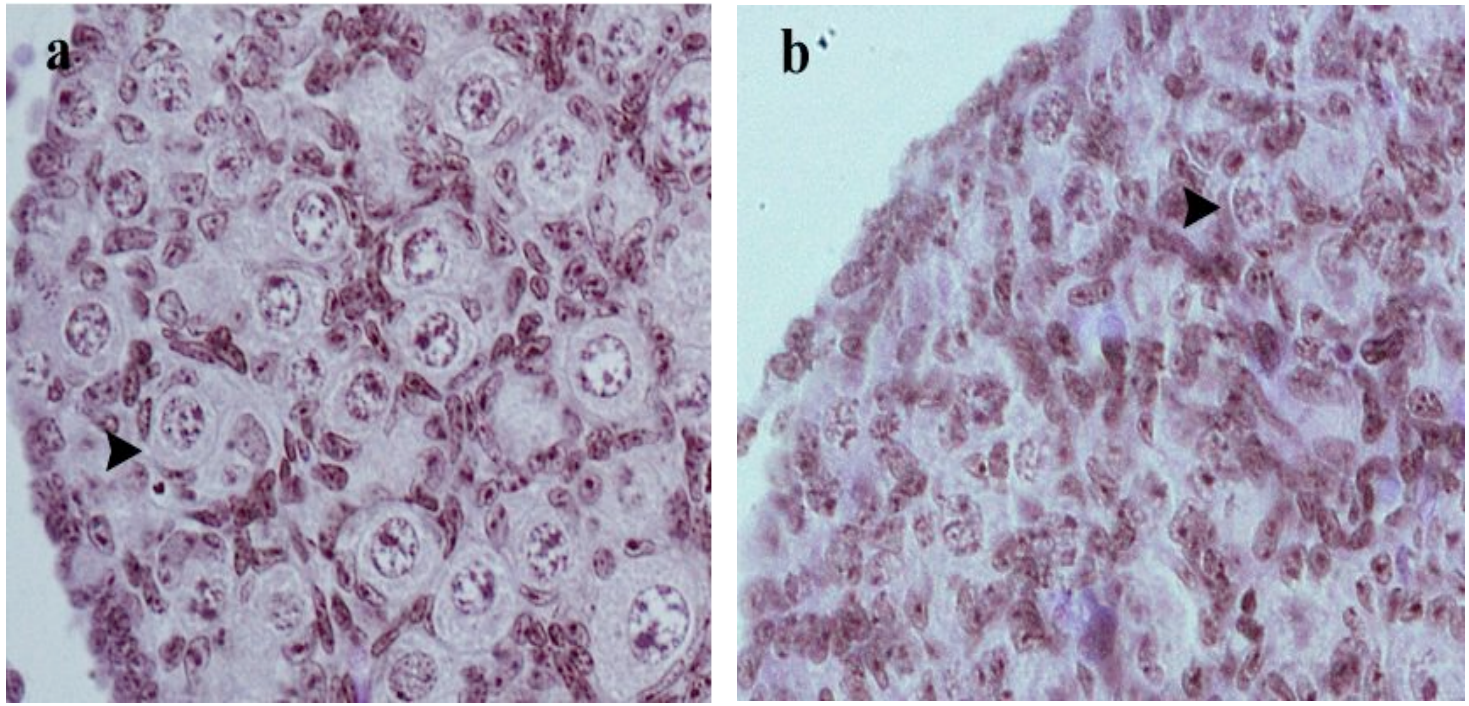
Primordial follicle formation



Oocyte cluster

Primordial follicle

Neurotrophins in the rodent ovary



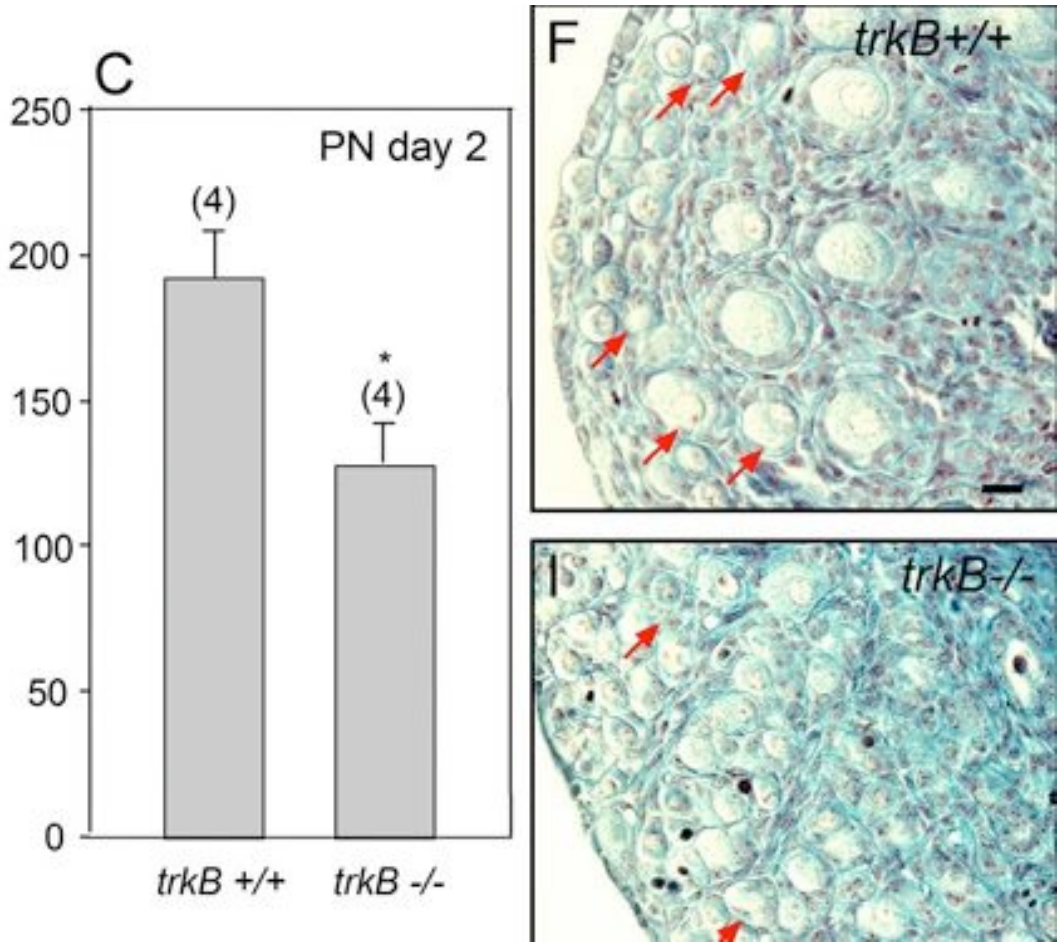
Wild type

Trk B mutant

