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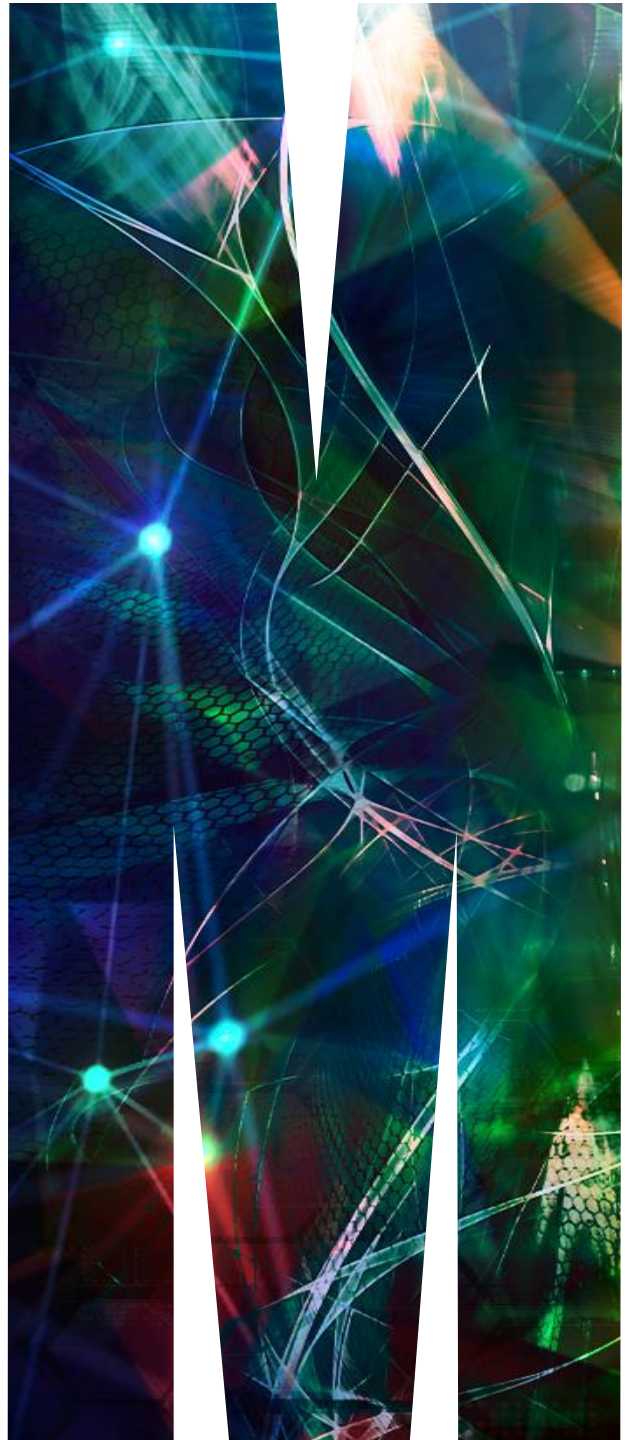
Engineering TGF-β to improve Women's Lifetime Health

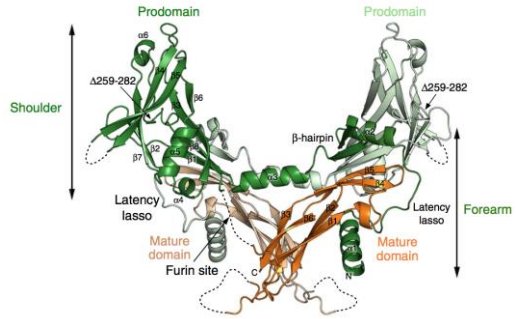
Assoc. Prof. Craig Harrison and Dr. Kelly Walton

July 2019

Biomedical Discovery Institute, Monash University



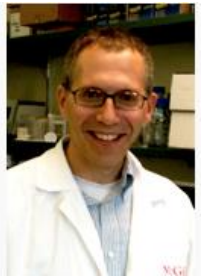
TGF-β Program



- Fertility Preservation — AMH analogue
- Infertility — GDF9 analogue
- Post-menopausal — Inhibin analogue

- Transforming growth factor β (TGF-β) superfamily proteins are potent, naturally occurring molecules that play a key role in the growth and repair of various tissues
- Our research focuses on developing therapies based on TGF-β superfamily biology to target diseases that affect skeletal muscle and the reproductive system
- Our strategy is two-fold:
  1. Engineer TGF-β superfamily proteins to generate potent agonists
  2. Modify the prodomains of TGF-β proteins to generate specific antagonists
- Our understanding of TGF-β biology will enable us to continue to build innovative products with life-altering therapeutic potential

The Team



Professor Dan Bernard
MCGILL UNIVERSITY

Professor Tom Thompson
UNIVERSITY OF CINCINNATI

Prof Dana Gaddy
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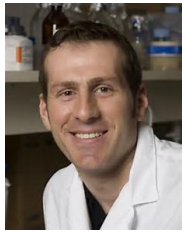

