Project Details	
Project Code	MRCPHS26Ex Kudoh
Title	Phenotypic and epigenetic analyses of Foetal Alcohol Spectrum Disorder (FASD) in the zebrafish model and human patients
Research Theme	PHS
Project Type	Wet lab
Summary	Foetal Alcohol Spectrum Disorder (FASD) occurs via alcohol consumption in pregnancy with 1-5% frequency in humans, causing distinctive facial features alongside brain development defects. In this interdisciplinary project, we will use the zebrafish embryo as an animal model for FASD and utilise human data with epidemiological approaches, linking phenotype of FASD with epigenetic 'omic data (DNA methylation). The data will be utilised for improving detection of prenatal alcohol exposure and fetal alcohol spectrum disorder and designing targeted therapies to improve outcomes.
Description	Foetal alcohol Spectrum Disorder (FASD)is caused by alcohol exposure during pregnancy. As well as neurodevelopment impairmentsit leads to a variety of physical symptoms including flat facial structures, smaller eyes, under-developed jaw, microcephaly, and defects in other tissues including spinal cord and heart. The frequency of FASDis estimated between 1-5% within the general population with varying severity of symptoms. However, little is known about the epigenetic mechanisms that lead to harm, and whether there are particularly sensitive periods in which prevention should be prioritised. We have recently investigated molecular, cellular and developmental mechanisms of FASDs using zebrafish embryos as a model system for human FASDs (Alsakran et al. 2024, 2025). The data suggested that the most sensitive embryonic stage against alcohol was the gastrula stage when dynamic cell movement occurs to form head and trunk, and cells for internal organs migrate deep inside of the embryo. This dynamic cell movement is highly affected by alcohol and cause cell movement defects inducing the symptoms mentioned above. The gastrula stage in human embryos are around 2-3 weeks post fertilisation, a stage before many pregnant individuals are aware of pregnancy, causing higher risk of alcohol consumption (Frennesson et al. 2025). Subsequently, after gastrulation at the organogenesis stage, another wave of dynamic gene expression changes and cell movement occurs in specific tissues such as brain, spinal cord and facial cells (neural crest cells), therefore in the subsequent stages with alcohol exposure also induces embryonic abnormalities in morphology and tissue functions (e.g. brain). From animal studies such as mice and zebrafish, it has been known that such cellular abnormalities caused by alcohol are largely induced by gene expression changes and associated epigenetic modification of the genome represented by DNA methylation. However clear link between the human FASDs and DNA methylation profile are not fully understood. In addition, embryonic stage-specific effect of alcohol on epigenetic profiles are not known in any model animals and humans. In this project, we aim to conduct DNA methylation analyses using different stages of zebrafish embryos exposed to alcohol. We will also utilise human data from the Avon Longitudinal Cohort of Parents and Children (ALSPAC) who have FASD screening and detailed measures of

	maternal alcohol exposure alongside genome-wide DNA methylation profiles of the blood cells (McQuire et al. 2019; Relton et al. 2015). Using the data from both the zebrafish and humans, we will identify epigenetic signatures of FASD, including early embryonic exposure, later embryonic exposure, severe and mild cases. By identifying such signatures, many inconclusive cases of FASDs in humans can be better diagnosed, and therapies can be designed. This is an interdisciplinary, translational project including toxicological studies using zebrafish embryo as a model organism, and epidemiological studies of human prenatal alcohol exposure linking the epigenetic signature of the patient (babies/children) and their mothers. The supervisor team has specific expertise in zebrafish FASD phenotypic studies (TK), zebrafish epigenetic analyses (ES) and human epigenetic epidemiological studies (HRE & CM). Reference: Alsakran A, Kudoh T. Front Pharmacol. (2021) doi: 10.3389/fphar.2021.721924. Alsakran A. et al. Biol Open (2025) doi: 10.1242/bio.061777. Epub 2025 Jun 6. Frennesson et al. Front Public Health. (2025) doi: 10.3389/fpubh.2025.1525004. McQuire C, et al. Prev Med. (2019) doi: 10.1016/j.ypmed.2018.10.013. Relton CL, et al. IJE. (2015) doi: 10.1093/ije/dyv072.
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