P4 ovary: near complete loss of primordial follicles

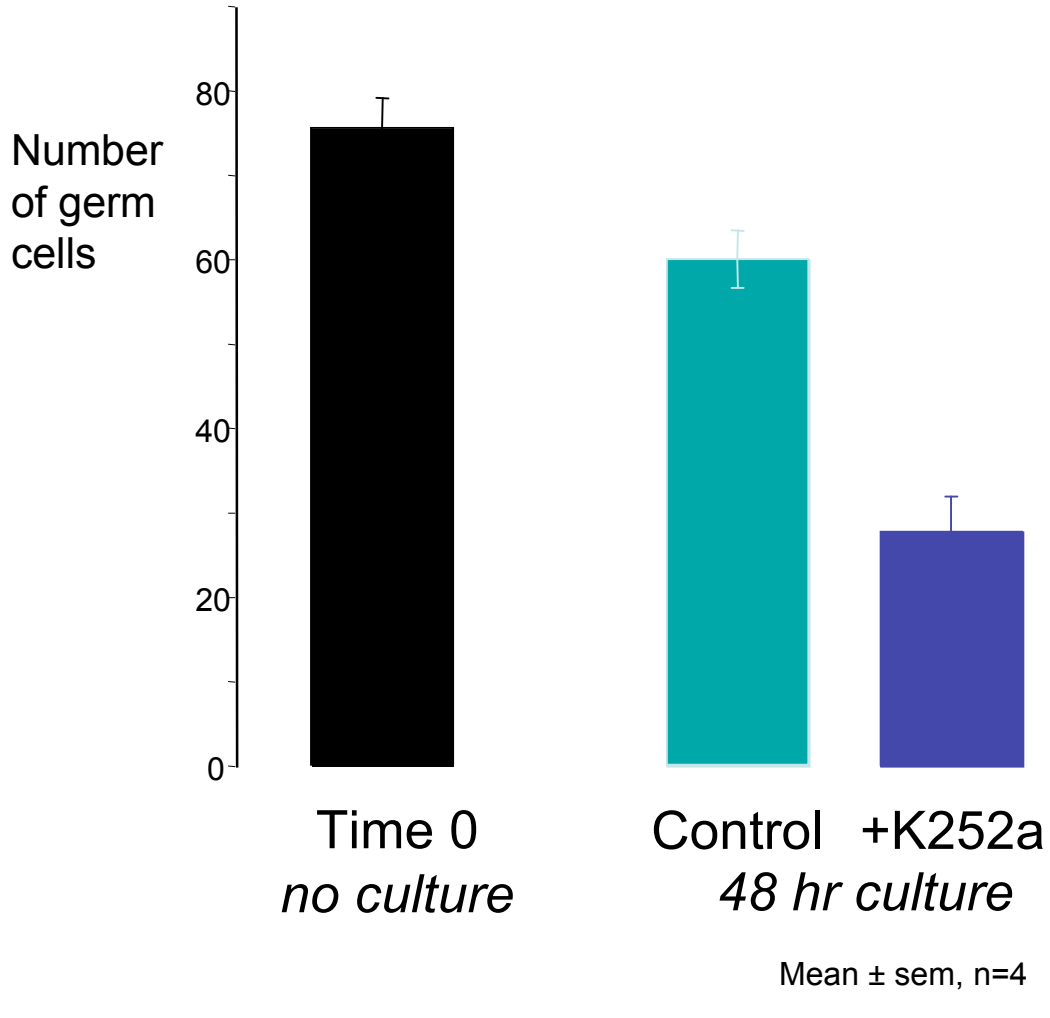
Spears et al 2003, Development 130, 5481

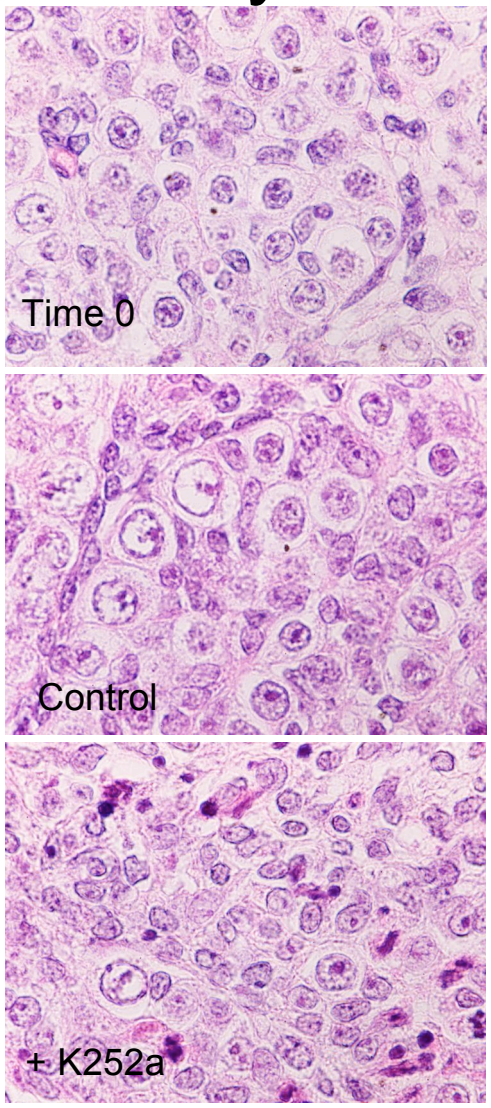
‘TrkB receptors facilitate follicle assembly in the mouse’



