MONASH University

MONASH INNOVATION

TREATING INFERTILITY: ENHANCING ASSISTED REPRODUCTIVE TECHNOLOGY

An engineered form of the human oocyte-derived growth factor GDF9, which potently stimulates granulosa cell signaling and function. Our 'Super-GDF9' has great potential to promote oocyte maturation and advance the clinical implementation of the assisted reproductive technique, IVM.

- **Improved 'Super-GDF9' growth factor**
- **Benefits over native oocyte growth factors: ease of production, yield and activity**
- **Experimentally validated mechanism of action**
- **Improve the oocyte quality and the reduce costs of assisted reproductive technologies**

THE CHALLENGE

Oocyte quality is the key rate limiting factor in female fertility. An important practical reason to improve our understanding of the determinants of oocyte quality is to enhance the clinical implementation of oocyte *in vitro* maturation (IVM). IVM is a reproductive technology that enables oocytes to be matured *in vitro* from ovaries that have received no or low levels of gonadotrophic hormone stimulation. Hence IVM drastically reduces the use and cost of gonadotrophins, and the accompanying stress and adverse consequences for patients.

The low pregnancy rate resulting from *in vitro* maturation of human oocytes represents a major obstacle for its clinical application as an adjunct to, or replacement for, costly IVF practices.

We, and others, have recently described a newly identified heterodimer of the TGF-ß family cumulin, comprising GDF9 and BMP15. Cumulin potently stimulates granulosa cell signaling and function, and promotes oocyte quality.

However promising, GDF9/BMP15 (cumulin) heterodimers are difficult to produce and purify, limiting their potential uptake in IVM.

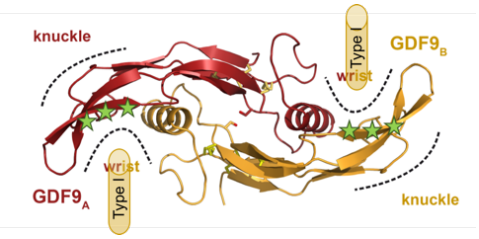

Figure 1: Based on the molecular model of cumulin (GDF9/BMP15 heterodimer), BMP15 residues were introduced into human GDF9 (green stars), creating two high affinity type I receptor binding sites.

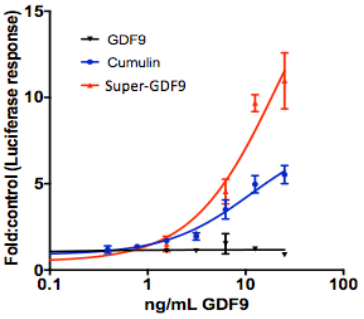

Figure 2: In a SMAD2/3-responsive luciferase reporter assay in COV434 granulosa cells, wild-type hGDF9 is inactive, cumulin displays moderate activity, while our modified Super-GDF9 is extremely potent.

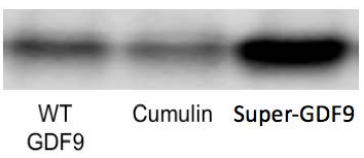

Figure 3: The expression levels of the modified Super-GDF9 in HEK293 cells are 2-4-fold higher than those obtained for wild type GDF9 or cumulin.

To address these issues, we have developed a GDF9 analogue with 'cumulin-like' activity. This Super-GDF9 can be produced easily and has 4-fold greater potency than cumulin.

THE TECHNOLOGY

The Monash team led by Prof. Craig Harrison, have modelled the type I receptor binding sites in cumulin, identified the BMP15 residues that contribute to high affinity receptor binding, and introduced these residues into human GDF9 (*Fig. 1*). The resultant Super-GDF9 has 1000-fold greater potency than wild-type GDF9 and 4-fold greater potency than cumulin (*Figs. 2 & 3*).

The team has generated data supporting that Super-GDF9 potently activates the SMAD2/3 pathway, which is critical for granulosa cell growth and differentiation, and subsequent oocyte maturation.

Current research is aimed at demonstrating the potential of Super-GDF9 for use in IVM.

Intellectual property: An Australian provisional application, directed to methods and agents for treating infertility, has been filed (May 2018).

THE OPPORTUNITY

Monash University seeks a commercial partner to develop Super-GDF9 for use in assisted reproductive technology.

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