Could you explain what motivated you to enter the pharmacology field and why you decided to focus specifically on opioid addiction?

It’s a roundabout story. I’m not really trained as a pharmacologist – I’m a cell molecular biologist, and when I started my career my real interest was in developmental biology and the things that regulate development. I began my professional career at Yale. This was back in the mid-1980s when I was working on a protein that turned out to be very important for brain function. I hadn’t actually thought about the brain until I worked on this protein. For years, I tried to set up a collaboration with a neuroscientist at Yale who’s pretty famous – but she kept on rejecting the idea of me getting involved in a collaboration with her because she didn’t see where we overlapped. Then one day she approached me because she was looking for someone who could make antibodies – something we could do very well – and asked if I would be willing to collaborate with her on making antibodies against dopamine receptors. So that was my entrance into the brain and receptors.

Why did you focus on dopamine receptors in particular, and why are they important in human health?

Dopamine receptors are the targets that are used to treat schizophrenia, so for about five years I made antibodies with this professor. Eventually, I got tired of making antibodies but I became very interested in the concept of dopamine receptor biology and its role in schizophrenia. What struck me as being the central paradox was that all the drugs that were available at the time worked through dopamine D2 receptors – and so one would have naively thought: ‘Well, there must be something wrong with dopamine receptor in the brains of schizophrenics’. The paradox was that when you compared the primary structure/expression of these receptors between schizophrenic and normal brains, you saw that there was absolutely nothing wrong with them! So the question was: how did the drugs provide therapeutic efficacy at a target which, for all intents and purposes, seems to be normal?

What accounts for the sudden rise in opioid-related deaths in recent years?

In the US now, the number of deaths caused by opioid abuse outnumbers the deaths caused by auto accidents. That’s pretty astounding – and there are many reasons why the death rate has been increasing. One is that the number of people using these drugs has increased – and there is a direct correlation between the number of people using the drugs and the number of people who are overdosing on them. The other reason is that heroin has become so cheap that it is replacing prescription opioid drugs as the drug of choice. Opioid medications are expensive and it’s getting harder for drug addicts to get hold of those drugs. More people are now turning to heroin – and part of the problem with heroin is that you don’t know what you’re getting. A lot of heroin is mixed with pretty toxic substances and many heroin addicts use heroin synergistically with other drugs of abuse – so the drugs actually become more powerful. And now there’s another problem: fentanyl, a synthetic opioid that is cheaper than heroin and about 100 times more powerful. So all of these factors contribute to the increase in drug-related deaths.

Do you anticipate that your research will feed into the development of therapeutics?

That would be the long-term goal for sure. It’s difficult to predict when this would happen, because we still don’t know if the targets we have uncovered have any real impact on drug addiction or relapse. That is the stage we are at, at present. If we can really convince ourselves and the scientific community that the molecular targets we have identified do impact drug taking or drug seeking, then it’s pretty clear that they would be targets for the development of novel drugs.
Of opioids and overdoses

The human relationship with opioid drugs is long and sordid – but today, researchers at Penn State University in the USA are hot on the trail of molecular answers to age-old problems like addiction; their results could change the face of pain relief.

OPIOID DRUGS ARE drugs that act on the opioid receptors to produce analgesic effects – that is, they kill pain. Opiates derived from natural sources, such as poppies, have been used recreationally and as painkillers for many centuries – but their use has always been associated with side effects like addiction, as well as premature death.

Although opiates are recognised as being among the most problematic drugs of abuse today, opioid drugs that activate the same receptors can still be obtained; even these improved forms of drug can cause harm, however. In 2014 alone, the Centers for Disease Control and Prevention (CDC) attributed more than 47,000 deaths to prescription drug abuse. The CDC estimates that 44 people die each day from prescription pain medication overdoses, with nearly 7,000 people treated in emergency rooms for misusing these medications.

The nonmedical use and abuse of prescription opioid drugs has become a substantial public health problem in many countries, including the USA. In January this year, the American Association of Medical Colleges and the Congressional Academic Medicine Caucus held a Capitol Hill briefing to highlight efforts at medical schools and teaching hospitals that are responding to the opioid epidemic that has been gripping communities from small towns to large urban centres. The figures quoted at this event were shocking, to say the least: the National Institute on Drug Abuse asserts that from 1992 to 2003, misuse of opioid prescription painkillers increased by 140 per cent – and, according to the 2013 National Survey on Drug Use and Health, almost 2 million Americans are opioid-dependent.

REDUCING RELAPSE

Opioid addiction is characterised by craving, evidence of self-harm, the illicit purchasing of opioids, taking of non-prescribed opioids and other aberrant behaviours. The consequences of this epidemic in the US include overdose deaths, which now outnumber deaths caused by auto accidents.