Kerr et al 2009 Reproduction

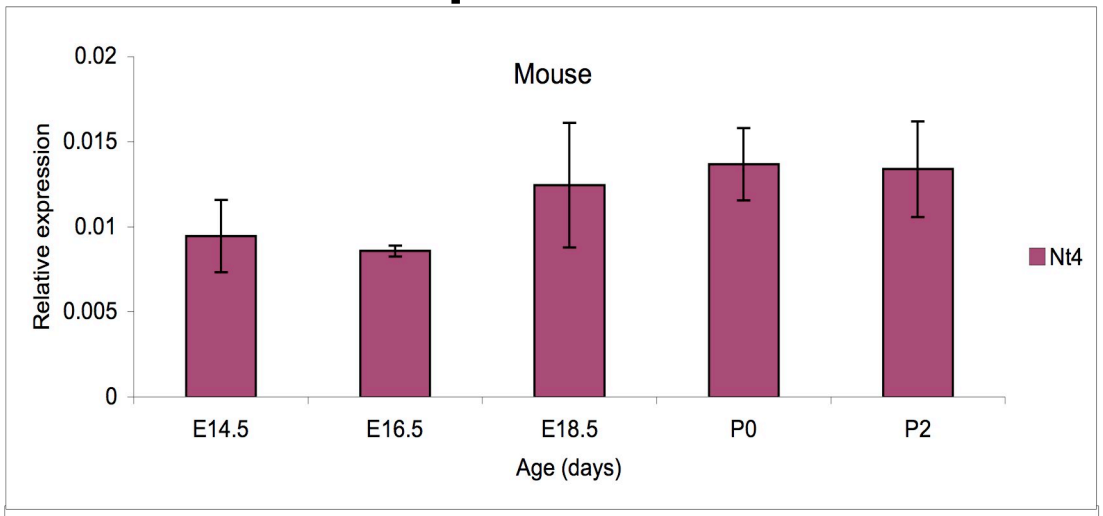
Trk receptor blockade reduces germ cell survival in fetal human ovary