A/Prof Paul Gregorevic
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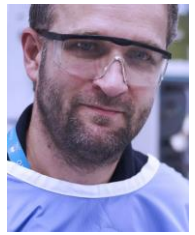
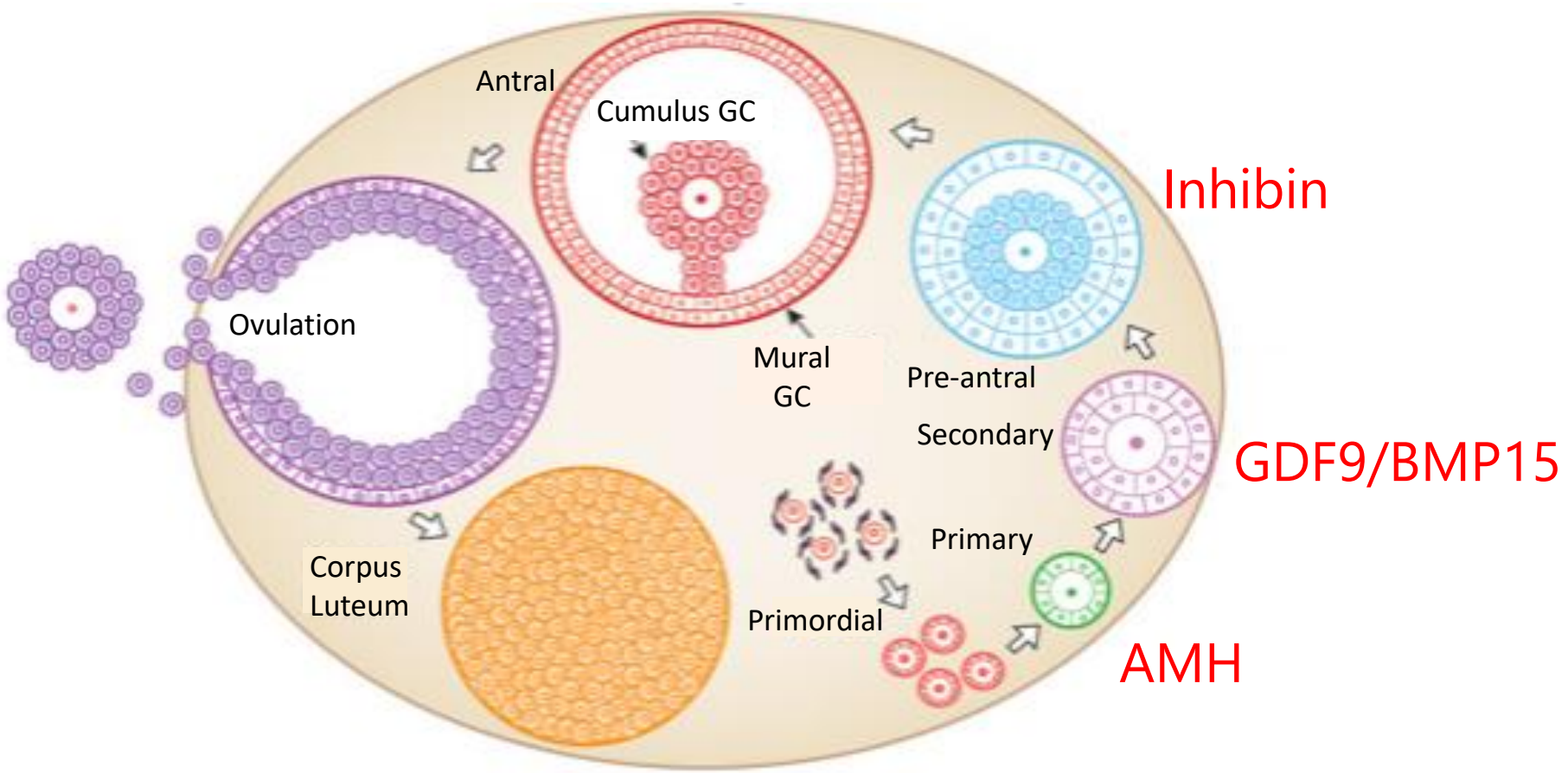
Prof Rob Gilchrist
UNSW

A/Prof Craig Harrison
Dr Kelly Walton
MONASH UNIVERSITY



Prof George Lovrecz
CSIRO

TGF-β proteins involved in female reproduction



Project 1:
Engineering Anti-Müllerian Hormone for Fertility Preservation in Oncology Patients

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Therapeutic Opportunity

- In 2018, there were 18.1 million new cases of cancer diagnosed globally, with around 1.8 million cases occurring in people <45 years of age

