A functional dissection of human nicotinic receptor polymorphisms linked to addiction and schizophrenia (iPS&BRAIN)

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Smoking is the single most important cause of mortality worldwide. It is an addiction to nicotine, that acts in the brain on nicotinic receptors, called nicotinic acetylcholine receptors (nAChRs). Human genetic studies have found alterations in the genome that increase the risk for smoking. These are found in several genes coding for nAChR proteins.
Additionally, human genetic studies have also highlighted a link between schizophrenia and alterations in nAChR genes. Schizophrenia hits about 1% of the population, and is a very debilitating, chronic relapsing disorder, that will not allow most patients to pursue a productive professional live. On top, smoking levels are very high, more than 80% of patients are heavy smokers, and so it is also important to study the link between schizophrenia and smoking.
We are proposing here a substantial project that analyses the function and the alterations in nicotinic receptors in human neurons in culture, and after transplantation into the mouse brain. This will be completed by recordings from human brain tissue obtained through surgery. Finally, transgenic rodents will be used to study the consequences when these genetic alterations are present.
This project will set the stage for renewed interest by pharmaceutical companies in developing medication targeting specifically the genetic alterations in the patients, in an approach referred to as “precision medicine”.