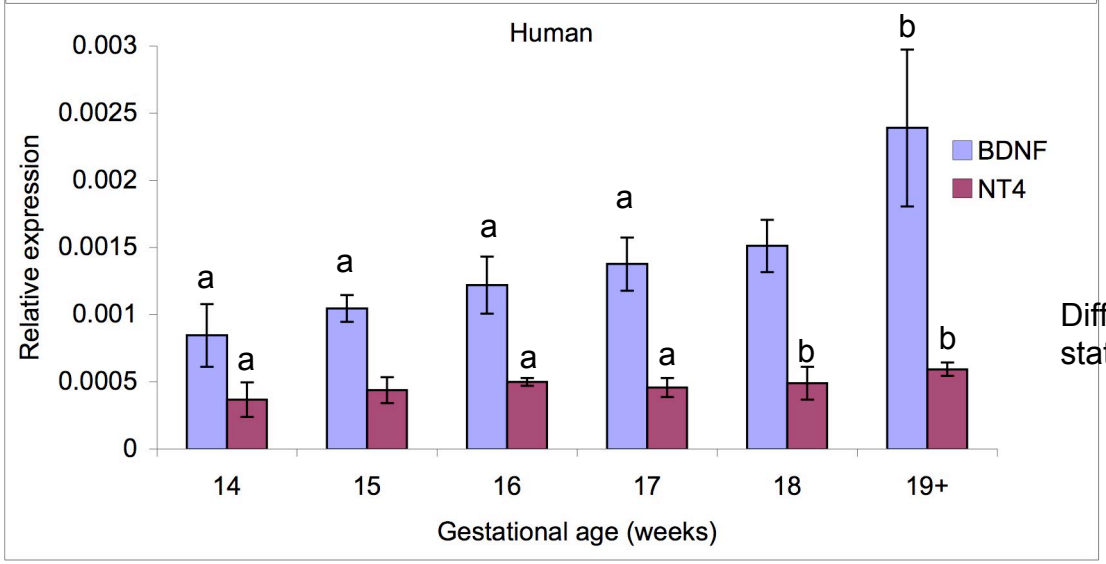




Spears et al 2003, Development 130, 5481

Human and mouse BNDF and NT4 expression

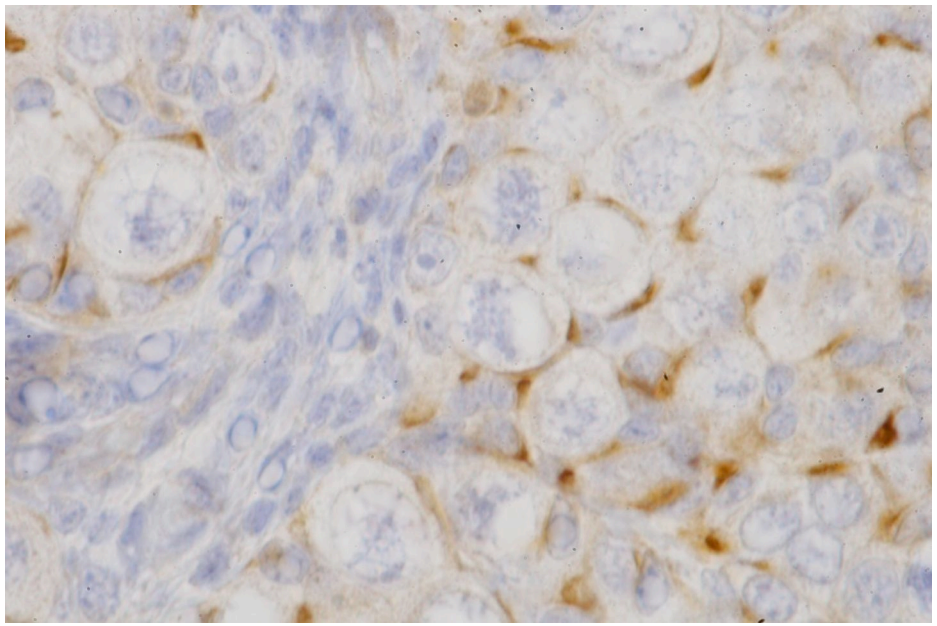




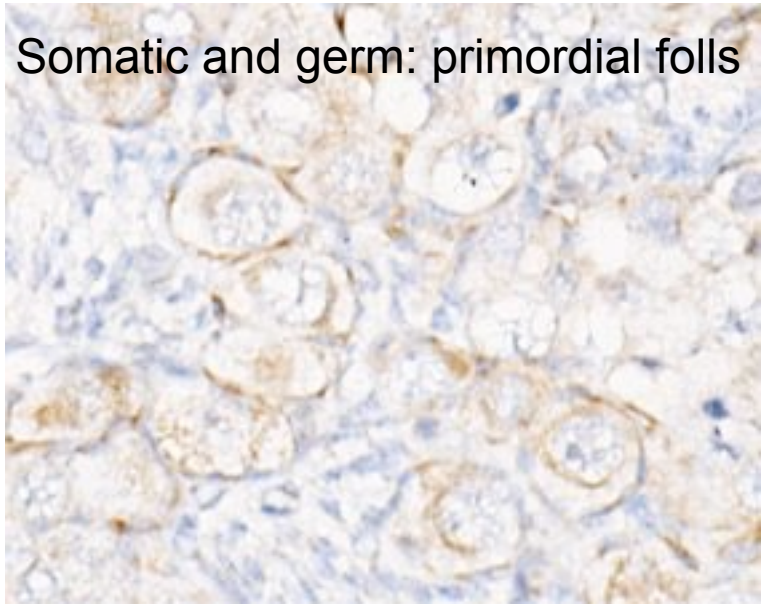
Different superscript= statistical difference