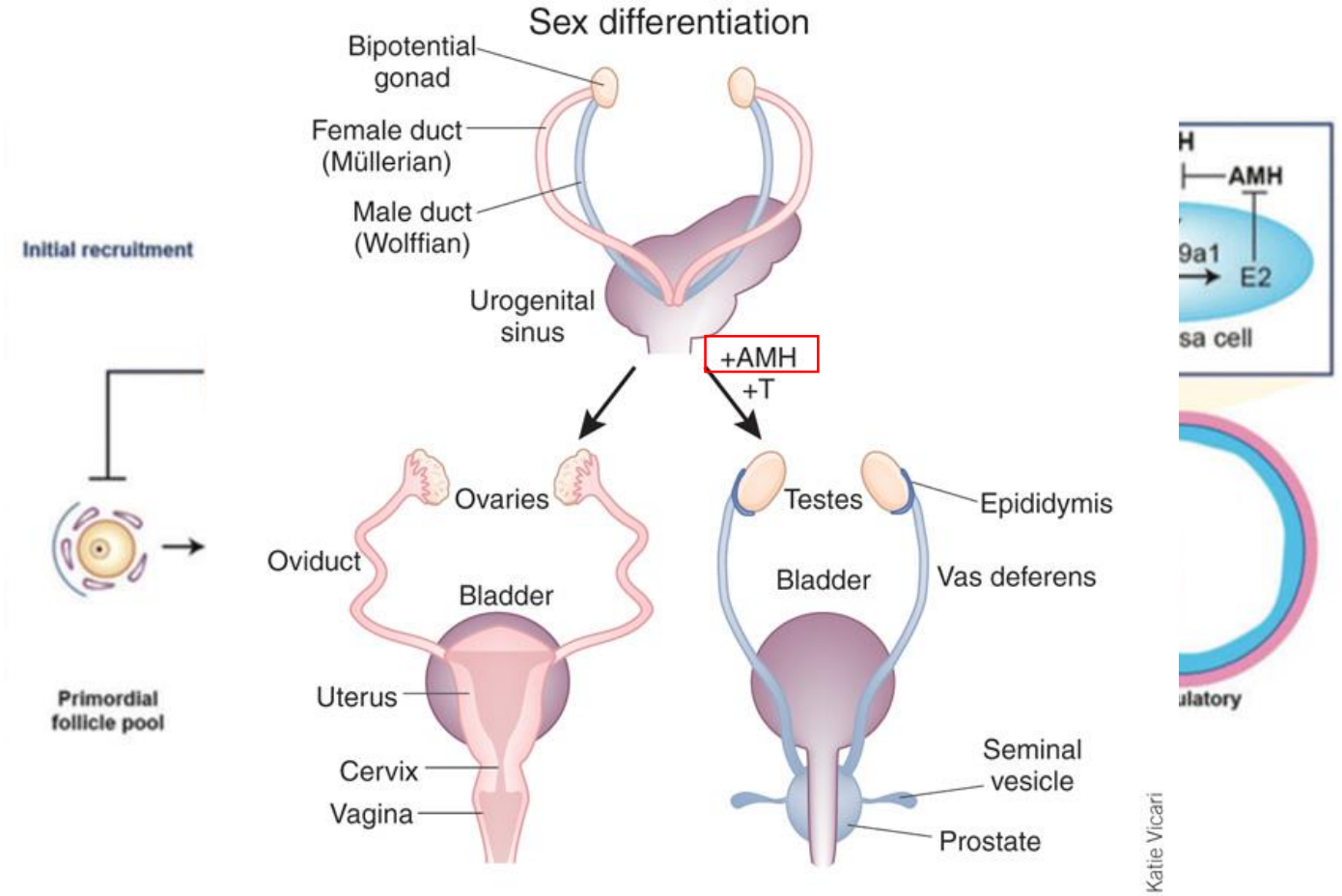
- Infertility or premature ovarian failure has been reported in 40-80% of female cancer survivors, which severely impacts their quality of life and can lead to prolonged psychological stress

- Existing treatments are all interventional with many limitations, including oocyte and embryo banking, and ovarian transplantation

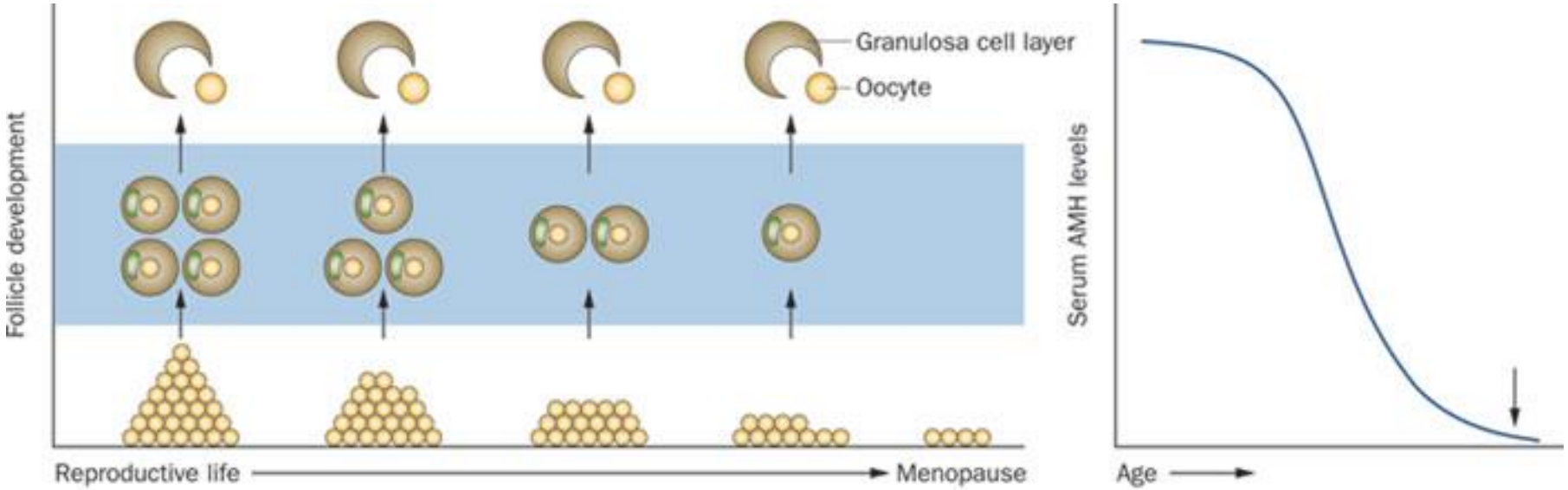
- There is no existing proven non-interventional drug available to protect against the loss of fertility in cancer patients
  - The only other is administration of Gonadotropin agonist before or after chemotherapy, which is largely unproven and remains controversial

