Organoid Models and Genome Editing to Investigate Fucosylation of Epithelial Receptors and Disease Resistance in Pigs

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Post-weaning diarrhoea (PWD) and oedema disease (OD) in piglets are a major cause of mortality and morbidity in the pig industry, and one of the main reasons for (preventative) antibiotic use worldwide. A leading cause of PWD and OD is infection by enterotoxigenic *Escherichia coli* (ETEC). It has been shown that a single nucleotide polymorphism in the pig genome of *fucosyltransferase-1* (FUT1) decreases risk of intestinal ETEC-F18^{+} infection, possibly attributed to altered fucosylation patterns. The aim of our study is to elucidate links between epithelial glycoprotein fucosylation and disease resistance through hereditary polymorphisms. To further understand mechanisms on polymorphism-pathogen interactions we aim to utilize intestinal and airway epithelium organoids. These provide genetically and phenotypically identical models to its host-derived tissue, which can be genetically modified using CRISPR-Cas technology to screen for genotype-to-phenotype susceptibility to pathogen infections. For example, we aim to determine the role of the MUC4-g.8227 G>C polymorphism in susceptibility to ETEC-F4+ variants, identify which epithelial glycoproteins are expressed at different locations in the intestine, and determine which receptors are used for colonisation by ETEC. We anticipate that this innovative approach will greatly increase our understanding of infectious disease resistance mechanisms in pigs. Our research could provide important contributions towards breeding programmes aiming to increase disease resistance, reducing antibiotic use and possibly antibiotic resistance for the benefit of humans and animals. Furthermore, the advanced models and methodologies we are developing will benefit scientific research on pigs, while reducing the need for experimental animals