Human fetal ovary: BDNF expression

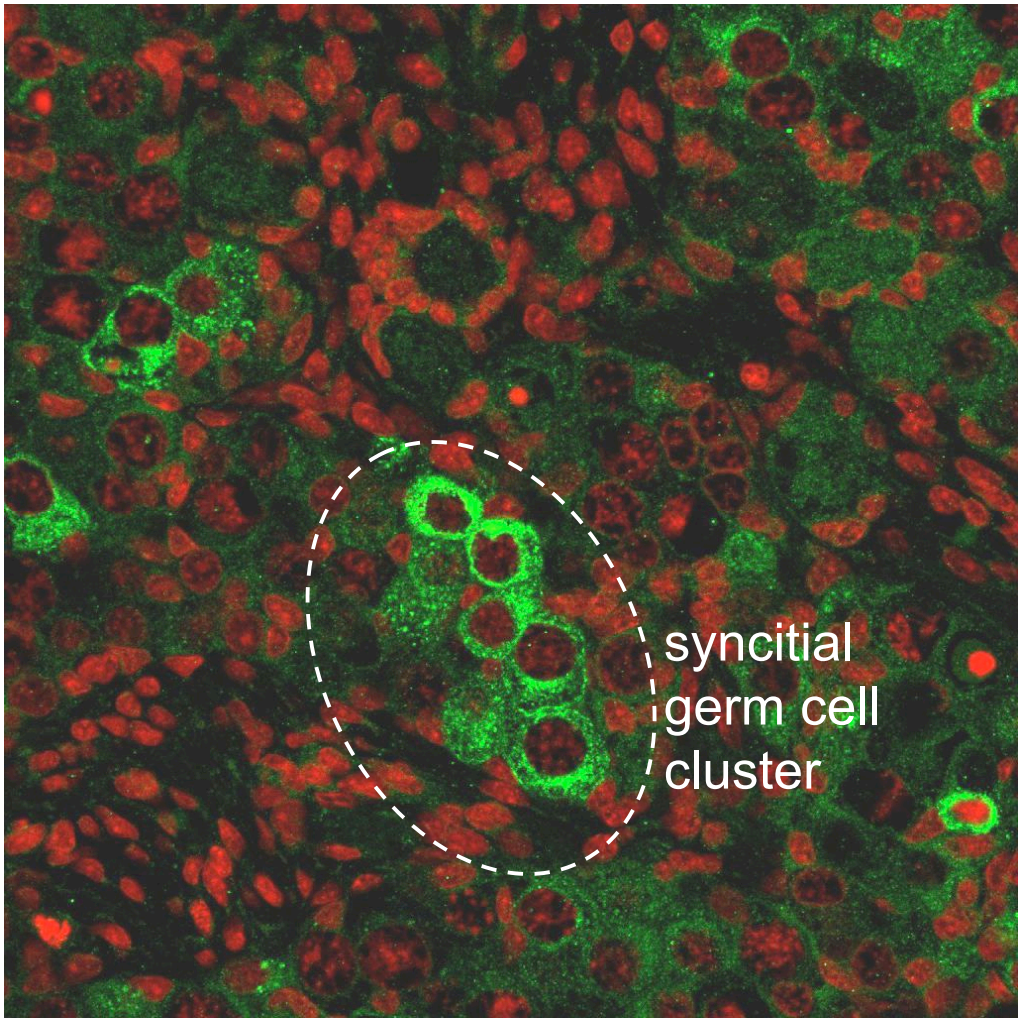
BDNF expression, 18-20 weeks



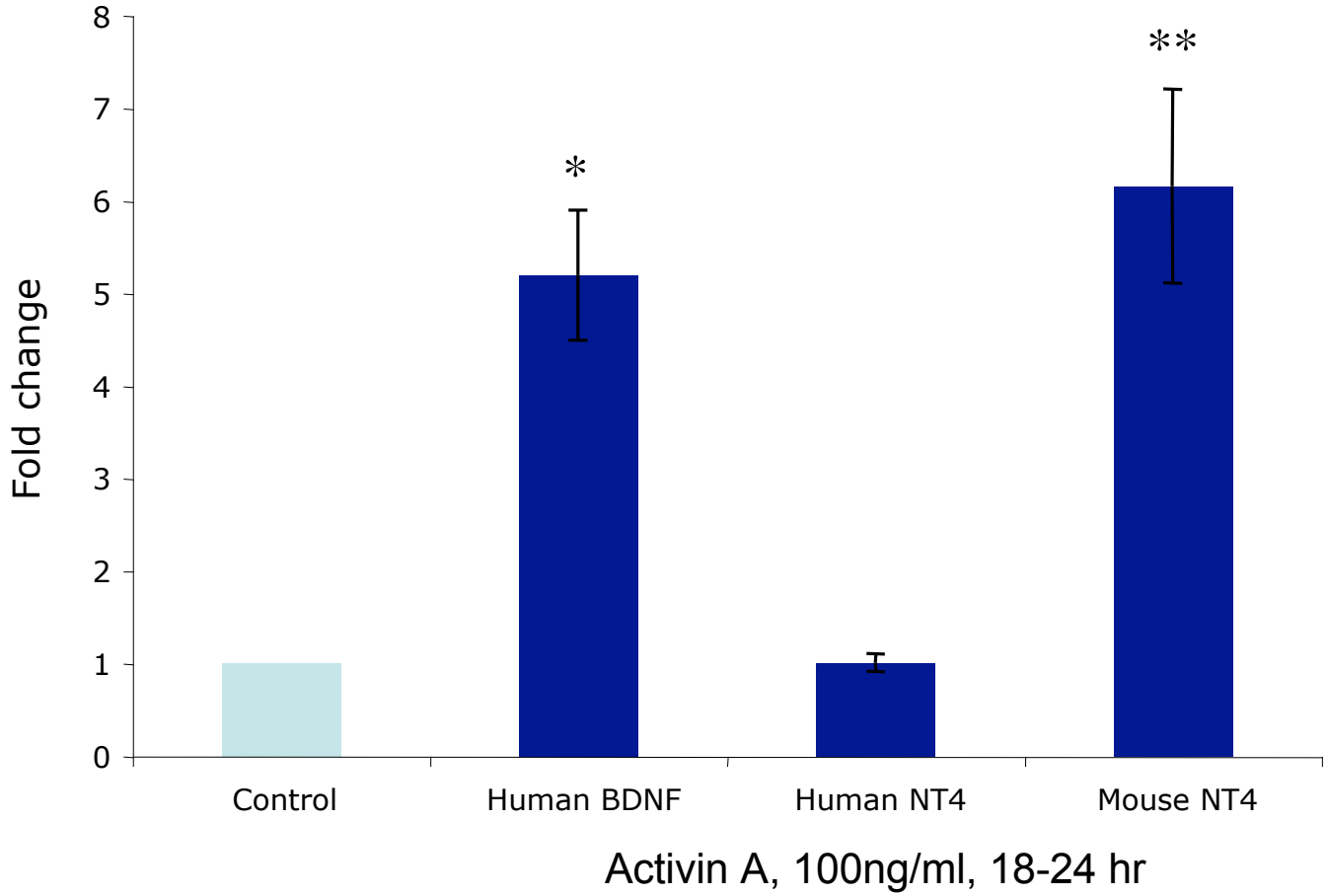
Somatic cells adjacent to oocytes



Expression of activin βA in clustered germ cells

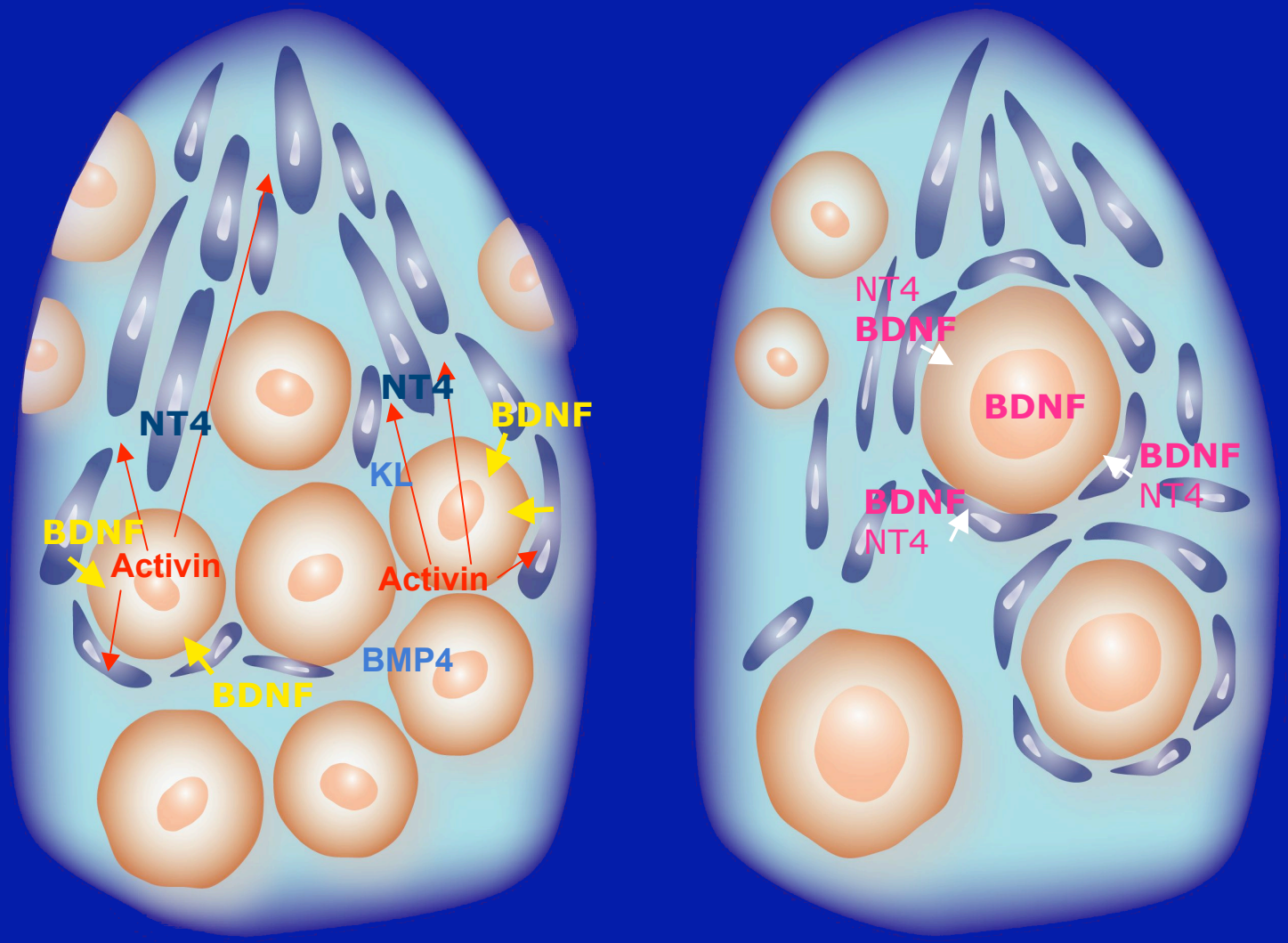


Activin A increases neurotrophin expression in vitro