Anti-Müllerian Hormone

- Male sex determination



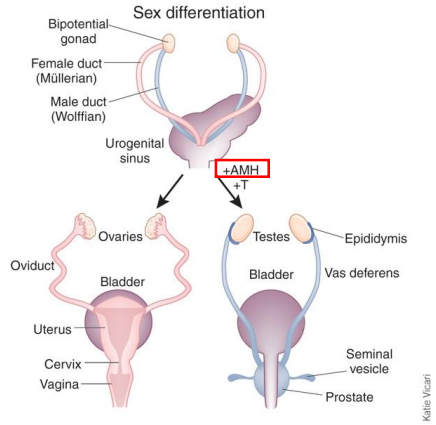
AMH is the best measure of ovarian reserve

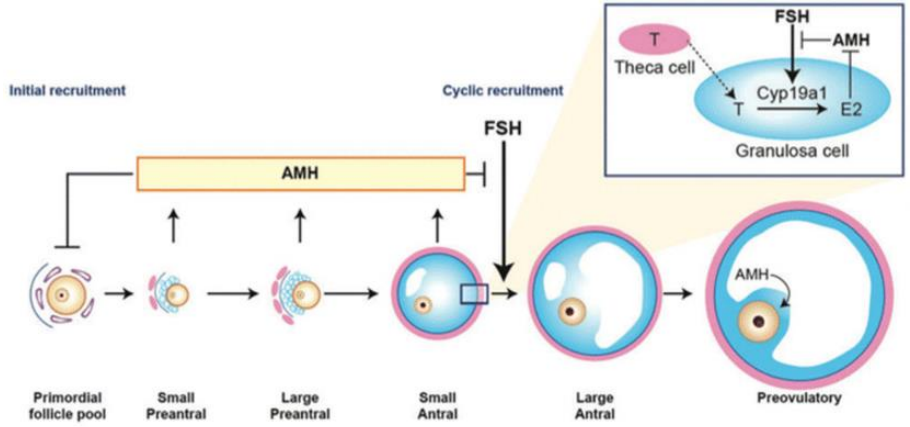


- AMH serum levels decrease with age and are negligible by menopause

Potential therapeutic applications of AMH in reproductive medicine

- Studies have shown the potential of AMH to inhibit the growth of gynaecological tumours
- AMH acts as a reversible contraceptive in mice
- AMH can protect the ovarian reserve during chemotherapy





CONFIDENTIAL

References:
1. M. Kano *et al.* (2017)
2. D. Pepin *et al.* (2018)
3. R. R. Wong *et al.* (2014)
4. V. A. Kushnir *et al.* (2017)
5. J. H. Kim *et al.* (2014)
6. D. Pepin *et al.* (2015)

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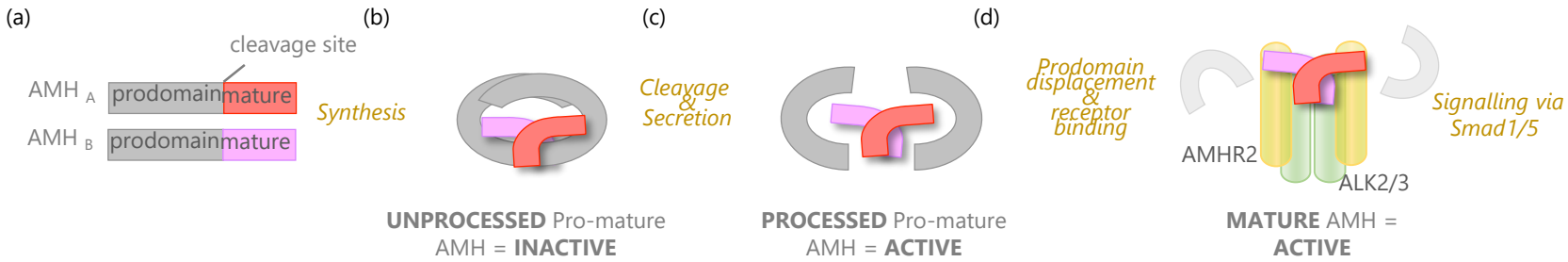
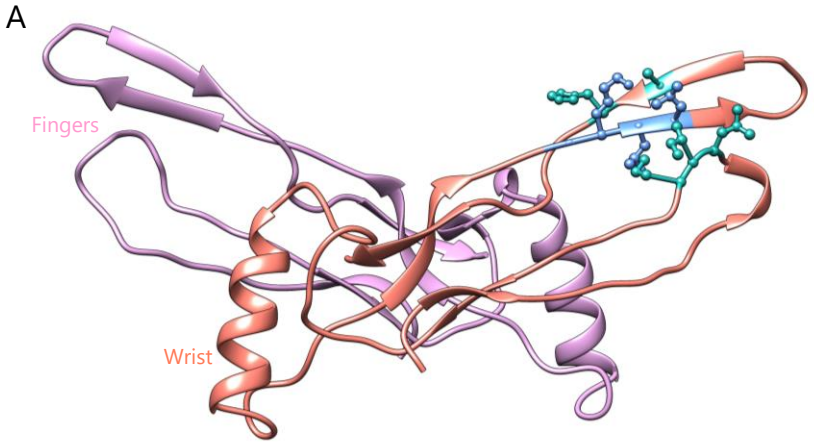
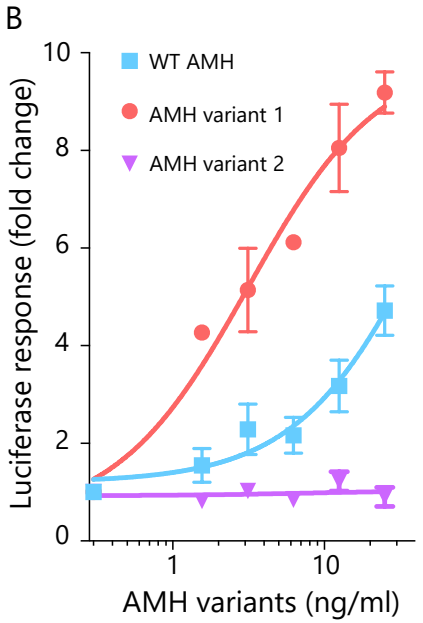
Project status







