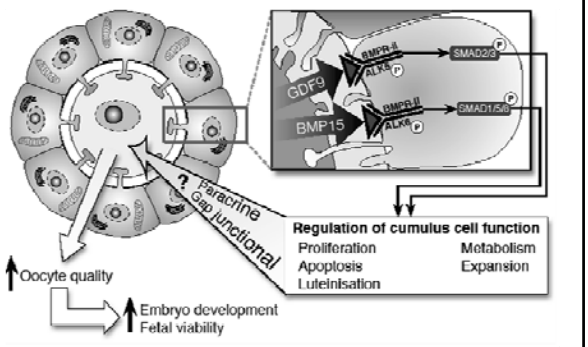
How cumulus cell function is regulated and why

Robert Gilchrist

Robinson Institute

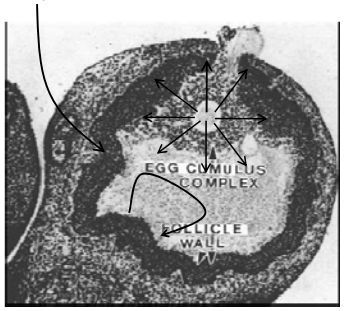
How cumulus cell function is regulated and why



Gilchrist RB (2011) *Reprod. Fert. Dev.* 23:23-31

Endocrine & paracrine signaling coordinate folliculogenesis & oogenesis

FSH, LH



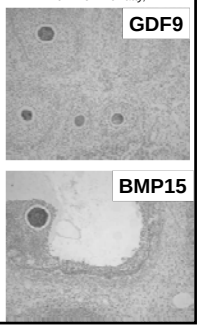
GDF9 and BMP15: species-specific effects on ovulation rate and fecundity

1. **Expression restricted to oocytes**
2. **Essential for follicular development & fertility**

	Mouse	Sheep
GDF9 -/-	**sterile**	**sterile**
GDF9 +/-	**fertile**	**high fertility**
BMP15 -/-	**sub-fertile**	**sterile**
BMP15 +/-	**fertile**	**high fertility**
GDF9+/-BMP15+/-	**fertile**	**super fertile**

(Dong et al 1996, Yan et al 2001, Galloway et al 2000, Hanrahan et al 2004)

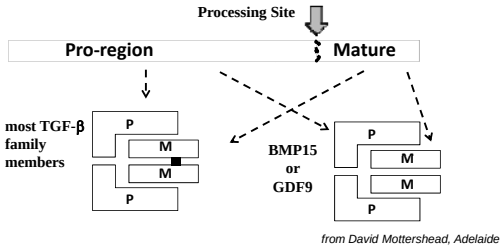
from Ken McNatty, NZ



GDF9/BMP15 and human fertility

- Premature Ovarian Failure:
  Mutations and sequence variations in GDF9 and BMP15
  - Di Pasquale *et al* (2004), Dixit *et al* (2006), Laissue *et al (2006)*
- DZ Twinning:
  Rare GDF9 variants in mothers of DZ twins
  - Montgomery *et al* (2004), Palmer *et al* (2006)
- PCOS:
  Aberrant oocyte expression of GDF9
  - Teixeira Filho FL *et al* (2002)
- OHSS:
  Polymorphisms in BMP15 predispose to OHSS??
  - Morón *et al* (2006)

Processing of GDF9 and BMP15



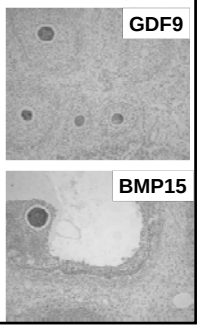
from David Mottershead, Adelaide

- Lack the 4th cysteine, so non-covalent homodimers. Heterodimer??
- Only unprocessed promature proteins in follicular fluid.
- Detection: no reliable assays. Poor quality antibodies

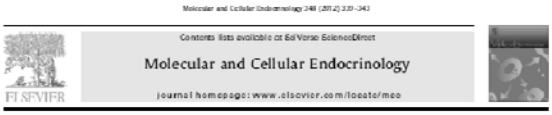
Control of relative bioavailability of GDF9 and BMP15?

