"I picked up the phone and heard two words: ‘it worked’."

This was the phone call Director of the Centre for Integrated Preclinical Drug Development (CIPDD) and UQ Pharmacy School’s Professor Maree Smith had been waiting to receive for about eight years. The pain researcher’s drug had passed its first test on the journey to becoming a prescription medicine, with the potential to improve the lives of millions.

Since receiving that phone call in 2012, Professor Smith’s mission to find a much-needed treatment option for people suffering from specific pain conditions is now closer to reality. Once the oral drug (or painkiller) called EMA401 is ready for doctors to prescribe to patients, it could provide significant relief for the many people suffering from nerve pain – which is often difficult to alleviate – and may also help those suffering chronic inflammatory pain – the type that often lingers for years.

It’s these debilitating forms of chronic pain that Professor Smith is tackling. She says that while the burden of chronic pain is similar to that of cancer or heart disease and affects one in three people aged over 65, it’s rarely spoken about. Many pharmaceutical companies have left the novel pain medicine discovery field due to the high failure rate of drug candidates that showed promise in animal studies but did not alleviate nerve or chronic inflammatory pain in clinical trials.

Nerve pain and chronic inflammatory pain affect a person’s physical and emotional wellbeing and, with a globally ageing population, the demand for effective and well-tolerated new treatment options is high. New painkillers like EMA401 are likely to have far-reaching potential for years to come.

In the early stages of development, EMA401 was initially targeted at nerve pain, which is commonly associated with cancer chemotherapy, post-herpetic neuralgia (PHN – a painful condition that can follow shingles) and other forms of peripheral nerve injury-induced pain such as sciatica.

“Nerve pain affects between two and eight per cent of the adult population globally and is often difficult to treat, either because the pain is resistant to relief with currently available pain medications or patients can’t tolerate the brain-related side-effects,” says Professor Smith.

Side-effects can include dizziness, drowsiness, blurred vision and a dry mouth. But through her research, Professor Smith has found that EMA401 may also relieve the most common form of chronic inflammatory pain, osteoarthritis. However, clinical trials are needed to show this.

While there have been new painkillers launched on the market in the past two decades, they are ‘work-alikes’ of known painkillers. Professor Smith’s EMA401 is the first orally active new painkiller for nerve pain that has a completely novel mechanism of action. It works by reducing the hyper-excitability of damaged peripheral nerves that carry pro-pain signals into the spinal cord and brain so that these nerves function more normally. More importantly, EMA401 doesn’t cross the blood-brain barrier, meaning it doesn’t cause the brain-related side-effects that are produced by currently available medications for nerve pain.

The EMA401 journey began in late 2003 when Professor Smith entered the inaugural UniQuest Trailblazer ‘ideas’ competition with a hypothesis that blocking the angiotensin II Type 2 (AT2) receptor may alleviate nerve pain. This idea was awarded one of three $8000 Trailblazer prizes on offer. Professor Smith gave the prize money to her UQ colleague, Associate Professor Craig Williams, to synthesise a batch of PD123,319, which was known in the literature as an AT2 receptor blocker ‘tool’ compound used in the cardiovascular research field.

Subsequent research in animal pain models in her laboratory towards the end of 2004 proved that her theory was right and this was a Eureka moment, she says. The breakthrough meant that the discovery could be patent-protected by UniQuest, which formed Spinifex Pharmaceuticals in mid-2005 with $3.25 million in venture capital from three firms. Spinifex was able to undertake a range of nonclinical studies and work in Professor Smith’s laboratory, resulting in data that collectively informed the selection of EMA401 as the drug candidate. The drug could then be progressed through the prerequisite preclinical safety and toxicology studies in preparation for the first human (Phase 1) clinical trials to assess EMA401’s safety and tolerability in healthy humans.

Phase 1 clinical trials showed that EMA401 was safe and well tolerated in healthy humans. Following these positive results, the
drug was used in a placebo-controlled Phase 2 clinical trial in 183 patients with post-herpetic neuralgia. The clinical trial results announced in August 2012 showed that EMA401 alleviated this type of nerve pain without causing brain-related side effects.

In the United Kingdom, another clinical trial of EMA401 was undertaken in cancer patients with nerve damage in their fingers and feet as a result of cancer chemotherapy treatment. EMA401 showed a significant improvement in comparison to the control drug, and a large proportion of patients reported a reduction in pain intensity. There were also no serious treatment-related adverse events reported.

The prospect for sufferers continues to be extremely promising. Last year, EMA401 was the basis for Australia’s largest-ever biotech deal when pharmaceutical giant Novartis International AG bought Professor Smith’s technology in a $260 million upfront cash deal through the acquisition of Spinifex Pharmaceuticals. Financial media have estimated the total deal at around $1 billion.

“To change people’s lives you have no choice but to go down the commercialisation track because without patent protection, no one is going to commercialise your invention,” says Professor Smith.

“Novartis has the deep pockets needed to fund the large international clinical trials of EMA401 that are due to start soon and, if they go as planned, the drug is expected to be approved in the next few years.

“Drug development is a very long journey, so from the point of discovery until approval for doctors to prescribe can be 15 years or more. But the wait will be worth it once it’s available for doctors to prescribe for the patients who need it most.”

For Professor Smith, the phone call she’s now eager to receive is the one where she finds out that the first person has been prescribed EMA401. This will be the culmination of the drug’s development journey, enabling many millions of people – particularly those suffering from debilitating nerve pain – to obtain significant pain relief and experience an improved quality of life.

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The EMA401 journey so far:

November 2003: Professor Maree Smith wins $8000 in UniQuest Trailblazer ideas competition to investigate blocking of the angiotensin II Type 2 receptor for relief of neuropathic pain

Late 2004: First data from animal studies shows positive results for neuropathic pain

June 2005: UniQuest forms spin-off company Spinifex Pharmaceuticals to develop AT2 receptor antagonists as new therapy for neuropathic pain, with initial $3.25 million raised by UniQuest to form Spinifex in mid-2005 from Symbiosis, GBS Ventures and Uniseed

2006: Unexpected discovery by Professor Smith that AT2 receptor antagonists alleviate chronic inflammatory pain in animal models; this discovery also licensed to Spinifex Pharmaceuticals for commercialisation

August 2012: Successful proof-of-concept clinical trial of EMA401 in patients with post-herpetic neuralgia is announced

2014: Phase 2 clinical trial of EMA401 in patients with post-herpetic neuralgia is published in The Lancet

May 2015: Topline Phase 2 data for clinical trial of EMA401 in patients with chemotherapy-induced peripheral neuropathy (CIPN) is first presented at the NeuPSIG conference held in Nice, France

June 2015: Spinifex Pharmaceuticals is acquired by Novartis in a deal comprising a US$200 million upfront payment plus undisclosed milestone payments

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