DESCRIPTION FOR THE GENERAL PUBLIC

The domestic pig has long been a key species for meat production. Now domestic pigs and minipigs are also being used in biomedical studies. This has been facilitated by advances in reproductive technology and new methodologies such as genome editing, which enable pigs to be genetically modified to model serious human diseases such as cancers. Although the reference sequence for pig genome was released several years ago, its annotation and the mechanisms of gene expression are still poorly characterized.

Colorectal cancer (CRC) is a serious and common human disease. Development of strategies to prevent, diagnose or treat CRC will be aided by animals that model the condition. This study will use domestic pigs with an engineered genetic predisposition to CRC modelled on a human inherited predisposition to CRC, familial adenomatous polyposis.
Our pigs carry a mutation in the Adenomatous Polyposis Coli (*APC*) gene termed APC^{1311}. Histological and molecular analysis of colorectal polyps has shown that the porcine model recapitulates all major features of early stage human CRC. As in humans, endoscopic examination of pigs has revealed considerable variation in the stages of polyps present at one time within the same animal. Typically these range from 5 mm low-grade adenomas to 2-4 cm carcinoma with local invasion. Given that all polyps are initiated by the same APC^{1311} mutation, this reflects the diversity of spontaneous genetic events in each polyp.

We will microdissect characterised regions of individual polyps at defined disease stages and use next generation sequencing technology to determine the key expression changes and methylome of each. Comparison of each group will enable us to identify key expression changes, epimutations and signalling pathways involved in disease progression. Comparison of multiple polyps at the same stage will allow non-causative 'passenger' mutations to be distinguished from causative 'driver' mutations because the latter are more likely to be held in common. A similar approach can also be extended to monitor individual polyps over time. The study we propose highlights the advantage of a representative animal model of CRC, because such an investigation would be very difficult in human patients. A successful outcome will advance our knowledge of the molecular mechanisms involved in the development of CRC and aid the identification of drug targets to treat or prevent the disease in its early stages.