Europain

Understanding chronic pain and improving its treatment

Summary

Only 30% of patients with chronic pain receive effective treatment and when it comes to neuropathic pain, which results from nerve fibres being damaged, dysfunctional or injured, this figure is even lower. By creating unprecedented levels of cooperation among industry, academia and SMEs, Europain transformed the neuropathic pain field in a number of ways. Firstly, it generated the knowledge and tools which will make conducting pre-clinical and clinical trials more reliable and effective. Secondly, it came up with a new way of classifying patients which could lead to the development of more personalised medicines. Thirdly, the project made its mark on European regulatory guidelines and a number of its outputs are already being used by the pharmaceutical industry. In the long-term, patients could reap many benefits by gaining access to more affordable, personalised treatments.

Casting the net wide, producing more than 200 publications

Chronic pain affects one in five Europeans and 7-8% of the whole population has neuropathic pain, a type of pain which results from the nerve fibres themselves being damaged, dysfunctional, or injured. Despite the prevalence and high cost to society, only 30% of people with chronic pain get an effective treatment and in the neuropathic group that figure is even lower. Even though there are a number of different products for treating pain, the last big pain drug concept was invented in 1995. New, more personalised and effective ways of treating pain are sorely needed.

By bringing together 12 academic institutions, 11 pharmaceutical companies and an SME, IMI’s Europain project set out to improve our understanding of the mechanisms of pain, and overcome bottlenecks in the development of analgesics (pain killers). The result was a very wide-ranging project which transformed the pain field, resulting it over 200 scientific publications. Its learnings and outputs improved both preclinical and clinical studies, as well as the ability to translate results from animal to patient studies.

Pre-clinical studies: happy rats burrow, socialise and venture into light

In the pre-clinical phase of pain medication studies, one of the main problems is measuring the impact of potential new drugs on laboratory animals, usually rats. In order to improve the situation, Europain scientists set out to provide something that was missing: a standardised and structured way of measuring pain in rats based on their natural behaviour. When healthy and pain-free, rats burrow, socialise and spend more time in the light. When in pain, they burrow and socialise less, and spend more time hiding in the dark. Project scientists measured these behaviours, and validated them across different laboratories in both industry and academia, performing the first multi-centre, double-blind study in a pre-clinical setting. Thanks to this work, four quantitative ways of measuring spontaneous pain behaviour in rats are now available, along with detailed protocols which other scientists can use.

From animals to humans: translating results made easier

One of the difficulties in drug discovery is using the results of animal studies to predict what will happen in human patients. In an effort to facilitate this process, Europain scientists were able to show that a technique used to measure pain-related nerve signals, called microneurography, measures the same pain patterns in animals and humans. The European Medicines Agency (EMA) acknowledged that this technique – which involves sticking a fine needle into a nerve to measure pain – can now be used to demonstrate whether a potential drug works. Drug companies are already using the method to help them identify early on which drugs are likely to be effective.

Preparing for a clinical study: the power of imaging

Clinical studies are lengthy and expensive, and before investing in them, pharmaceutical companies want to know if a potential drug is likely to work in patients. European scientists found that brain imaging could be used to predict
early on, in limited groups of patients, whether a potential drug works. They showed that certain areas in the brain are more active when a patient is in pain, and become less active when the patient is given efficacious treatment. They further validated brain imaging as a method which can show whether a potential drug works to reduce pain (proof of mechanism). Some companies are already using this method, which has the potential to save money and ensure that more effective drugs reach patients.

Clinical studies: minimising the placebo effect

Another obstacle in clinical studies is the placebo effect, in which a fake treatment (such as a sugar pill) causes a patient’s condition to improve. If large, the placebo effect makes it harder to measure the real effect of a potential drug. In order to understand factors which trigger a placebo response, Europain project scientists studied how different factors in the design of the study affect the placebo response. Out of all the possible factors which could influence the patients, such as the size or the location of the study, they found that the information given to patients at the beginning of the study, likely may be the factor having the greatest impact. For example, patients who knew they were being tested for over-the-counter pain medications had a much lower placebo response than patients who knew they were being tested for morphine-like drugs. This led the scientists to conclude that researchers could be more successful in eliminating the placebo effect if they write the information in the consent forms in a more neutral way, thus lowering patients’ expectations.

