Aims of Projects
To determine how womb smooth muscle cells control expression of genes and regulate activity of ion channel proteins needed during human labour.

Outline
In the developed world, being born too early (premature birth) complicates 6-10% of pregnancies and the incidence of birth before 28 weeks gestation (severely preterm) is increasing; those babies having greater risks of major long-term mental and physical disabilities. Globally, premature birth affects roughly 15 million babies per year. Of this number roughly one million premature babies will die because of their prematurity. The majority of these deaths are in those babies are born extremely prematurely before 28-30 weeks gestation. To put this into a local context, the Jessop Wing manages in the region of 7,000 deliveries per year: the annual global death toll attributable to premature birth is, therefore, equivalent to their being no live births in the Jessop for the next 150 years. Those babies that do survive being born too early also have a disproportionate effect on health-care budgets world-wide: a recent U.K. estimate of the total cost of preterm birth to the public sector was £2.95 billion. Since the antenatal health of a baby influences subsequent adult health, reducing the incidence of premature birth is very important.

In humans, the biology by which the womb changes from a relaxed state which cannot contract regularly, to an organ which undergoes the regular contractions seen in labour is not known. At present, our current knowledge about the human birth process suggests that normal human labour is a highly-regulated inflammatory process similar to that which occurs when the body is injured or ill (Cookson and Chapman, 2010). The work ongoing in my lab aims to understand this biological problem and aspects of it have previously been highlighted by the BBC. At present the lab has four related projects to offer. These projects all aim to extend our previous work in this field of research; please see the references below.

Projects 1 and 2 extend our data described in Webster et al., (2013) and Cookson et al. (2015). These projects offer two students the opportunity to work closely on two related but separate projects. Project 1 examines regulation of inflammatory mediators while project 2 investigates ion channel gene control. Both projects use the same methods and it is envisaged this will enable students to discuss the work between them more effectively.

Projects 3 and 4 extend our data described in Waite et al., (2014) and Cookson et al. (2015). Again, these projects offer two students the opportunity to work closely on two related but separate projects and it is envisaged this will enable students to discuss the work between them more effectively. Project 3 examines what other proteins the MaxiK potassium and L-type calcium channels associate with within the smooth muscle of the womb and to determine how these associations are linked to contractility. Project 4 investigates what genes the L-type calcium channel (LTCC) transcription factor (CCAT) regulates within the smooth muscle cells of the womb, to determine if this regulation is stimulatory or inhibitory and to understand how this regulation is linked to contractility.

General References
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**Aims of Project**
To determine how womb muscle cells control expression of pro-inflammatory agents needed during human labour. This will be done by examining how cells select different parts of a gene’s regulatory system to ensure expression occurs at the right time, in the right place for the correct amount of time.

**Projects 1**: The inflammation seen in the womb at term modifies how the blueprint of the womb muscle cells (the DNA or genome) works to regulate the womb contracting. If one imagines the genome as a book, the genes are chapters within such a book and each index guides the reader (transcription machinery) to the relevant part of the chapter. Our recent work (Cookson *et al.*, 2015) used microarrays to show how certain transcription factors controlled important genes associated with human labour. Significantly, that work predicted that the transcription factors bound to different parts of the gene’s control sequence depending on whether a pro-inflammatory signal was present or not. This is illustrated in Fig.1 below.

![Fig. 1](image-url)  
**Fig. 1:** Schematic representation of the loci of both TNF-induced NF-kappaB-enriched regions (red bars) and unstimulated NF-kappaB enriched-regions (blue bars) around selected genes including COX-2 (A); Jun (B) and IL6RN (C). For COX-2 and Jun, kappaB DNA motifs corresponding to the consensus were found in the TNF-induced RelA enriched regions (1A; 1B). With IL6RN, both TNF-induced RelA enriched regions and unstimulated RelA-enriched regions were observed. Arrows indicate the direction of transcription, not actual transcription start sites.

As such, this project, which will run in parallel to Project 2 and will require the student to “mine” the data from the arrays. Here the student will look for inflammatory genes and then map the locations of the NF-kappaB-enriched DNA to the genome. This will then build up a picture of where such NF-kappaB binding...
sites are and will inform future studies aimed at defining how such sites are occupied during inflammation.

Example target genes will include COX-2, Jun and IL1RN although we identified a great many putative targets as reported in Cookson et al., (2015) which can also be examined if required. You will also learn skills including gel electrophoresis and both protein and nucleic acid manipulation skills. As a group we aim to hold a weekly journal club where a research paper will be discussed and an ongoing consideration of your project data will be made.

References

Aims of Project
To determine how womb muscle cells control expression of ion channels needed during human labour. This will be done by examining how cells select different parts of a gene’s regulatory system to ensure expression occurs at the right time, in the right place for the correct amount of time.

Project 2: The inflammation seen in the womb at term modifies how the blueprint of the womb muscle cells (the DNA or genome) works to regulate the womb contracting. If one imagines the genome as a book, the genes are chapters within such a book and each index guides the reader (transcription machinery) to the relevant part of the chapter. Our recent work (Cookson et al., 2015) used microarrays to show how certain transcription factors controlled important genes associated with human labour. Significantly, that work predicted that the transcription factors bound to different parts of the gene’s control sequence depending on whether a pro-inflammatory signal was present or not. This is illustrated in Fig. 1 below.

As such, this project, which will run in parallel to Project 1 and will require the student to “mine” the data from the arrays. Here the student will look for ion channel genes and then map the locations of the NF-kappaB-enriched DNA to the genome. This will then build up a picture of where such NF-kappaB binding sites are and will inform future studies aimed at defining how such sites are occupied during inflammation.
Example target genes will include KCNMB3, CACNB3 and KCNB1 although we identified a great many putative targets as reported in Cookson et al., (2015) which can also be examined if required. You will also learn skills including gel electrophoresis and both protein and nucleic acid manipulation skills. As a group we aim to hold a weekly journal club where a research paper will be discussed and an ongoing consideration of your project data will be made.

References