Could you outline the main objectives of your current investigations?

We are mapping neuronal circuits and nicotinic acetylcholine receptor (nAChR) subpopulations that underlie the nicotine withdrawal syndrome, as well as identifying genes that predispose carriers to nicotine addiction and exacerbated withdrawal symptoms. As a result of this, it will become possible to pursue personalised therapeutics that more effectively treat nicotine addiction. We are interested in finding drugs that can be safely combined with current smoking cessation aids to increase the success rates of quitting smoking. We are also interested in studying the mechanisms of nicotine co-abuse with several other addictive drugs. For instance, smokers are more likely to drink, while a high percentage of alcoholics and cocaine users are known to smoke.

How has your research progressed since its inception? In what way has your professional background prepared you for work in this field?

Over my career, I have been able to take advantage of many techniques and I am constantly re-training in order to fully benefit from the technical advances made in genetics, molecular biology and biophysics. I was fortunate to be able to interact and collaborate with Art Beaudet and Jim Patrick when the technology for the creation of genetically modified animals first became available, thanks to Allan Bradley, who back then was a faculty member at Baylor College of Medicine in the US. We were able to characterise a number of nAChR gene knockout mice that continue to help us in our quest to define the molecular and circuit level mechanisms underlying nicotine dependence and withdrawal. We are currently using optogenetics and designer receptors exclusively activated by designer drugs (DREADDs) to manipulate neuronal circuits during self-administration and withdrawal from nicotine and other drugs that are often co-abused with nicotine. We combine those techniques with viral approaches for the re-expression of the gene(s) of interest in specific brain areas. Such approaches allow us to query the role of an exact gene or gene variant related to nicotine abuse in a particular neuronal circuit.

What is the role of the habenula, and how is it affected by nicotine withdrawal?

The habenula is a small brain structure located near the pineal gland and the third ventricle. It is shaped like a ‘little rein’ – ‘habenula’ in Latin – and is involved in pain, stress, anxiety, sleep, reward, depression, schizophrenia and drug addiction. There are two main nuclei in the habenula: the lateral habenula (LHb) and the medial habenula (MHb). The LHb regulates the reward system by influencing dopaminergic activity in the ventral tegmental area. The Mh2b has been characterised by my lab and others as a centre that regulates...
Smoking cessation

Researchers based in the Department of Psychiatry at the University of Pennsylvania, USA, are investigating how genetic and neurological factors influence nicotine addiction and withdrawal symptoms.

ESTIMATED TO KILL almost 6 million people per year, smoking is a significant threat to global public health. Addictive and toxic, it substantially increases the risk of developing numerous pulmonary and cardiovascular disorders, as well as cancer. Alarming, according to the World Health Organization (WHO), due to the time lag between starting to smoke and the onset of negative health effects, the epidemic of tobacco-related disease and death is likely to continue unabated unless significant measures are taken. Projected to cause 1 billion deaths throughout the 21st Century, there is an urgent need to continue raising awareness about the specific health risks of tobacco use and ensure the implementation of effective strategies and programmes that help individuals across the world to give up smoking.

Promisingly, many high-income countries have seen renewed efforts to help smokers overcome the habit in recent years. However, success rates vary widely between different individuals. While this is often attributed to environmental factors such as access to counselling or level of support among family and friends, research from the University of Pennsylvania and several other institutions has shown that genetic factors could account for up to 50 per cent of the variance in quitting success. “While the severity of withdrawal symptoms is largely determined by how nicotine is consumed, certain short nucleotide polymorphisms (SNPs) have been shown to predispose individuals to consuming larger amounts of nicotine more frequently, as well as experiencing more severe symptoms of withdrawal when trying to quit,” explains Dr Mariella De Biasi, Associate Professor in the Department of Psychiatry at the University and Director of the Program on Cholinergic Mechanisms in Addiction and Mental Illness.

De Biasi’s current research operates at the intersection of neuroscience, pharmacology and genetics – and her seminal studies have revealed key insights into the molecular basis of nicotine dependence and withdrawal. With an academic background in pharmacology and toxicology, she has advanced knowledge about the role of nicotinic acetylcholine receptor (nAChR) subunits in the brain. At present, work in her laboratory is focusing on how nicotinic receptor gene variants impact nicotine dependence, nicotine and alcohol co-dependence, interactions between stress and nicotine and, additionally, cholinergic influence on neurodegenerative disease and mental illness.