Human: disaggregated ovary, 14-17 wks
Mouse: purified P0 somatic cells; both n=4

Primordial follicle formation

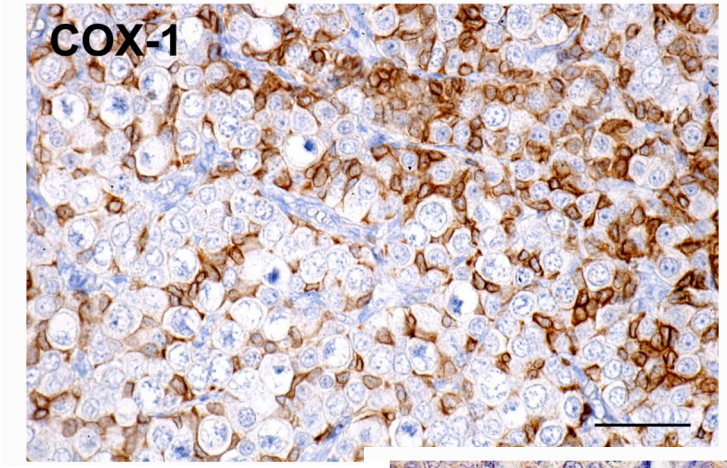


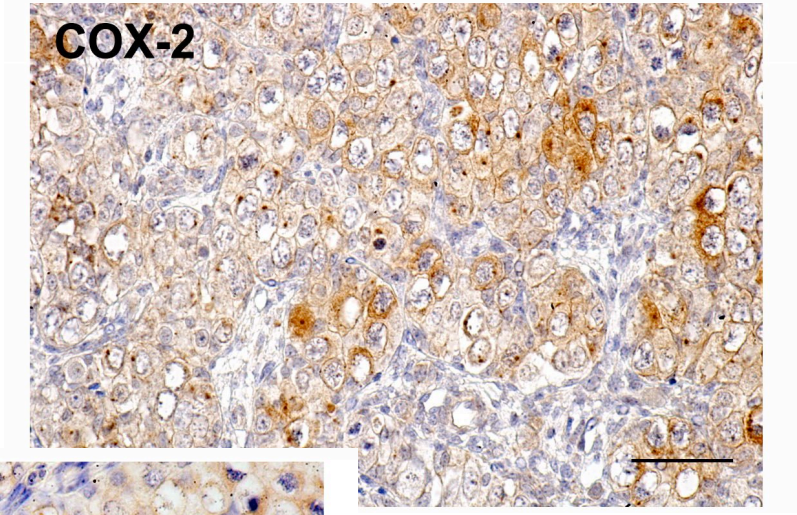
Oocyte cluster

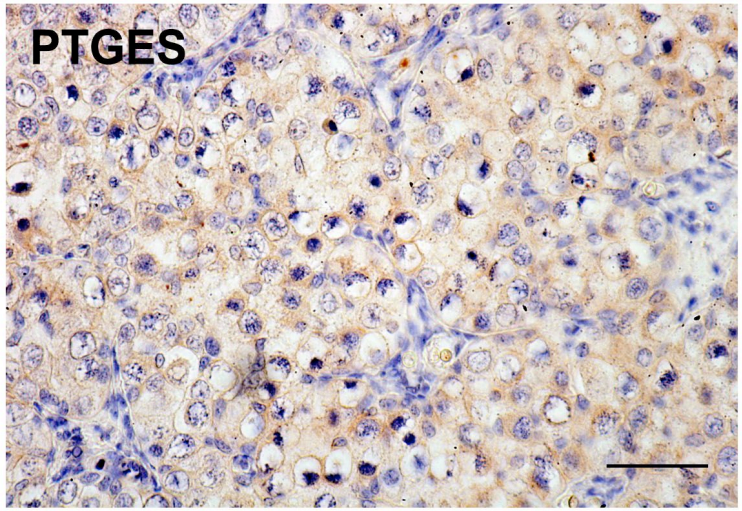
Primordial follicle

Prostaglandins regulate ovarian development?

