# SRF Vacation Scholarship report 2018

The form below should be completed by the student, then forwarded to the supervisor for approval and submission to srf@conferencecollective.co.uk within 8 weeks of completing the project. Please submit the form as a Word document.

A maximum of one figure (with legend of less than 100 words) may be appended if required.

**Please note:** excerpts from this form may be published on the SRF website, so please ensure content is suitable for website publication, and does not compromise future dissemination of data in peer-reviewed papers etc. The SRF reserves the right to edit responses to ensure suitability for publication on the website, newsletter or in promotional material.

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| **Student’s Name:** | Robert Kay | **Student’s Institution/University:** | University of Edinburgh |
| **Degree Title and year of study:** | Year 4 - Medicine (MBChB) |  |
| **Supervisor’s Name:** | Professor Hilary Critchley | **Supervisor’s Department and Institution:** | MRC Centre for Reproductive Health, University of Edinburgh |
| **Project Title:** | Study of the Impact of Selective Progesterone Receptor Modulators upon Apoptosis in the Human Endometrium |

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| **Briefly outline the background and aims of the project** *(max 200 words)* |
| **Background:** Heavy menstrual bleeding affects around a quarter of reproductive aged women in the UK, causing various gynecological and systemic morbidities to the affected individual. Despite the high prevalence of heavy menstrual bleeding and great suffering that it presents, current treatments are either ineffective or carry significant side effects. A unique drug class, termed selective progesterone receptor modulators (SPRMs), provide an alternative pharmacological approach. These compounds exert a mixed agonistic and antagonistic effect on the progesterone receptor. Their ability to reduce menstrual bleeding in patients with fibroids has been demonstrated; however, their exact mechanism of action is not fully understood. The impact of SPRM administration has been well documented in uterine fibroid tissue, where it has been reported to increase apoptosis and reduce proliferation. However, there is currently a dearth of data pertaining to apoptosis in the uterine endometrium following SPRM treatment. Consequently, this project aimed to investigate how apoptosis is modulated in the human endometrium following exposure to the SPRM, ulipristal acetate. **Aims:** This project aimed to describe how the presence and location of specific apoptotic markers (Caspase-3, BAX and BCL-2) are altered in the endometrium following administration of the SPRM, ulipristal acetate. |
| **Did the project change from that proposed in the application? If so, what changes were made and why?** *(max 100 words)* |
| In the project proposal, it was suggested that RNAscope® (a novel form of in situ hybridization) might be used to study the localization of various apoptotic markers (BAX, BCL-2 and Caspase-3) following UPA treatment. Due to time constraints this was not possible, as priority was placed on completing immunohistochemical investigations.  |
| **What were the main results/findings of the project?** *(max 300 words)* |
| **qRT-PCR**: To investigate the impact of UPA upon BAX, BCL-2 and Caspase-3 mRNA transcription in the endometrium, qRT-PCR was employed across a range of treatment stages: before treatment, at 6 months treatment and at 12 months, following treatment withdrawal and a menstrual bleed. Tissue samples were grouped according to their menstrual stage prior to treatment, to allow for a valid comparison. The samples collected at 12 months represented a wide variety of menstrual stages, therefore analysis focused on comparisons between ‘no treatment’ and ‘6 months treatment’. Data indicated reduced BAX mRNA expression in proliferative stage base-line samples following 6 months treatment, although there was no statistically significant difference (p=0.126), while BAX mRNA expression in secretory stage base-line samples exhibited no apparent trend (p=0.8441). Proliferative base-line BCL-2 data showed an increase in relative mRNA expression following 6 months of UPA treatment (p=0.032), while secretory phase BCL-2 data showed no significant change during the same period (p= 0.094). Caspase-3 mRNA expression exhibited no significant change between 0 and 6 months for both secretory and proliferative data (p>0.999 for both). Previous literature has demonstrated that endometrial apoptosis varies across the physiologically healthy menstrual cycle, with highest levels seen during late secretory and menstrual phases (Maybin & Critchley, 2015).**Immunohistochemistry**: Due to time constraints, it was only possible for the anti-apoptotic marker, BCL-2 to be inmmuno-stained, histoscored and analysed. The slides were blinded and then scored by three separate observers. The data showed an increase in glandular BCL-2 staining between 0 and 6 months in the secretory base-line samples. All other histoscore results revealed no obvious trends. *Maybin JA & Critchley HO (2015). Menstrual physiology: implications for endometrial pathology and beyond. Human Reproduction Update 21, 748–761.* |
| **What do you conclude from your findings?** *(max 150 words)* |
| Although results lacked statistical significance across the board, the findings presented here suggest there may be a decrease in endometrial apoptosis following ulipristal acetate administration. Caspase-3 and BAX (pro-apoptotic markers) expression was generally observed to decrease following UPA treatment while BCL-2 (an anti-apoptotic marker) expression increased. However, this conclusion is based on statistically insignificant trends; therefore limiting the extrapolation of these findings. Apoptotic activity is only part of the equation however, as the balance between proliferation and apoptosis ultimately governs cell turnover within a tissue. It is therefore important that the interaction and equilibrium between apoptosis and proliferation in the endometrium is fully understood before conclusions are drawn. Therefore a possible future direction may be to utilize another means of measuring apoptosis, for example a TUNEL assay, to confirm the effect of UPA upon endometrial apoptosis.  |
| **How has this experience influenced your thinking regarding your future/ongoing studies, and/or career choice?** *(max 150 words)*  |
| Having undertaken two years of medical school prior to intercalating in reproductive biology, I had relatively limited experience of practical research. For this reason, I decided that I would like to gain practical laboratory experience during my intercalated year, as this was an area in which I had always been interested. I was fortunate to undertake my honours project in the MRC Centre for Reproductive Health, (MRC CRH), Edinburgh, supervised by Prof. Hilary Critchley. I really enjoyed this experience and therefore applied for the SRF summer vacation scholarship.Having now completed my summer project, I feel I have benefited hugely from the scholarship. Having known very little about research only 9 months ago, I now feel comfortable with some common laboratory techniques, I am able to analyse data more confidently and have a much greater understanding of how a research group functions in the real world.  |
| **Please use the space below to add any other comments/thoughts about the SRF Vacation Scholarship** *(max 100 words)* |
| ***Student:*** *I am hugely grateful to have been a recipient of the SRF summer vacation scholarship, it gave me a great opportunity to continue working in the MRC CRH over summer and to learn more about biomedical research.****Supervisor:*** *Robert worked diligently and proved himself to be a valued contributor and member of my laboratory team. He always responded well to constructive comments and advice. I believe this further laboratory-based experience will have helped him understand better steps involved in translating bench-science to the bedside. I hope he may wish to return to work with us again if opportunity arises.* |