Next steps for development

- Lead series optimisation and PoC studies
  - Complete lead optimisation of AMH analogues
  - Efficacy studies to evaluate fertility preservation during cancer treatment (*in vivo* studies)
  - Profiling studies – limited physicochemical, metabolic stability, exposure, fraction bound/unbound plasma, immunogenicity and non-GLP PK studies
  - Early preclinical studies

- Manufacturing
  - Optimisation of stability and manufacturability for the lead AMH analogue

Intellectual Property

- IP owned by Monash
  - Patentable subject matter identified around novel composition of AMH analogues – will be filed following further optimisation of analogues

- Our IP is distinctly different from IP held by Provulis LLC, a Boston-based preclinical stage biotech
  - Provulis's lead candidate PV100 (preclinical) is a human recombinant protein analogue of AMH
  - Their patent covers alteration of AMH to increase the protein yield by modification in the cleavage site of AMH, and incorporation of a non-AMH leader sequence

- Our first-generation AMH analogue has already demonstrated 5-10 fold potency over PV100

Project 2:
Therapeutic Potential of TGF-β proteins for use in Assisted Reproductive Technology

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Therapeutic Opportunity

- Around 12-25% of women find themselves experiencing issues of infertility – unable to become pregnant after a year of trying to conceive

- The global IVF market size is expected to reach USD 32.6 billion by 2026, with CAGR of 10.2%

- Current gold standard in fertility treatment is in vitro fertilisation (IVF)
  - Hormones are given to stimulate the ovulatory process, and the mature eggs are harvested and then fertilized in the lab
  - Embryo is then implanted back into the body

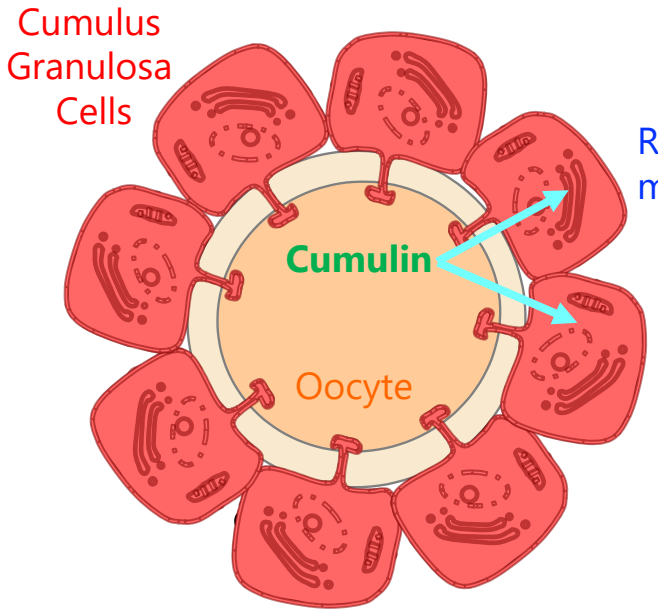
- In vitro maturation (IVM) is an alternative method of fertilisation, where immature eggs are retrieved from the body, and matured in a lab setting
    - Limited use in clinic due to low success rates

Cumulin – regulation of granulosa cell function

- Found to potently stimulate granulosa cell signalling and function, and promotes oocyte quality

- Currently being investigated in the clinic to improve success rates in IVM
  - Oocyte quality is the key obstacle in widespread clinical implementation of IVM

- Cumulin is a heterodimer comprising of GDF9 and BMP15
  - Activity appears to be dependent upon the activation of the GDF9-Smad2/3 axis



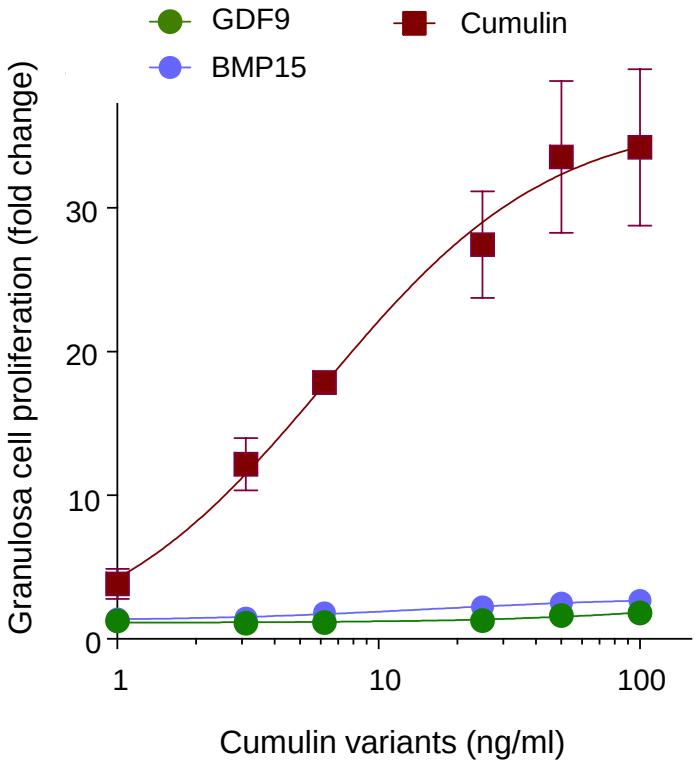
Regulate proliferation, differentiation, metabolism and expansion