PGE2 Synthesis Enzyme Location

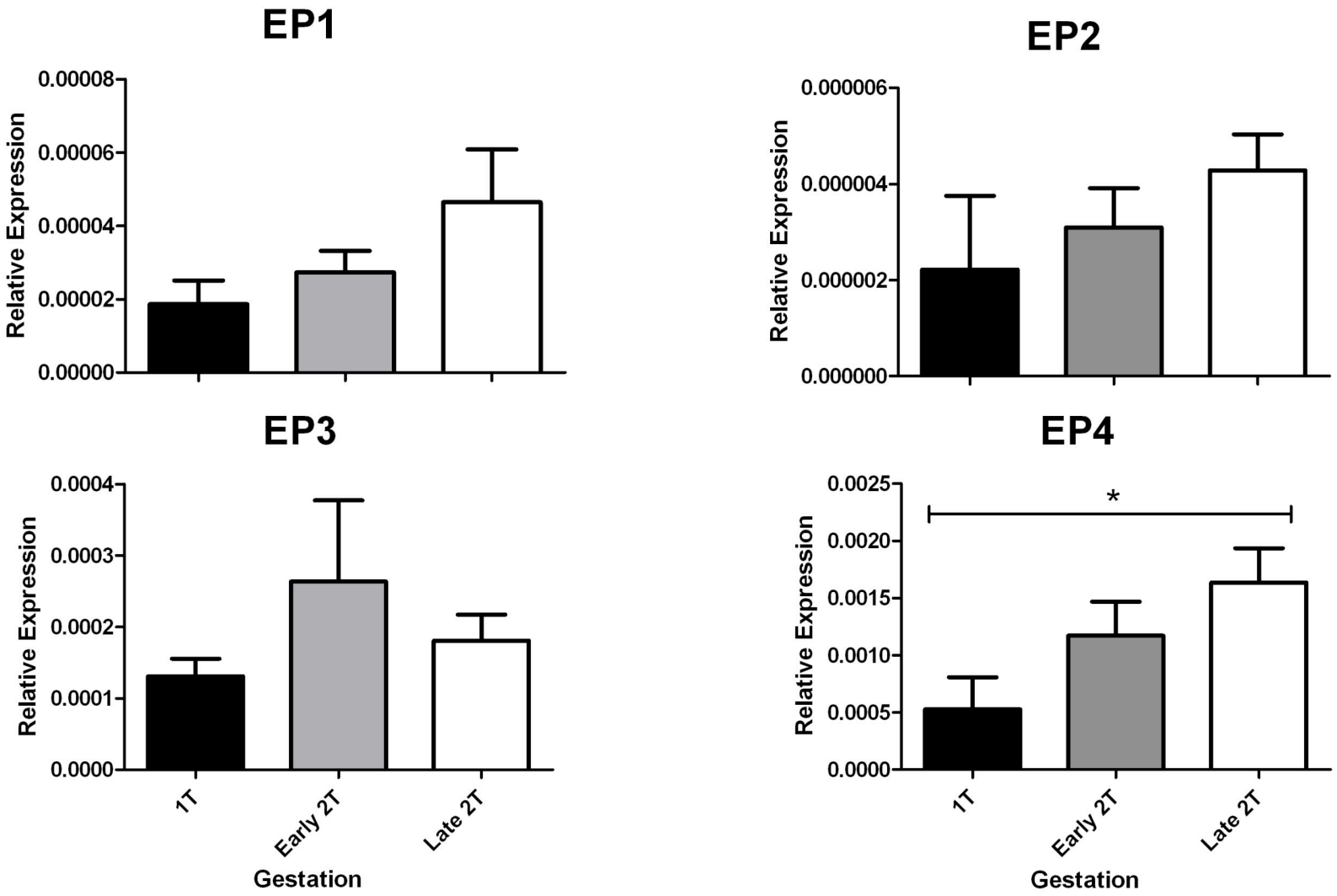




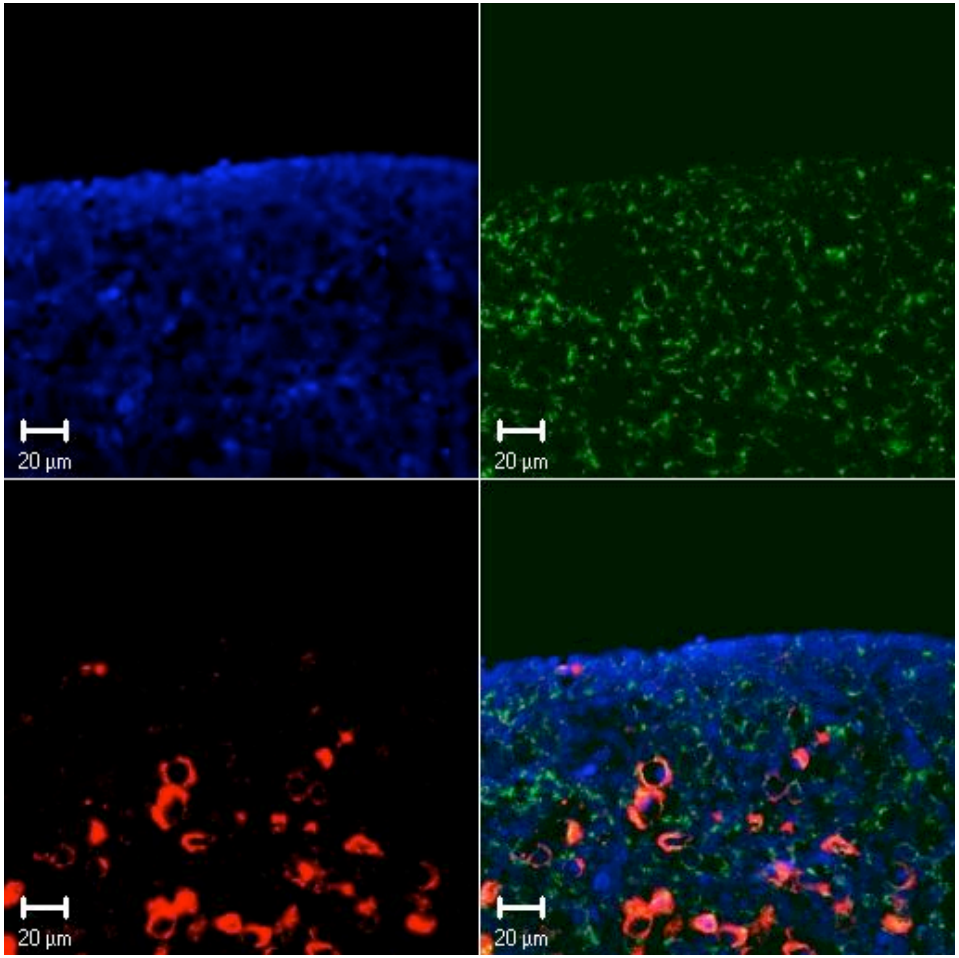


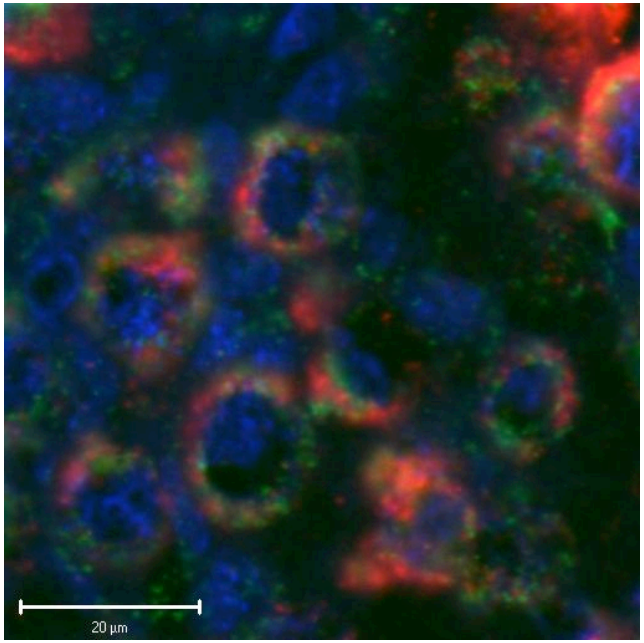
Bayne et al 2009 JCE&M in press

PGE2 Receptor Expression



EP2/EP4 co-localisation in germ cells





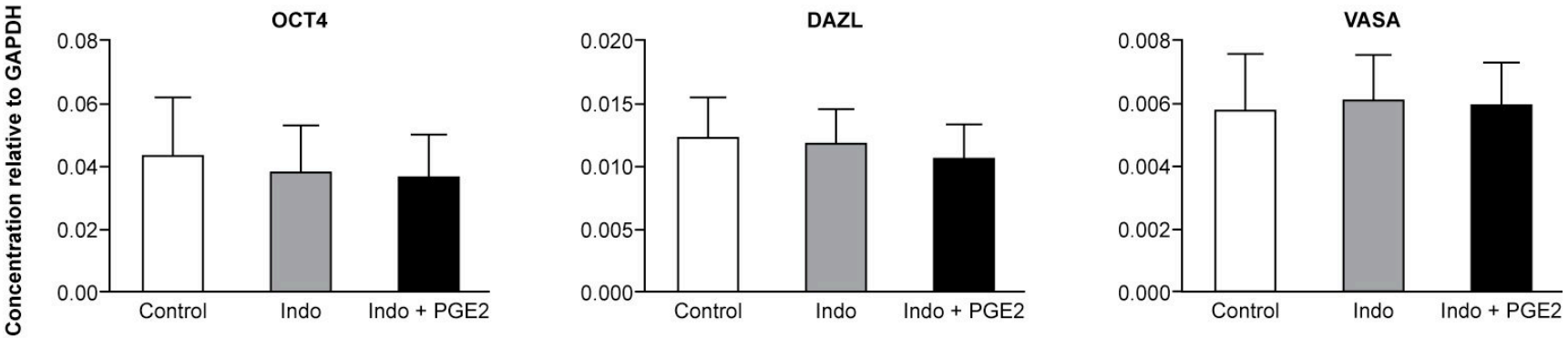
EP2 Red

EP4 Green

Dapi Counterstain

Bayne et al 2009 JCE&M in press

PGE_2 regulates growth factor expression in fetal ovary

