Abstract for the general public

According to the World Health Organization tobacco use kills more than 7 million people every year and costs an estimate of US$1.4 trillion in global economic burden resulting from loss of productivity and healthcare costs. Smoking addiction has long been linked to the cholinergic system, specifically nicotinic acetylcholine receptors, through the principal addictive component in cigarettes: nicotine. These receptors bind a chemical signal (neurotransmitters) and convert it to an electrical signal (ion conductance). They belong to a class of ligand-gated ion channels composed of five individual similar or sometimes identical protein subunits that form an ion channel, otherwise known as pentameric ligand-gated ion channels. This family of receptors is involved in all major functions of the central nervous system. Numerous years of pharmacological and therapeutic research targeting the neurotransmitter and modulatory binding sites of nicotinic acetylcholine receptors has not yet produced any robust anti-addiction therapies. Recent genomic studies have identified a specific gene cluster and therefore the α3-, β4-, α5-subunits of the nicotinic acetylcholine receptor family which are correlated to smoking addiction. An inhibition of this assembly of nicotinic receptor subunits has been shown to reduce the reward effect caused by drug interactions in the brain, and thereby attenuate nicotine as well as other drug addictions.

This project expressly aims to synthetically generate and isolate selective single-domain antibodies which act as inhibitory modulators of α3-β4 nicotinic acetylcholine receptor subunits. These small versatile antibodies are derived from camelids such as llamas, alpacas, camels, and dromedaries. Very recently it has been possible to create synthetic libraries of single-domain antibodies and thereby avoid the use of camelids to generate them. These synthetically generated and selective nanobodies will also be used as tools to properly localize various α3β4 receptor assemblies in the brain, thereby better understanding the role of they play in the brain's reward pathway.

Understanding the role nicotinic acetylcholine receptors play in addiction is an important aspect to developing efficient therapeutics. This proposal attempts to develop therapeutics to help alleviate the drug dependence of smoking and other drug addictions, thereby reducing the economic burden that cancer and other addiction-related diseases have on the healthcare system. The use of single-domain antibodies as tools to study receptor localization will also elaborate upon the current understanding of the addiction/reward pathway in the brain.