Inhibit apoptosis and luteinisation

Improve oocyte quality, and subsequent embryo development and foetal viability

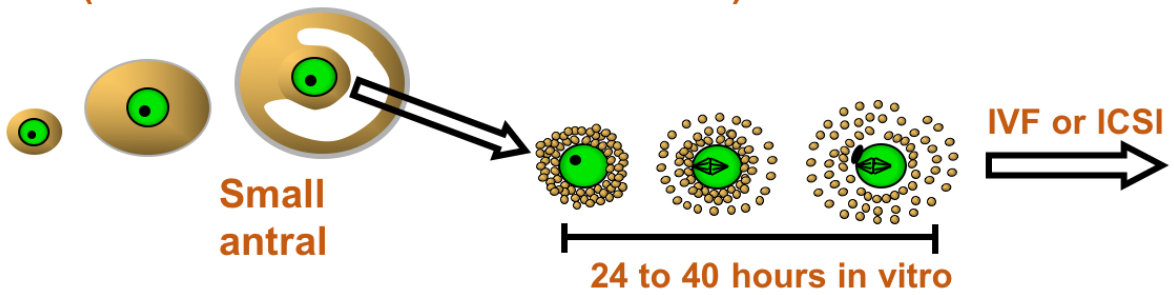
Cumulin

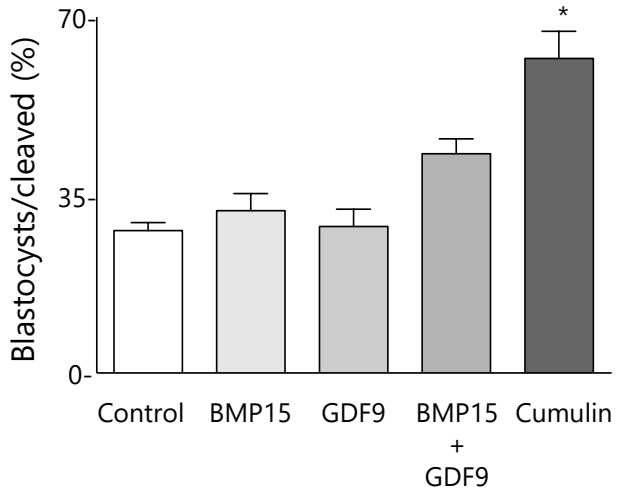
Granulosa cell proliferation



- **In Vitro Maturation (IVM)**

(No or minimal ovarian stimulation)





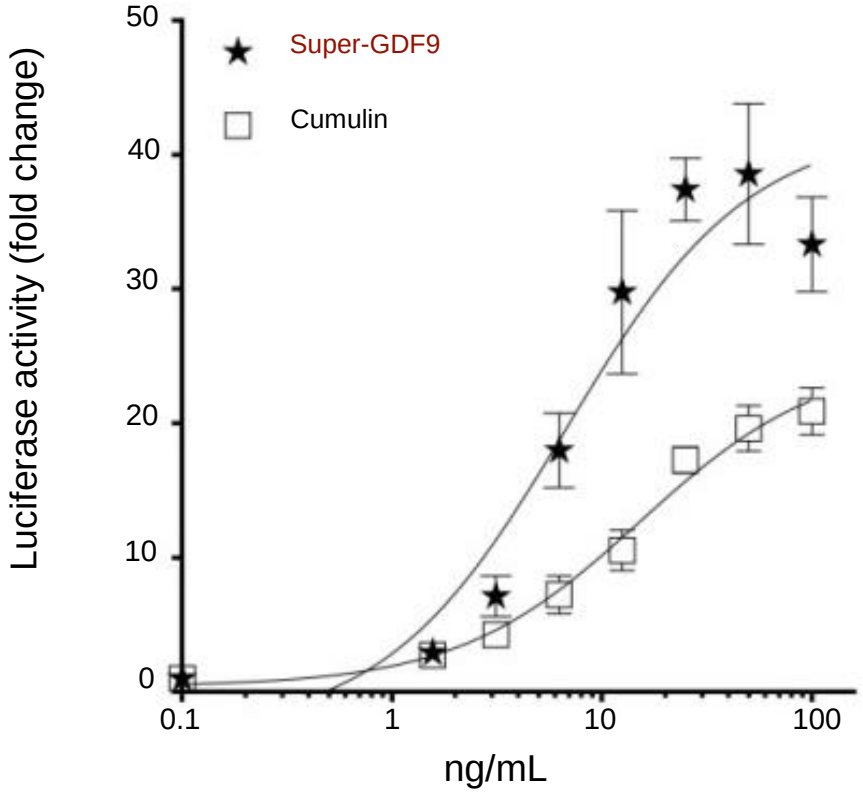
Super-GDF9 for assisted reproductive technology