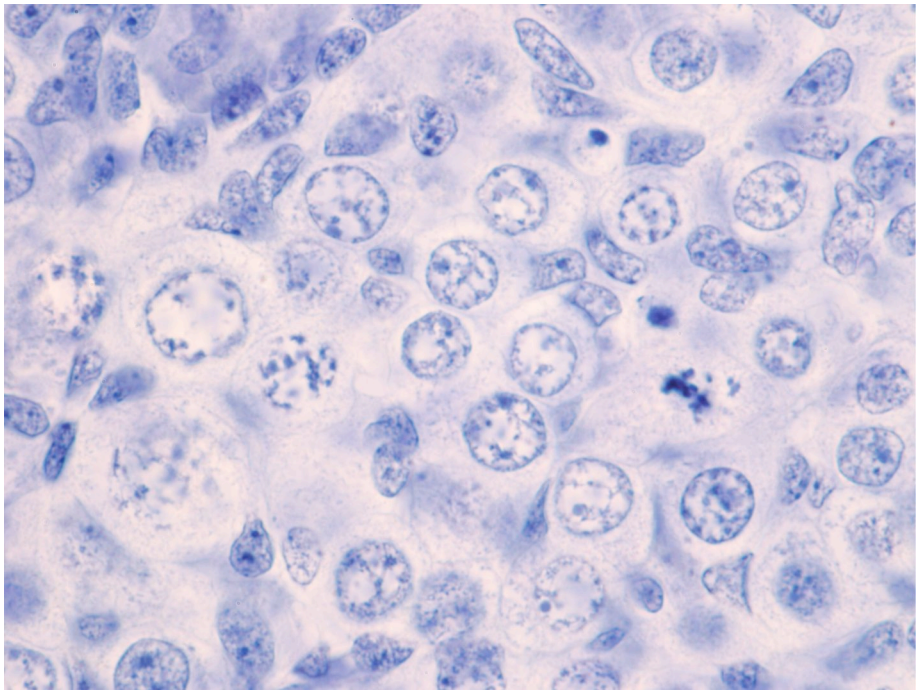


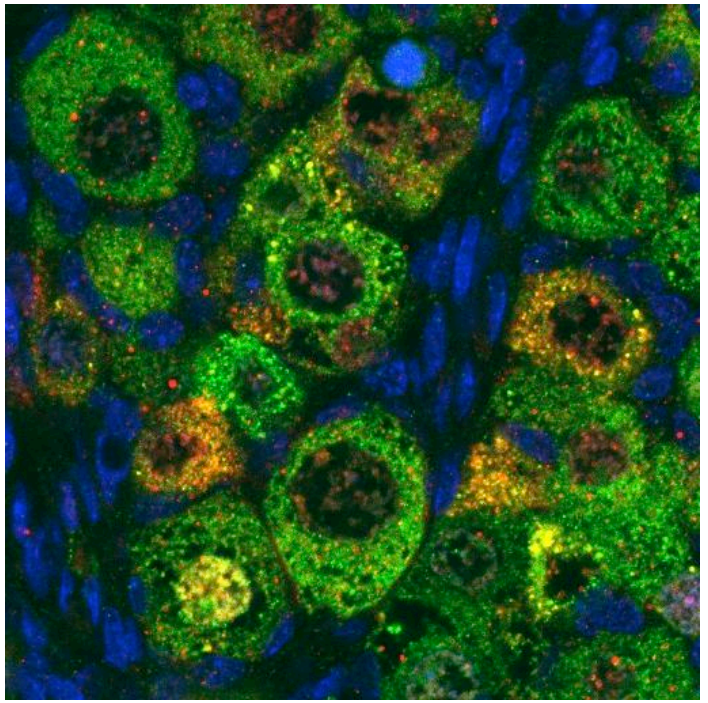
Bayne et al 2009 JCE&M in press

Conclusions

Ovarian development

- Complex interaction of germ and somatic cell growth factors
- Interaction with onset of meiosis although not exclusively linked





Acknowledgements

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Joan Creiger
Anne Saunderson
Isobel Morton
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