ADDITION AND WITHDRAWAL

Importantly, nicotine triggers addictive behaviour by influencing the neural circuitry connected with rewards. For instance, the mesocorticolimbic dopamine system is known to shape behaviour and optimise behavioural outcomes, thereby playing a key role in processing the environmental reward: “Research has shown that rewarding stimuli promote the learning of goal-directed behaviours, generate positive emotions and subsequently stimulate the repetition of those learned behaviours,” De Biasi elucidates. “Intrinsic neural responses to rewards have evolved to ensure the continuance of successful behaviours that perpetuate the genetic material of the individual and its species.” Yet, alongside rewards as a result of survival-enhancing behaviours, such as eating and intercourse – as well as from more complex monetary, cognitive and social stimuli – the dopamine system also fuels the acquisition of behaviours that are reinforced by damaging psychostimulant drugs such as nicotine. Furthermore, following the chronic nicotine aversion and some of the manifestations of nicotine withdrawal.

Have you encountered many challenges or been rewarded with significant successes to date?

The genes that encode the α5, α3 and β4 nAChR subunits are now one of the ‘hot topics’ in nicotine addiction. I studied those receptors long before the human genetics studies made them so popular. I remember many comments from reviewers and colleagues saying that those receptors and subunits were not very interesting because they happen to be abundantly expressed in the autonomic nervous system and are present in very few brain areas. There is some satisfaction in having been ‘ahead of the curve’ on this.

Do you have plans to translate your research for use in clinical settings in the near future?

Yes, being at the University of Pennsylvania gives me the opportunity to interact with a large community of scientists interested in drug abuse. In addition to a number of colleagues doing basic research, the University is home to many prominent scientists that have contributed to the understanding of drug addiction mechanisms in humans using genetics, functional MRI, behavioural studies and drug testing in clinical trials. We are currently preparing several proposals that will have important preclinical and clinical components. This is exciting because the clinical studies inform the animal work and vice versa with a ‘bench to bedside and back’ approach.
Studie have suggested that the impact of the CHRNA5/CHRNA3/CHRN4 haplotypes on nicotine dependence is most pronounced among individuals who began smoking in early life.

use of these drugs, their removal results in withdrawal symptoms of varying degrees of severity, including stress, anxiety and a negative emotional state. Such symptoms are a major deterrent for people who want to quit smoking.

EXPLORING THE GENETIC COMPONENT

De Biasi and her team have made significant strides in understanding the genetic components that underpin nicotine withdrawal. To this end, they primarily rely on preclinical mouse models to systematically analyse the addiction process through the observation or manipulation of environmental and biological variables: “When studying human addiction we have a limited ability to intervene in the genetics, personal environment or neurobiology of drug abusers,” De Biasi states. “Animal models allow us to study drug-related phenotypes such as dependence, tolerance, sensitisation and withdrawal with a precision that cannot be achieved in human subjects.”

The researchers’ work has largely focused on a small brain structure called the medial habenula (MHB), which have characterised as a key centre involved in the regulation of nicotine aversion and some manifestations of nicotine withdrawal. Here, they have made two particularly important discoveries in nicotine addiction. The first is that nicotine binds to the nAChRs that contain subunits encoded by the CHRNA5/CHRNA3/CHRN4 gene cluster – and that the activation of these receptors in the MHB triggers the release of proteins associated with pain and inflammation. The second key finding is that the MHB and the same nAChRs are involved in the physical symptoms associated with nicotine withdrawal. A third important observation is that common inherited genetic variants in the CHRNA5/CHRNA3/CHRN4 gene cluster are involved in increased nicotine consumption in an animal model: “It should be noted that CHRNA5/CHRNA3/CHRN4 has been reproducibly associated with nicotine dependence, smoking behaviours and lung cancer risk,” discloses De Biasi. “More recently, the same genes have been shown to influence the outcome of smoking cessation treatments.”

Interestingly, studies have suggested that the impact of the CHRNA5/CHRNA3/CHRN4 haplotypes on nicotine dependence is most pronounced among individuals who began smoking in early life. This implies that early-life tobacco exposure increases the risk associated with these genes, highlighting the need for smoking prevention strategies that target children and adolescents.

TOWARDS TRANSLATION

As well as providing fresh insights into the genetic components that underpin nicotine dependence, De Biasi and her team have devoted time and attention to exploring the role of neuronal mechanisms. For instance, the researchers have successfully highlighted the circuits that have measurable impacts on nicotine dependence and withdrawal through the use of advanced technologies, including electrophysiology, imaging techniques, biochemistry and behavioural paradigms in genetically modified animals. Their work has emphasised the importance of the MHB-IPN axis in the circuit that underpins abstinence symptoms from nicotine.

However, as a pharmacologist by training, De Biasi’s ultimate goal is to translate her seminal research findings for use in clinical settings – and she is currently investigating potential new drug targets for the development of pharmacological tools that could help smokers to quit the habit and prevent future relapses. Their studies to date pinpoint nAChRs as a promising target; however, new targets are beginning to emerge as they continue forging a deeper understanding into the impact of nicotinic cholinergic function on neurotransmitter systems and molecular pathways involved in the addiction process.