1. FINAL PUBLISHABLE SUMMARY REPORT

This section normally should not exceed 2 pages.

This is a comprehensive summary overview of results, conclusions and the socio-economic impacts of the project. The publishable report shall be formatted to be printed as a stand alone paper document. This report should address a wide audience, including the general public.

Please ensure that it:

- *Is of suitable quality to enable direct publication by the REA or the Commission.*
- *Is comprehensive, and describes the work carried out to achieve the project's objectives; the main results, conclusions and their potential impact and use and any socio-economic impact of the project. Please mention any target groups such as policy makers or civil society for whom the research could be relevant.*
- *Includes where appropriate, diagrams or photographs and the project logo, illustrating and promoting the work of the project.*
- *Provides the address of the project Website (if applicable) as well as relevant contact details.*

SUMMARY REPORT

Introduction: The pathophysiological mechanisms causing schizophrenia are not well known. In patients, schizophrenia is characterized by several devastating symptoms including hallucinations, emotional isolation and serious cognitive deficits. Altered neurotransmission through the glutamate neurotransmitter system has been linked to this devastating psychiatric illness. In particular, observations that functional antagonism of the N-methyl-D-apartate (NMDA) glutamate receptor by phencyclidine (PCP) worsens all symptom groups in patients and induces a schizophrenia-like psychosis in healthy volunteers have implicated this receptor system in schizophrenia. The NMDA receptor, which is principally expressed in postsynaptic neurons, is amultimeric protein assembly consisting of the obligatory NR1 subunit in different constellations with NR2A or NR2B subunits. Through alternative splicing of the NR1 subunit, several regulatory domains are introduced in the receptor, which significantly influence early processing of the receptor including its assembly and forward trafficking. In a similar way, receptors assembled from NR2A and NR2B proteins contribute with functional specialization of the receptor. Studies in postmortem brain indicate that mechanisms associated with early NMDA receptor processing might be altered in schizophrenia. This includes evidence for altered NR1 splicing and compromised trafficking of NR2B-type NMDA receptors in cortical dendrites.

Project objectives: Based on a hypothesis of altered NMDA receptor processing, in this project we will use an animal model to study changes in early events associated with alternative splicing, assembly and trafficking of new NR2A and NR2B receptors in schizophrenia. Furthermore, we will test how peptides that have been demonstrated to enhance cognition in animals, alters NMDA receptor processing at the molecular and behavioral levels. Due to the specialized roles NR2A and NR2B receptors play during complex functions such as during neuro-cognition, improved understanding of how this receptor system is altered in schizophrenia might lead to improved treatment of symptoms not well treated today.

Main results: During the funding period, our research has focused on expression analyses of several NMDA receptor subunits in rats treated briefly with phencyclidine (PCP) during early postnatal development. This procedure is a validated model for altered cognitive behaviors with relevance to mental illnesses such as

schizophrenia. Validation of this model at the molecular level is a central part of the specific aims for this research project. Specifically, we have analyzed expression of the NR2A, NR2A and NR1 receptor subunits and the KIF17 and APBA1 transporting proteins in several brain regions with relevance to cognitive function, including frontal cortex, hippocampus, and striatum and are currently in the process of processing the data for preparation of a publishable scientific manuscript.

Conclusions and their potential impact: Selectively altered expression of the NR2B NMDA receptor subtype in prefrontal cortex in animals with PCP induced reductions in cognitive ability indicates the involvement of this receptor subtype and cortical area in higher cognitive processing. This has direct relevance to better understanding of the changes that occurs in patients with schizophrenia and the present results therefore will inform at a molecular level to potential ways signalling is altered in this psychiatric illness. The impact of this and similar observations therefore might lead to the development of new and more specific ligands for the NMDA receptor. Such therapeutic developments would represent a significant innovative and necessary advance in the understanding of cognitive behaviour and how this is altered in schizophrenia and other serious brain diseases. The impact of such knowledge might lead to novel ways of treating these debilitating symptoms that are not well targeted by the current medication.