Drug overdoses still frequently occur despite the availability of the opioid blocker, naloxone, for the rapid treatment of respiratory depression. This is, in part, because addiction is nothing if not complex. Efforts to treat the problem with standard agonists and antagonists have failed. While the causes of this epidemic are complex, they likely include over-prescription of pain medications – and recidivism rates are also a notable problem.
This is a national problem, and new approaches to it are sorely needed.

One group of researchers at Penn State University in the US is working on advancing such novel approaches through a better understanding of the underlying mechanisms of vulnerability to addiction and relapse. Dr Robert Levenson is Distinguished Professor of Pharmacology and Neural and Behavioral Sciences and Co-Director of the MD/PhD Program at the University’s Department of Pharmacology, in addition to his role as leader of this research team. “If we are to develop novel therapeutics that can effectively prevent opioid addiction and relapse in humans, we need innovative ways of approaching this problem,” Levenson remarks.

**THE BARE BONES OF ADDICTION**

Addiction, by nature, is a chronic disease of relapse – and humans are known to relapse to drug-seeking and taking behaviour following months or even years of abstinence. The goal of this research is to develop an understanding of the molecular mechanisms underlying vulnerability to addiction and relapse – that is, the causative factors of addiction at the molecular level. Knowledge of these molecular mechanisms could serve as a platform for the development of novel therapeutics to prevent relapse to drug use without the stigma or risk associated with opioid replacement therapies such as methadone or buprenorphine treatment.

To achieve this goal, Levenson and his colleagues have focused on a cellular protein termed the μ-opioid receptor – a protein expressed on the membranous surface of cells which interacts with opioid drugs and mediates their effects on the cell. When the gene for this protein is deleted in animal models, they become resistant to addiction – but they also no longer experience relief from pain when treated with the drugs.

**GOING WNTLESS**

The Levenson lab began its present course of study in 2010 when Jay Jin, then an MD/PhD student in Levenson’s laboratory, made the surprising observation that, in neurons of the mammalian brain, the μ-opioid receptor also interacts with another protein called Wntless. The Wnts, the family of proteins to which Wntless belongs, regulate a variety of events during embryogenesis including proper development of the brain. In the adult brain, the Wnt signalling pathway also regulates neuronal activity, including the numerous contacts the dendritic spines of neurons make with other neurons that are important for intercellular communication, and the production of neuronal stem cells.

Opioid drugs, as Jin discovered, interact with this signalling pathway. The important neuronal functions of the Wnts are blocked via the effects of opioid drugs, and the interaction between Wntless and the opioid receptors is enhanced via treatment with opioid drugs. Jin’s experiments therefore suggested, for the first time, that the Wnt signalling pathway may play an important role in the manifestation of addiction-like behaviours and relapse to drug taking after abstinence. Since the publication of the paper describing these important results was published, a number of other labs have reported that Wnt signalling also plays an important role in mediating cocaine-induced behaviours as well as relapse to addictive drugs such as ketamine.

**FIGHTING FIRE WITH PHARMACOLOGY**

To better understand the role of Wnt signalling in opioid addiction, Levenson developed on these revelations by analysing the expression of the Wntless protein in a rodent behavioural model in which rats were trained to self-administer heroin. These behavioural studies were carried out by Diana Tacelosky, an MD/PhD student in his lab, in collaboration with Dr Sue Grigson, an internationally recognised expert in the field of addiction research at Penn State. Using this model, in which drug self-administration was similar for all subjects during the acquisition phase of training, the team showed that reduced expression of Wntless in the prefrontal cortex of rats was associated with greater addiction-like behaviour for heroin in general, and with a greater willingness to work for the drug in particular.

These data thus linked reduced Wnt signalling to the explicit motivation for the drug rather than to differences in total drug intake, and gave the Pennsylvania researchers an idea: by stimulating Wnt signalling, they hypothesise, they could prevent acquisition and/or relapse to addiction-like behaviours in the context of heroin.

“The focus of our current research programme is therefore designed to test this hypothesis,” Levenson explains – and, in order to do this, the team is taking a pharmacological approach to determine whether it is possible to prevent relapse to drug-seeking behaviour in heroin-addicted rats after a period of abstinence. The idea here is to overcome the inhibiting effect of opioids on Wnt signalling by treating rats with a synthetically produced small organic molecule that has previously shown by others to stimulate Wnt signalling in the brain.

A positive outcome from this type of approach would establish the Wnt signalling pathway as a key cellular component contributing to vulnerability for opioid addiction and relapse – and could lead to new avenues for the pharmacotherapy of drug addiction in human opioid addicts.”