PhD Position - Queen Mary University of London

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Project Description

Project aim:
Our aim is to use genetic and developmental analysis of zebrafish to identify novel alleles and molecular mechanisms contributing to core behaviors predictive of vulnerability to drug addiction: drug seeking and impulse control, with a focus on nicotine addiction.

Significance:
Addiction is one of the major mental health disorders in the world. In the US the cost of addiction in health care and associated costs is estimated at over $700 billion each year with tobacco being responsible for over half of these costs ($425 billion) [1, 2].

Tobacco use was declared a world-wide epidemic by the World Health Organization (WHO, 2008) due to its dramatic impact on a diverse set of disease-related mortalities including cardiovascular disease and cancer. In 2014 cigarette use cost the US $170 billion in excess health care expense and another $156 billion in productivity loss per year [1, 3]. Despite the overall encouraging reduction of smoking rates, approximately one in five adults in America continues to smoke, a rate largely unchanged in the last five years[1, 3].
Despite the many novel insights from psychosocial, genetic, neurocognitive, neuroimaging, and pharmacological addiction research, currently available treatments are still not very effective and addiction, including smoking, remains a chronic-intermittent disorder for the vast majority of patients seeking treatment: Relapse rates of 50-70% within a year are common [4]. Thus there is a vital need for increased understanding of the factors influencing vulnerability to addiction to help identify vulnerable individuals and to inform treatment strategies and uncover novel druggable targets.

Although estimates vary, there is clear evidence for a genetic link between vulnerability to addiction, as well as quit rates and likelihood to relapse [5,6]. For example, results from twin studies suggest that 33–71% of the variation in liability to nicotine dependence and 48–66% of the variation in alcohol dependence can be attributed to heritable influences. A similar range for genetic heritability of illicit drug addiction and gambling has been reported ([9] and refs therein). Furthermore, genetic factors are partly responsible for, not only the comorbidity across addictions, but also between addictions and other mental illness (for example, autism and bipolar disorder). Increased understanding of the genetic factors that influence vulnerability to addiction and the cell biological mechanisms by which they act will, ultimately, lead to the development of novel therapeutics and a consequent impact on public health: ‘Each discovery of a biologically relevant locus is a potential first step in a translational journey’ [10]

Research Design:
Our group aims to use screens of ENU-mutagenized zebrafish lines and analysis of empirically derived candidate mutants to identify genes affecting two addiction phenotypes: nicotine reward and impulsivity. There is strong evidence that the neural circuits that underlie reward and addiction are evolutionarily conserved between humans and zebrafish [11-16]. Zebrafish show a robust conditioned place preference (CPP) reward response to nicotine that is ameliorated by drugs used in human cessation therapy demonstrating conserved neural pathways. Further our pilot data indicates that genes found to influence zebrafish CPP or impulse control also influence human behavior. These findings support the argument that zebrafish screens can be used to identify genes and pathways for reward and addiction as well as potential therapeutics as for other human disorders [17, 18].

This PhD is part of a collaboration with Elisabeth Busch-Nentwich at the Sanger Institute and Cambridge University. The successful candidate will work with bioinformaticians at Cambridge to identify changes in gene expression following chronic and/or developmental exposure to nicotine that correlate with changes in behaviour predictive of vulnerability to drug addiction. We shall then generate and characterise lines of fish carrying mutations in these candidate genes. The student will be trained in RNAseq analysis, developmental neurobiology and behavioural techniques.

Funding Notes

The studentship, expected to start January 2019, is funded by NIH and is open to applicants worldwide. It will cover tuition fees and provide an annual tax-free maintenance allowance for 3 years at Research Councils UK rates (£16,777 in 2018/19).

Applications are invited from outstanding candidates with or expecting to receive a first or upper-second class honours degree in an area relevant to the project. A masters degree is desirable, but not essential.

Informal enquiries can be sent to Dr Caroline Brennan (c.h.brennan@qmul.ac.uk). For formal applications, please submit an online application before the stated deadline.

References

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