

## **Abstract for the general public**

Neurological disorders such as Alzheimer's disease, schizophrenia, and Parkinson's disease, in addition to drug addiction have long been linked to the cholinergic system, and specifically nicotinic acetylcholine receptors. These receptors bind a chemical signal (neurotransmitters) and convert it to an electrical signal (ion conductance). They belong to a class of pentameric ligand-gated ion channels composed of five individual similar or sometimes identical protein subunits that form an ion channel. They have a conserved general structure which includes three domains. The extracellular domain, the protein region located outside of the cell, contains the neurotransmitter binding site. The transmembrane domain forms the ion channel pore that selectively allows ions to flow along their concentration gradient. The intracellular domain, the protein region inside of the cell, is thought to be primarily involved in the regulation and trafficking of the receptor. This family of receptors is involved in all major functions of the central nervous system. An enhanced understanding of the mechanisms for functional modulation, in addition to the structural determination of the neurotransmitter binding site, resulted in many pharmacological advances. Yet the numerous years of research have not produced any robust therapies for the maledictions caused by a dysfunction of nicotinic acetylcholine receptors.

This project expressly aims to study the mechanism(s) of functional regulation of nicotinic acetylcholine receptors through their intracellular domain, for which very little is known. Targeting the regulatory system of these receptors may form the basis for developing new therapeutics against neurological disorders.

Within the project a protein composed of an intracellular domain of nicotinic acetylcholine receptors linked to a soluble homologous protein will be created. Using this soluble linked-protein as a tool to identify proteins which interact with the intracellular domain, this project will determine novel targets for current pharmaceutical therapeutic objectives. These newly discovered targets will generate more successful remedies for neurological disorders such as Alzheimer's and schizophrenia.

Additionally this project will study the mechanisms of action of the identified regulatory proteins. The subtype selective regulation may be identified by studying the role that the various subunit compositions of the receptor, otherwise known as stoichiometry, play in regulatory protein binding. Understanding the intricate mechanism of receptor regulation is important to combat neurodegenerative diseases. Through the development of small single-domain antibodies, nanobodies, against specific receptor stoichiometries this project will answer questions about regulatory differences and develop an understanding of regulatory mechanisms. These same nanobodies will also be used in the future projects as tools to properly localize given stoichiometries in the brain, creating a translational bridge between the biochemical mechanisms of regulation to the neurobiological system composition.

Understanding the mechanisms of regulation of nicotinic acetylcholine receptors, an aspect that has thus far remained elusive, is the key to developing efficient therapeutics for neurological disorders. This proposal attempts to develop such an understanding in the hope that a more effective forthcoming pharmaceutical approach may arise as a result.