- **Major differences in role of GDF9/BMP15 between mono & poly-ovular species**
- **Multiple complex processes possible, incl.:**
  - **Relative expression levels of GDF9 and BMP15** (Crawford & McNatty 2012)
  - **Inactivation (latency) of GDF9 or BMP15** (Simpson et al 2012)

from Ken McNatty, NZ



Species-specificity of GDF9:BMP15 ratios


Molecular and Cellular Endocrinology 348 (2012) 339–343

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Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

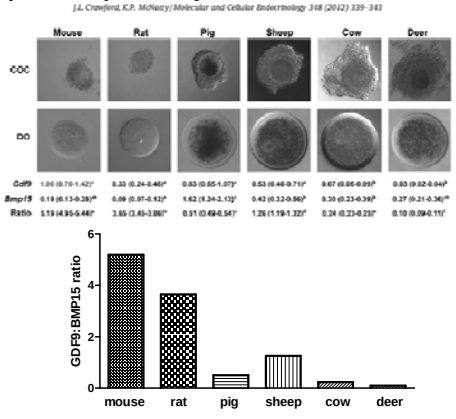
The ratio of growth differentiation factor 9: Bone morphogenetic protein 15 mRNA expression is tightly co-regulated and differs between species over a wide range of ovulation rates

Janet L. Crawford *, Kenneth P. McNatty

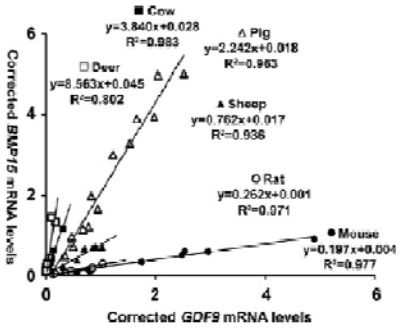
Victoria University of Wellington, School of Biological Sciences, P.O. Box 600, Wellington 6140, New Zealand

Crawford JL & McNatty KP (2012) *Mol. Cell. Endocr. 348*:339-343

Species-specificity of GDF9:BMP15 ratios



Species-specificity of GDF9:BMP15 ratios



Crawford JL & McNatty KP (2012) *Mol. Cell. Endocr. 348*:339-343

Activation of latent human GDF9

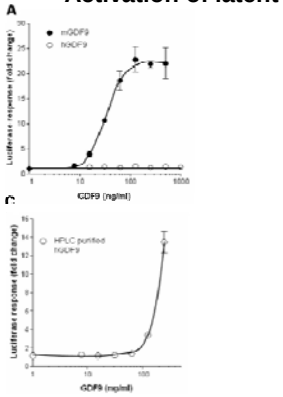
Activation of Latent Human GDF9 by a Single Residue Change (Gly^{391}Arg) in the Mature Domain

Courtney M. Simpson, Peter G. Stanton, Kelly L. Walton, Karen L. Chan, Lesley J. Ritter, Robert B. Gilchrist, and Craig A. Harrison

Prince Henry's Institute of Medical Research (C.M.S., P.G.S., K.L.W., K.L.C., C.A.H.), Clayton, Victoria 3168, Australia; Department of Biochemistry and Molecular Biology (C.M.S.), Monash University, Clayton, Victoria 3800, Australia; and Robinson Institute (L.J.R., R.B.G.), Research Centre for Reproductive Health, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia 5005, Australia

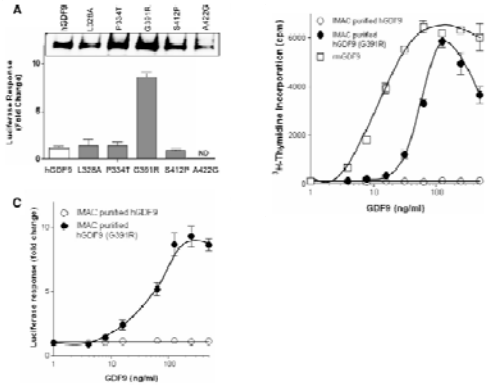
Simpson CM *et al* (2012) *Endocr.* 153:1301-1310

Activation of latent human GDF9



Simpson CM *et al* (2012) *Endocr.* 153:1301-1310

Activation of latent human GDF9



Simpson CM *et al* (2012) *Endocr.* 153:1301-1310

Synergistic interactions between GDF9 and BMP15

Molecular Human Reproduction, Vol.18, No.3 pp. 121–128, 2012
Advanced Access publication on September 12, 2011 doi:10.1093/molehr/gar056

