Major depression is the leading cause of global disease burden, with over 300 million sufferers. The most severely disabled group are those with treatment-resistant depression (TRD), who comprise almost than half of the total. Until recently advances in antidepressant therapy had minimal success in helping people with TRD. There are now some effective treatments, involving electrical deep brain stimulation (DBS) or novel drugs (notably, the anaesthetic drug ketamine), but neither option is likely to supersede traditional antidepressant drugs in the near future. There has also been minimal success in developing adjunctive treatments to overcome resistance to antidepressant drugs. Part of the problem in advancing this area of research has been the absence of good animal models of TRD.

In earlier work, we have developed and validated an animal model of TRD. The model uses chronic mild stress (CMS) to induce a depression-like state in rats, which we study using a battery of behavioural tests: this procedure, which we developed some 30 years ago, is the most widely used animal model of depression. The model of TRD utilises a particular rat strain, the Wistar-Kyoto rat, which unlike standard (Wistar) rats, fails to respond to antidepressant drug treatment in the CMS model. However, WKY rats do respond to DBS or ketamine. We have also used a novel technique, optogenetic stimulation (OGS), which applies light stimulation to the brain. Using OGS, we have begun to map out a pathway in the brain where stimulation can overcome resistance to antidepressant drug treatment in WKY rats. Specifically, antidepressant non-responders could be converted into antidepressant responders by stimulation of projections from hippocampus (HPC) to prefrontal cortex (PFC), and from PFC to nucleus accumbens (NAc). (These three structures feature prominently in neuroscientific research on depression.)

In this project we aim to investigate two hypotheses: that resistance to antidepressant drug treatment results from structural and functional abnormalities within the HPC of treatment-resistant individuals, and that treatments which are effective in TRD activate the PFC and its output pathways, bypassing the compromised HPC. This will involve several series of experiments. First, we will use a second cutting-edge technique, chemogenetics, to ask whether stimulating the outputs from PFC will overcome antidepressant resistance in WKY rats, while inhibiting them will induce antidepressant resistance in Wistar rats. Next, we will use OGS to study the role of outputs from PFC to other structures that are implicated in depressive pathology and antidepressant drug action (amygdala and lateral habenula, LHb)), asking whether stimulation of these pathways can also overcome antidepressant resistance. We will also examine the effect of Deep Brain Stimulation (DBS) in the LHb, a site where clinical antidepressant effects have been reported: we suspect that LHb DBS may have antidepressant-like effects in Wistar rats, but may be ineffective in the WKY model of TRD; we will also test the hypothesis that antidepressant-like effects results from inhibition of the LHb. Finally, we will deploy a wide range of neurochemical and immunohistochemical techniques to investigate the morphological, cellular and molecular mechanisms of the behavioural effects that we observe. Inter alia, these studies will ask whether effective adjunctive treatment in antidepressant non-responders is achieved by the same mechanisms that are effective in antidepressant responders.

This research has significant translational implications. Elucidation of the substrate for resistance to antidepressant action in an animal model of TRD will provide a basis for a better understanding of the critical features of the brains of patients with TRD that are responsible for their non-response to antidepressant drug treatment. While this project does not directly search for better drug treatments, an understanding of the cellular and molecular substrates for adjunctive treatment would have implications for development of novel treatment strategies for TRD; and as treatments for TRD enter the clinic it will be important to know whether novel and conventional treatments represent alternative means of reaching common endpoints. And clarification of the circuitry underlying successful treatment in an animal model of TRD will also be important, inter alia, for the interpretation of clinical neuroimaging data.