**University of Leicester**

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| **Project Reference** | BRC Studentships |

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**Section 2 – *Project Information***

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| **Project Title** | COLO-PREVENT ex vivo: the application of patient derived tissue models for investigating mechanisms of action of aspirin, metformin and resveratrol in the prevention of colorectal cancer. | |
| **Project Highlights:** | 1. | Work alongside a world first cancer prevention trial platform to help us understand mechanisms of action for aspirin, metformin and the dietary derived compound resveratrol |
| 2. | Use state-of-the-art explant technology, imaging and analysis methods |
| 3. | Gain insight into how obesity contributes to colorectal cancer development and how we might counteract the molecular effects |
| **Project Summary** | | |
| **Background:** Over the last 15 years, we have taken the naturally occurring phytochemical resveratrol from bench to bedside. Building on our preclinical work and early phase studies, we are investigating the efficacy of resveratrol in the COLO-PREVENT trial - a world first platform prevention trial embedded within the NHS Bowel Cancer Screening Programme for evaluating the efficacy of CRC preventive therapies in high-risk individuals, based on polyp recurrence. In addition to assessing the effects of resveratrol, COLO-PREVENT will also compare whether combining the anti-inflammatory drug aspirin with the diabetes medication, metformin is superior to aspirin alone.  A greater understanding of the anti-cancer mechanisms of action of aspirin, metformin and resveratrol, particularly in combinations, is needed for a precision prevention approach whereby therapies can be tailored to individuals and potential efficacy monitored over time on the basis of measurable biomarkers. Whilst COLO-PREVENT includes a programme of translational research, sample availability limits the extent of mechanistic work that can be conducted, therefore, parallel studies are needed using ex vivo models designed to mimic the patient population, to identify novel modes of action and key mechanisms that are most likely to contribute to efficacy in humans.  **Research Plan:** This project will involve refinement of our established ex-vivo model of patient derived colorectal explants, to incorporate an environment of metabolic dysregulation associated with excess adiposity and consumption of a diet high in fat. This will be achieved through modification of the culture medium and incubation conditions, as well as using normal and premalignant colorectal tissue to represent the target patient population in COLO-PREVENT. Cell viability will be measured, and explants characterised by assessment of multiple phenotypic and functional biomarkers using techniques such as multiplex immunofluorescence. Once optimised, the model will be used for investigating the efficacy and mechanisms of action of resveratrol, aspirin and metformin alone and in combination and for identifying candidate pharmacodynamic biomarkers in the tissue and secreted in the medium.  **Expected outcomes and impact:** We expect the COLO-PREVENT platform will identify several safe effective therapies for use in conjunction with screening/surveillance to prevent polyp recurrence and ultimately decrease colorectal cancer risk. A greater understanding of the mechanisms of action of resveratrol, aspirin and metformin will generate hypotheses that can be tested using clinical samples from the COLO-PREVENT trial and will help tailor specific therapies to individuals in a precision prevention approach that maximises the chances of participants experiencing a benefit. | | |
| **References**   * Cai H, Scott E, Kholghi A, Andreadi C, Rufini A, Karmokar A, Britton RG, Horner-Glister E, Greaves P, Jawad D, James M, Howells L, Ognibene T, Malfatti M, Goldring C, Kitteringham N, Walsh J, Viskaduraki M, West K, Miller A, Hemingway D, Steward WP, Gescher AJ, Brown K. (**2015**) Less is more for cancer chemoprevention: evidence of a non-linear dose response for the protective effects of resveratrol in humans and mice. *Sci. Transl. Med.* ***7,*** *298ra117.* * Patel KR, Andreadi C, Britton RG, Horner-Glister E, Karmokar A, Sale S, Brown VA, Brenner DE, Singh R, Steward WP, Gescher AJ, Brown K (**2013**) Sulfate metabolites provide an intracellular pool for resveratrol generation and induce autophagy with senescence. *Sci. Transl. Med.* 5, 205ra133. * Brown K, Aburido G, Britton RG (**2020**) Resveratrol for cancer prevention: current gaps and opportunities. In: Pezzuto J., Vang O. (eds) *Natural Products for Cancer Chemoprevention*. Springer, Cham. * [**4**](file:///C:/Users/kb20/AppData/Local/Microsoft/Windows/INetCache/Content.Outlook/1O27OY18/4)**)** <https://le.ac.uk/lctu/trials/colo-prevent> * James MI, Iwuji CO, Irving GR, Karmokar A, Higgins JA, Griffin-Teale N, Thomas A, Greaves P, Cai H, Patel SR, Morgan B, Dennison A, Metcalfe M, Garcea G, Lloyd DM, Berry DP, Steward WP, Brown K (**2015**) Curcumin inhibits cancer stem cell phenotypes in *ex vivo* models of colorectal liver metastases, and is clinically safe and tolerable in combination with FOLFOX chemotherapy. *Cancer Lett.,* **364**, 135-141*.* * Khan S, Miles GJ, Demetriou C, Sidat Z, Foreman N, West K, Karmokar A, Howells L, Pritchard C, Thomas AL, **Brown K**. (**2022**) *Ex-vivo* explant model of adenoma and colorectal cancer to explore mechanisms of action and patient response to prevention therapies. *Mutagenesis* 37(5-6):227-237. | | |