MHR ORIGINAL RESEARCH

Signalling pathways mediating specific synergistic interactions between GDF9 and BMP15

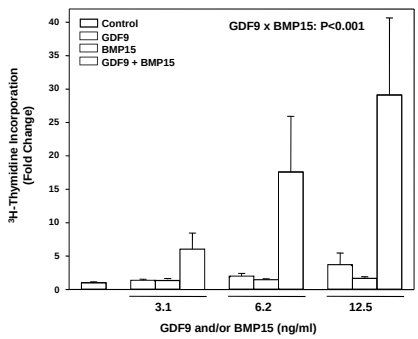
David G. Mottershead*, Lesley J. Ritter, and Robert B. Gilchrist

Research Centre for Reproductive Health, Discipline of Obstetrics and Gynaecology, Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide 5005, Australia

GDF9/BMP15 interactions:

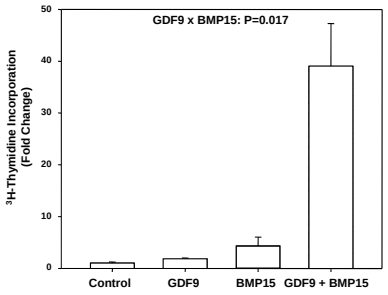
- McNatty *et al* 2005a,b *Mol. Cell. Endocr.*
- Edwards *et al* 2008 *Endocr.*
- Reader *et al* 2011 *Reprod.*

GDF9 and BMP15 synergism: MGCs



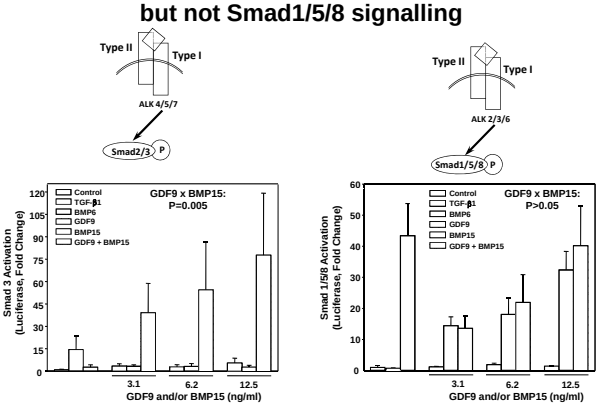
Mottershead DG *et al* (2012) *Mol. Hum. Reprod.* 18:121-128

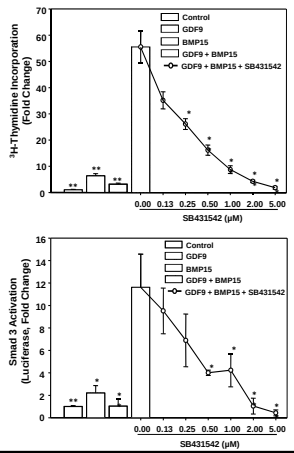
GDF9 and BMP15 synergism: CCs

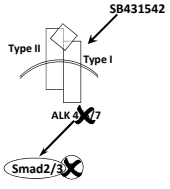


Mottershead DG *et al* (2012) *Mol. Hum. Reprod.* 18:121-128

GDF9 and BMP15 synergism: activation of Smad2/3 but not Smad1/5/8 signalling

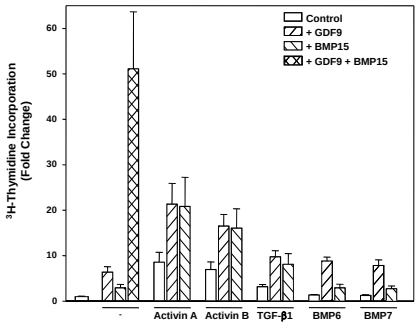






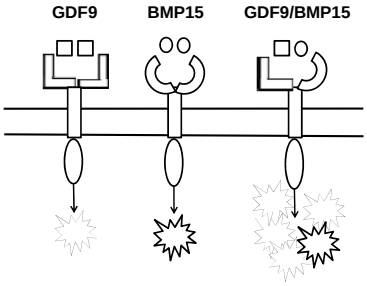
Mottershead DG *et al* (2012) *Mol. Hum. Reprod.* 18:121-128