Our Research

- Targeted modification of GDF9 in cumulin produced a series of analogues – Super-GDF9
- Super-GDF9 is more potent than cumulin and GDF9
- The team is in the process of exploring further modifications and conducting PoC studies *in vivo,* with human oocyte maturation studies conducted together with collaborators in Belgium

Intellectual Property

- IP owned by Monash
- PCT/Au2019/000054 filed on the 9th of May, 2019 – “Agent and method for enhancing fertility”
- Patent for use of cumulin in assisted reproductive fertility owned by University of Adelaide – will not impact FTO, as our analogues are notably different from cumulin



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Project 3:
The body has a brake: inhibin curbs fat accumulation

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Therapeutic Opportunity

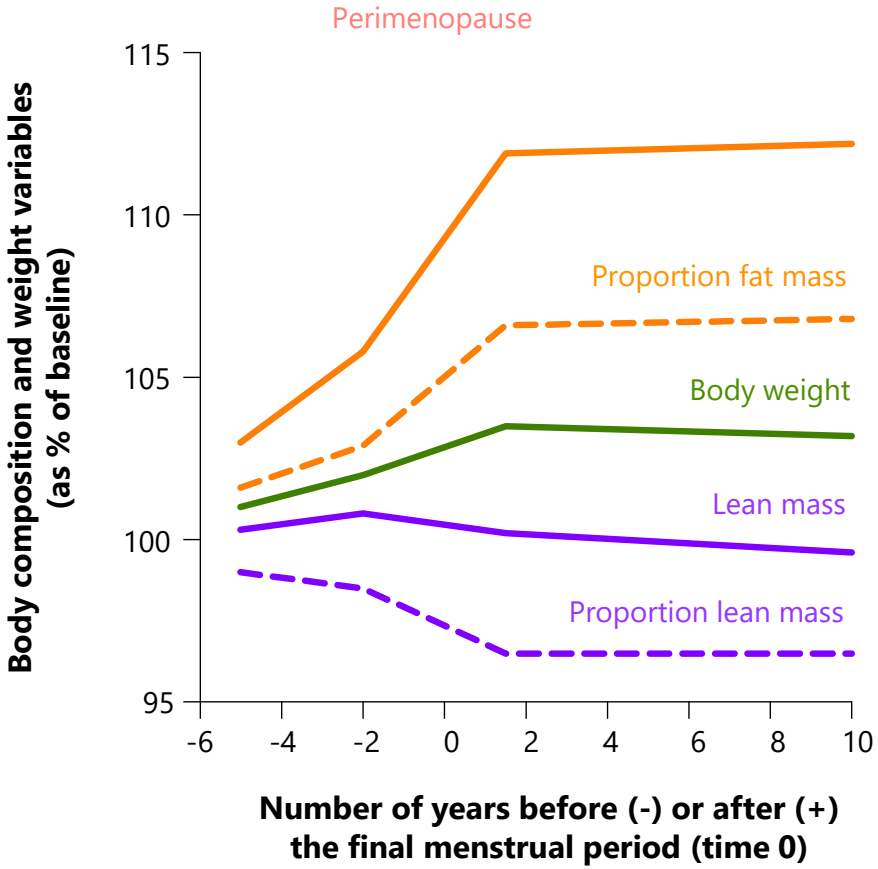
- During the menopausal transition, women experience accelerated loss of bone and muscle, as well as increases in body fat, due to loss of ovarian hormones

- This predisposes aged women to developing obesity and associated co-morbidities, such as diabetes and cardiovascular disease, and increases frailty, and can overall greatly reduce quality of life

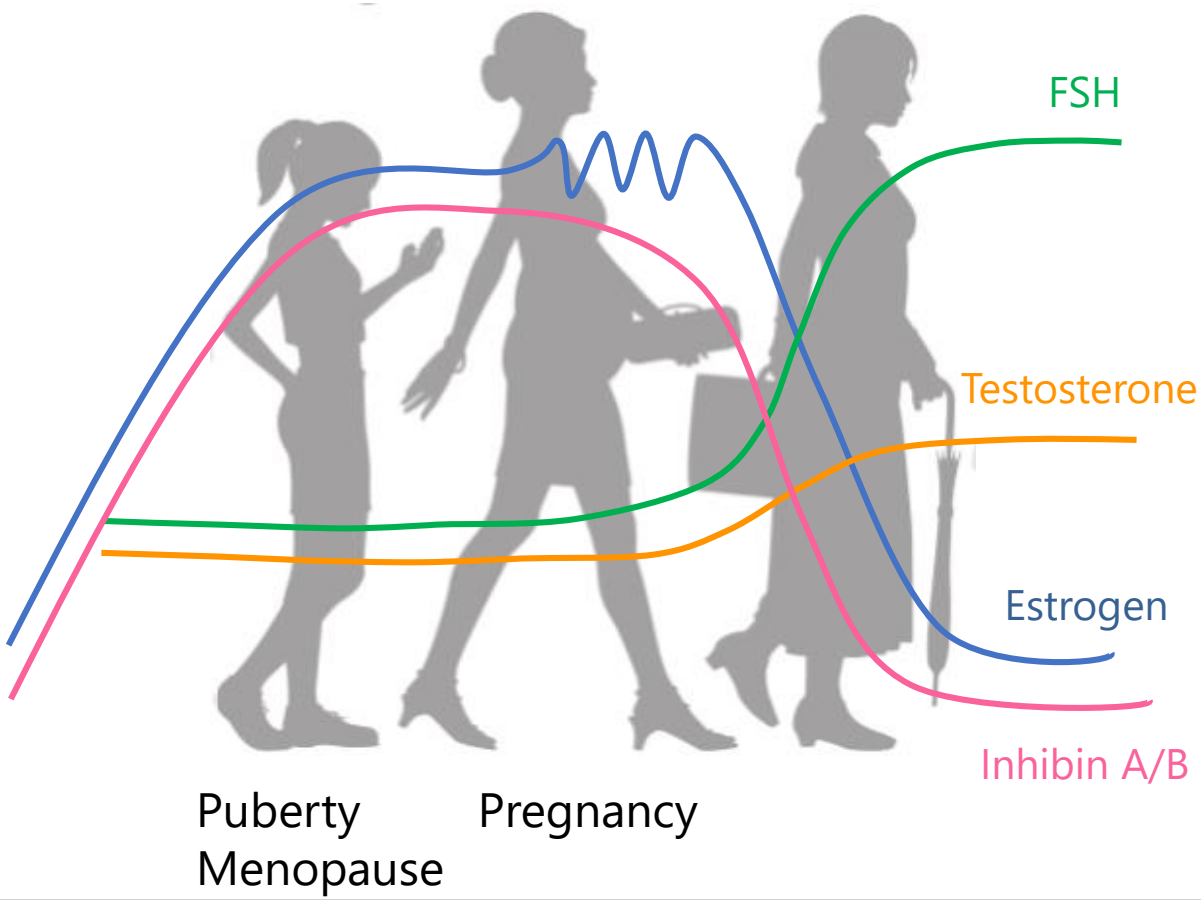
- Postmenopausal symptoms are “managed”
  - Steroidal hormonal replacement therapy (HRT) is the current leading treatment for postmenopausal complications, but long-term usage is fraught with complications, including increased risk of cancers and heart disease

