Project title	**Animal models of neurodevelopmental disorders**		
Key words	Rat, behaviour, pregnancy, gut, brain		
Expected duration of the project (years)	Five		
Purpose of the project	Basic research	Yes	
	Translational and applied research	Yes	
	Regulatory use and routine production		No
	Protection of the natural environment in the interests of the health or welfare of humans or animals		No
	Preservation of species		No
	Higher education or training		No
	Forensic enquiries		No
	Maintenance of colonies of genetically altered animals	Yes	
Objectives of the project	**Overall aim** To establish animal models of neurodevelopmental disorders (NDDs). Brain disorders cost €141 billion per annum in the UK, with a total 2010 cost of psychotic disorders of €16,717 (in million € purchasing power parity-PPP*). Existing drugs are not effective enough and have unpleasant side effects reducing compliance. Better treatments are therefore required, particularly for memory and social communication in schizophrenia while there is no drug treatment currently recommended for Autism Spectrum Disorders (ASD). Critical for the development of improved treatments is improved understanding of the cause and biological basis of such disorders which can only be achieved through carefully validated animal models. Existing animal models only allow testing of new treatments in adulthood once the illness has become established. Our two new models will allow testing of new treatments at an earlier stage of each illness, even before the illness manifests itself, particularly for schizophrenia at the prodromal stage, with the overall aim of finding a biological target for identification of the illness before it progresses into psychosis. A further aim of the new model is to identify the link between gut and brain abnormalities in ASD. Children with ASD have a high level of gut		

	disorders and strong scientific evidence supports the theory that this may be the cause of some of the brain disturbances and a new target for drug therapy. This project aims to establish two new animal models of brain disorders that have a developmental basis, ie that are partly produced by a disturbance in pregnancy.
Potential benefits likely to derive from this project	Humans will benefit from the project in a variety of ways. Psychotic disorders and ASD reduce the quality of life for patients and carers dramatically and have a large economic cost. Improved treatments have not been successfully developed due to a lack of understanding of the biological basis of these diseases due to limited animal models. For any disorder, prevention is better than cure and early treatment is more successful than late treatment. Our work aims to identify a biological target for early identification of the illness, early treatment and prevention of the illness becoming manifest as eg psychosis. This will limit the detrimental effects to the patient's social and academic life. The benefits will be economic and in quality of life for patients and carers. Animals (in our lab and others) will benefit from development of improved, food-rewarded ethologically relevant tests, see section on refinement above.
Species and approximate numbers of animals expected to be used, and anticipated period of time	2700 rats over 5 years
Expected adverse effects and the likely/expected level of severity. What will happen to the animals at the end.	The level of severity is expected to be moderate. Pregnant rats will be given an agent (reduced activated virus or bacteria or valproate, a drug used for epilepsy) at various times of pregnancy. This is likely to induce a mild and short-lived infection or pharmacological response in the mother, lasting less than 24 hours (increased body temperature and mild sickness). Behavioural techniques are generally not stressful and can, in certain cases, be considered enrichment for the animals. We intend to stress the animals using an ethological and disease relevant stressor such as mixing up cage groups or short-term social isolation or introduction of a relevant parasite into the GI tract. At the end of the study, or as part of the experimental procedure (eg to perform assessment of brain changes induced by the interventions) rats will be

	killed humanely and quickly by a Schedule 1 procedure.
Application of the 3 Rs	
1. Replacement Why do animals need to be used, and why non-animal alternatives cannot be used.	Studying the risk factors and mechanisms involved in neurodevelopmental disorders (NDDs) is extremely complex and involves understanding the interactions between several physiological systems (e.g. nervous, gut, immune). In addition to the changes in the brains of patients, these disorders are characterised by deficits in social behaviour, memory and mood, such key aspects of NDDs are not possible to model using cells or simulations. This work must entail the use of whole animals as behaviour is a central feature of the project. To date there is no suitable alternative to the use of whole animals for behavioural research. It is necessary to use whole live animals both to model NDDs and to measure behaviour, particularly complex behaviours such as memory and social interaction. We will perform extensive analysis of tissue samples from all animals as we are searching for biological and behavioural changes induced by our maternal infection. Some cell assays may provide valuable information about these biological changes and will be used where appropriate.
2. Reduction How the use of minimum numbers of animals will be assured	We will minimise the number of animals we use by testing the same animals at various stages of development, re-using the same animal in different behavioural tests, testing more than one drug in the same animals. All these repeat studies will only be conducted following an extensive examination of the animal by the veterinary Surgeon. We will use males and females from each litter as both men and women suffer from these disorders. We will consult a statistical expert to ensure we have minimum number of animals for maximum statistical power.
3. Refinement Reasons for the choice of species and why the animal model(s) to be used are the most refined, having regard to the objectives. General measures to be taken to minimise welfare costs (harms) to the	Rats are a popular choice for much preclinical work because of the detailed existing knowledge of their brain structure and function and its similarity to that of humans. The rat has been chosen as a subject for the present work for several reasons. Primarily much is already known about memory and brain mechanisms controlling complex behaviours in rats. We have extensive experience of studying behaviour in rats, all our current tests are validated for rats and our tissue analysis systems are validated using rats. Rats are larger than mice and more suitable for longitudinal imaging studies, from weaning. We have refined our techniques in the continued review of our current work. Welfare is critical for successful

animals.	experiments and we have extensive experience in behavioural analysis of rats which we will use continuously to ensure that all our rats are subjected to the minimum adverse events and that undue stress is minimised at all times, particularly when rats are handled and dosed. Specific on-going refinements include: reduced use of food restriction, increasing use of ethologically relevant tasks involving enrichment, improved dosing regimes, handling and dosing techniques, including reduced restraint.