GDF9 and BMP15 synergism is specific



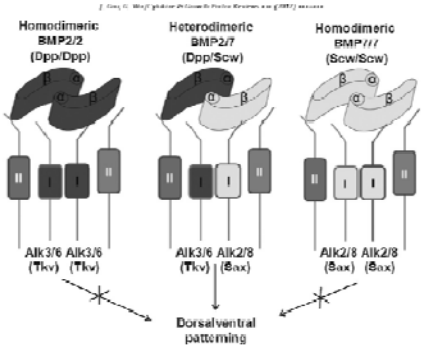
Mottershead DG *et al* (2012) *Mol. Hum. Reprod.* 18:121-128

What is the mechanistic basis of GDF9 / BMP15 synergism?



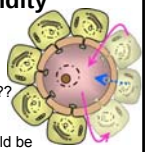
from David Mottershead, Adelaide

Consequenes of homodimeric vs heterodimeric signalling



Guo and Wu (2012) *Cytokine and growth factor reviews. Epub*

Unusual features of oocyte-secreted GDF9/BMP15 that affect CC function and fecundity



- Lack the 4th cysteine, so non-covalent homo- or hetero-dimers??
- Substantial GDF9/BMP15 synergism. Mechanism?
- GDF9 and BMP15 are expressed and function together – should be considered a functional unit, however….
- Expression ratios of GDF9 and BMP15 mRNA are tightly regulated within a species, but differ substantially between species
- GDF9 is predominant in rodents, BMP15 in non-rodents
- Prodomain–mature domain interactions have notable effects on activity, and there are major differences between species
- GDF9 is latent in humans and maybe most mono-ovular species
- Regulation of interactions or relative bioactivities of GDF9/BMP15 may be a fundamental determinant of oocyte quality, and mammalian ovulation rates and fecundity

Acknowledgements

Robinson Institute, RCRH, University of Adelaide, Australia

David Mottershead
Lesley Ritter
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Victoria University of Wellington, NZ
Ken McNatty

Prince Henry's Institute of Medical Research, Melbourne
Craig Harrison, Courtney Simpson, Peter Stanton, David Robertson

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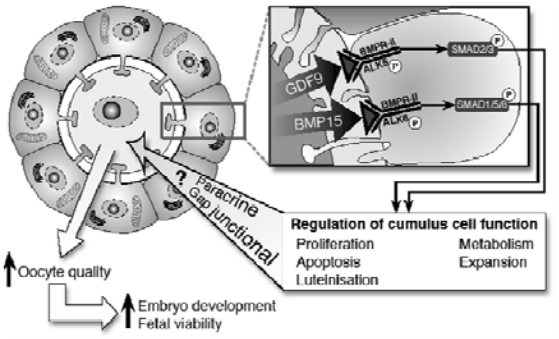
-**NHMRC Australia: Program, Program & Development Grants. CDA Fellowship**
- **Cook Medical**

Treatment with OSFs during IVM improves development

- Bovine: Native OSFs, BMP15, GDF9 improves embryo development and quality *(Hussein T et al 2006 Dev. Biol. 296:514-521)*
- Murine: GDF9 improves blastocyst quality and fetal survival *(Yeo CX et al 2008 Hum. Reprod. 23:67-73)*
- Bovine: Native OSFs, BMP15, GDF9 have different temporal effects on improved embryo development and quality *(Hussein T et al 2011 Reprod. Fertil. Dev. 23:576-584)*
- Caprine: Native OSFs improve embryo development of COCs from small antral follicles only *(Romaguera R et al 2011 Therio. Ref…)*
- Porcine: Native OSFs improve embryo development of parthenotes *(Gomez MNL 2011 Zygote ….ref)*
- Bovine: Native OSFs increase %MII, *Gpx1 and Star* expression, prevent zona hardening and improve embryo development *(Dey et al 2012)*

Oocyte-Secreted Factors Regulate CCs and Oocyte Developmental Competence



Gilchrist RB (2011) *Reprod. Fert. Dev.* 23:23-31