Other achievements: a new way of grouping patients

During its course, Europain tackled a wide range of questions and recorded a number of other achievements. Among the most significant are the following:

- Creating a database of more than 2 300 neuropathic pain patients and 1 000 healthy volunteers – the largest of its kind in the world. The scientists further classified patients in the database into groups based on their level of sensitivity to pain rather than the type of disease which is at the origin of their pain. The EMA has acknowledged that this is a valid way of classifying patients in early clinical trials and included this new stratification in their guidelines for the development of pain drugs. This represents a paradigm shift in the field of developing treatment for neuropathic pain.
- Several disease-relevant animal models have been developed and validated across laboratories in industry and academia. They can now be used to study chronic pain due to diabetes, antiretroviral treatment and chemotherapy.
- A new human model for chemotherapy-induced pain has been developed and validated. Scientists also discovered that sleep deprivation is a valid model for increased sensitivity to pain in both rodents and humans.
- A discovery that people prone to catastrophising (believing that something is far worse than it actually is) have a higher risk of developing chronic pain in the aftermath of surgery. The project also found that patients who undergo endoscopic (keyhole) surgery develop chronic pain after surgery to a lesser extent than patients who undergo open surgery. This is already helping doctors personalise post-surgery follow-up treatments in some countries.

For the benefit of industry, academia and patients

Europain created unprecedented levels of cooperation in the chronic pain field, and enabled the exchange of knowledge which benefitted both industry and academia. The industry gained new tools which could make pre-clinical and clinical trials cheaper, more reliable and efficient, speeding up the development of innovative medicines. Thanks to the partnership with the industry, the academic community was able to achieve much more than it could have done on its own, raising the profile of European research in this area. Last but not least, patients will reap significant benefits: for example, the new stratification of patients according to their level of sensitivity during clinical trials could lead to the development of more personalised treatments.

What happens next?
Europain project learnings and outputs have transformed the neuropathic pain field and triggered a lot of new research activity. A number of new projects are now building on the Europain results, and some of them involve one or several partners from the Europain team.

Read the interview with the project coordinator

Achievements & News

‘More successful than what we thought possible’ – an interview with the Europain project coordinator

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Europain study: early action needed to prevent chronic pain

Repeated exposure to pain can rapidly lead to increased sensitisation to pain and changes in the parts of the brain involved in processing pain, according to new research by researchers from IMI’s Europain project. ‘Similar changes can also be seen in the brains of patients to suffer from chronic pain,’ explained Professor Thomas Tölle of the Technical University of Munich, who led the research. ‘We should therefore begin pain treatment as soon as possible, in order to counter these changes in time to prevent the pain from becoming chronic pain.’ Writing in the journal Pain the researchers explain how they exposed 27 healthy people to both painful and non-painful heat stimuli over a period of 11 days. The people were asked to rate the pain on a scale from 0 to 10, with 0 being no pain and 10 being the strongest pain imaginable. While half of the people got used to the pain, the other half appeared to become more sensitive to the pain, rating it as more intensive as the study progressed. Meanwhile brain scans of the people revealed clear changes in the brains of the people who became sensitised to the pain. These changes were located in the parts of the brain involved in processing pain and closely resemble the brain changes seen in people with chronic pain. The next question for the researchers is whether people who quickly become sensitised to pain are also more likely to develop chronic pain. Chronic pain affects one in five Europeans, and it represents a major cause of long-term sick leave and forced early retirement. Europain is working to boost our understanding of the causes of chronic pain, knowledge that is needed for the development of new analgesics. (October 2013)

IMI team pinpoints molecule that puts the burn in sunburn

Scientists from the IMI project EUROPAIN have identified a molecule that causes the pain of sunburn, raising hopes for the development of new, more effective painkillers. Writing in Science Translational Medicine, the scientists explain how the molecule CXCL5 brings immune cells to the injured tissue, triggering pain and tenderness. ‘This study isn’t just about sunburn – we hope that we have identified a potential target which can be utilised to understand more about pain in other inflammatory conditions like arthritis and cystitis,’ commented King’s College London’s Stephen McMahon. ‘I’m excited about where these findings could take us in terms of eventually developing a new type of analgesic for people who suffer from chronic pain.’ Read a press release about the findings from King’s College London. (September 2011)

Participants

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• Eli Lilly and Company Limited, Basingstoke, United Kingdom
• Grünenthal, Germany
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• Sanofi-Aventis Recherche & Developpement, Chilly Mazarin, France
• Pfizer Limited, Sandwich, UK – Wyeth Pharmaceuticals, USA

Universities, Research Organisations, Public Bodies & Non-Profit

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• Region Hovedstaden, Hillerod, Denmark
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SMEs

• Neuroscience Technologies, S.L., Barcelona, Spain
### Facts & Figures

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### Links and Documents

- Project website: [www.imieuropain.org](http://www.imieuropain.org)
- **IMI funding per project participant**

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