Submitter Name: Munise Merteroglu
Submitted email: mm2124@cam.ac.uk
PI Name (if different): Elisabeth Busch-Nentwich
PI email (if different): emb81@cam.ac.uk

Gene regulatory responses to developmental drug exposures in zebrafish

Munise Merteroglu[1], Aleksandra M. Mech[2], Ian M. Sealy[1], Caroline Brennan[3], and Elisabeth M. Busch-Nentwich[1]

[1]Cambridge Institute of Therapeutic Immunology & Infectious Diseases, Department of Medicine, University of Cambridge, Cambridge, UK; [2]School of Biological and Chemical Sciences, Queen Mary University of London, UK

Developmental consequences of pre-natal drug exposure have been reported in many human cohorts and animal studies. The long-lasting impact on the offspring (including motor and cognitive impairments, cranial and cardiac anomalies and increased prevalence of ADHD and aggression) is a socioeconomic burden worldwide. Identifying the molecular changes leading to developmental consequences could help ameliorate the deficits and limit the impact. In humans, abuse patterns (type/combination of drugs, timing, dose and route) are difficult to document, making the true impact of pre-natal drug exposure on the fetus challenging to assess. In this study, zebrafish, a well-established behavioural and genetic model with conserved drug response and reward pathways, is used to identify changes in cellular pathways and behaviour in response to nicotine, oxycodone and amphetamine exposures during the first 5 days of development, a period equivalent to the first trimester of human fetal development. Rapid ex-utero embryogenesis of zebrafish allows non-invasive drug treatments at early embryonic stages. In a light/dark-induced locomotor assay, drug-treated larvae demonstrated slower recovery from light-induced freezing behaviour compared to untreated larvae, suggesting increased levels of anxiety. Whole embryo RNA-seq revealed a set of dysregulated biological processes such as innate immune response, cell death signatures and cell proliferation. To study the role of these genes in development of potentially long-lasting defects, further work will identify spatial expression patterns of these differentially expressed genes and determine localisation of increased cell death and proliferation in drug-exposed embryos. We will generate knockout models for functional studies of selected genes.