- Inhibin is a member of the TGFβ superfamily which is lost during menopause

Changes in weight and body composition during perimenopause



Hormones influencing perimenopausal adiposity



Greendale et al *JCI* (2019)

Novel inhibin analogues for treatment of perimenopausal symptoms

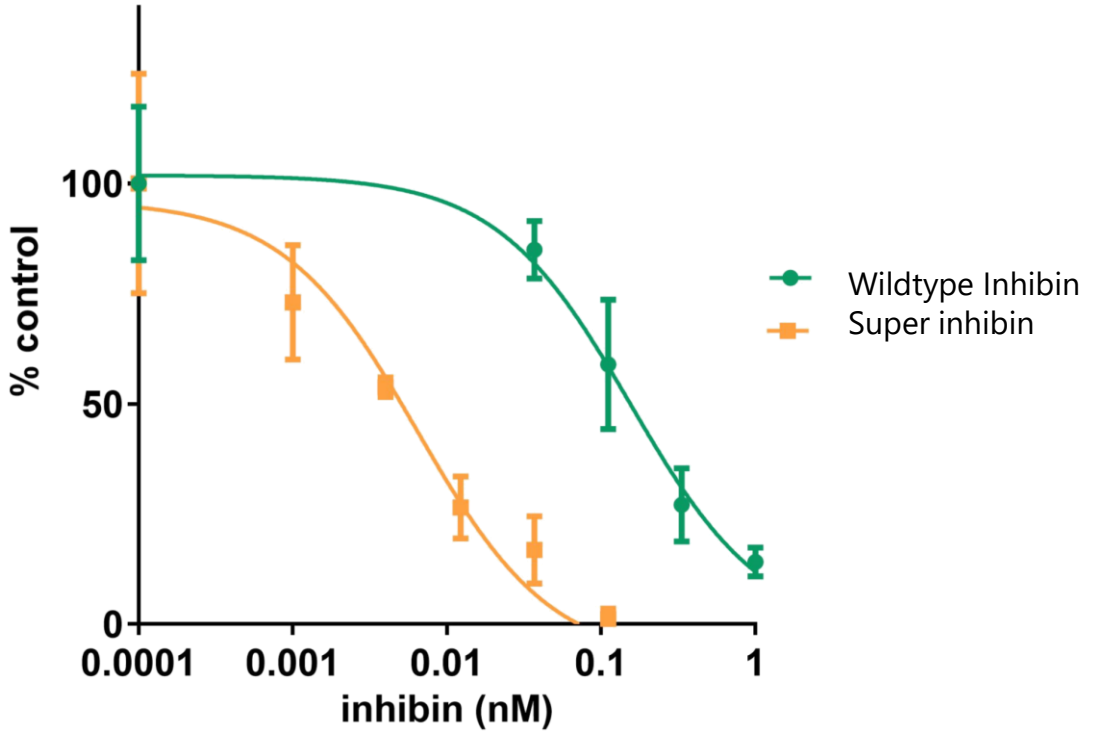
Our Research

- Significantly improved production of inhibin without activin contamination
- Potent inhibin analogues with increased receptor affinity
- PoC studies with lead inhibin analogues in our inhibin-knockout mouse model
- Optimisation of inhibin analogues and lead selection

Intellectual Property

- Undisclosed and IP for novel analogs will be filed following further optimisation
- Hudson Institute owns background IP - PCT/AU2016/051156 – “Inhibin analogs” (priority date 26th Nov 2015)
  - For the composition, method of production of recombinant inhibin analogs, and their use in therapy of certain diseases
  - National filing in Europe, Australia and United States
  - Craig and Kelly are the inventors on the patent

Inhibin suppression of activin-mediated luciferase activity in COV434 cells



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