Name of grant holder: S.M. Géranton

Project title: FKBP51 and chronic pain states

End of grant report

Background

While acute pain has a protective role and warns the organism of an imminent danger, chronic pain, which is defined as pain that lasts for more than 3 months, compromises the quality of life. Moreover, chronic pain is often accompanied by numerous debilitating side effects. For example, patients suffering from chronic pain often become depressed. Interestingly, major depressive and anxiety disorders are also frequently accompanied by chronic painful syndromes. The mechanisms that connect mood disorders and chronic pain states have remained poorly understood but a regulator common to both conditions now appears to be the FKBP51 protein.

FKBP51 is important for the regulation of the stress response and variations in the *FKBP5* gene have been repeatedly associated with anxiety related disorders, including major depression and post-traumatic stress disorder (PTSD). Moreover, inhibition or deletion of the protein in mice reduced anxiety-related behaviour. Our recent study has shown that male mice that lack the protein FKBP51 have reduced chronic pain after joint inflammation and nerve damage. Moreover, blockade of FKBP51 specifically at the level of the spinal cord could interrupt a pre-existing chronic pain states. This suggested that FKBP51 could regulate pain independently from its effect on mood, which presumably happens at brain level. Crucially, it was recently reported that genetic variants in *FKBP5* influence the severity of musculoskeletal pain symptoms experienced after motor vehicle collision and sexual assault, suggesting that targeting FKBP51 would be beneficial for the treatment of chronic pain in humans.

The first specific inhibitors of FKBP51 have been very recently developed. These inhibitors were able to reduce anxiety related behaviour in mice *in vivo*. These inhibitors are therefore the perfect tools to explore the potential of pharmacological inhibition of FKBP51 as a new therapeutic approach for the treatment of chronic pain states in mice.

Project aims

We have recently shown that deletion of the gene *FKBP5* could reduce persistent pain in mice. The aim of this project was to test the efficacy of a novel FKBP51 inhibitor, SAFit2, in reducing persistent pain in mice. In particular, we wanted to test the effects of FKBP51 blockade on pain behaviour in rodent models with high translational value. This project also used a range of molecular techniques to further our understanding of the mechanisms of chronic pain.

Results

With this grant, we were able to demonstrate that:

- FKBP51 regulates persistent pain states of various aetiologies in both male and female mice.
- Pain states regulated by FKBP51 are associated with increased stress axis activity.
- Crucially, pharmacological blockade of FKBP51 using the state-of-the-art ligand SAFit2 improves the increase in hypersensitivity seen in male and female mice with:

- joint inflammation
- nerve damage
- chemotherapy induced pain

Conclusion

With this project, we have significantly helped the Pain Relief Foundation achieve its aims:

1. We have brought new compounds, FKBP51 inhibitors, one-step closer to clinical trials for the treatment of chronic pain states.
2. We have proposed a new molecular pathway to alleviate chronic pain. This new approach can improve both physical and emotional health by working both at spinal level, inhibiting nociceptive mechanisms, and at brain level, reducing stress and anxiety. This new approach is therefore expected to be a significant improvement compared to currently available therapeutic options. Crucially, so far no negative side effects have been observed.
3. Finally, we have presented and will continue to present the results of our research at national and international meetings, such as the British Pain Society and the International Association for the Study of Pain meeting. Importantly, we have also disseminated our findings in a peer-reviewed publication published in Pain.

Data dissemination

The data obtained with this grant is presented in a manuscript that has been accepted for publication in Pain:

- M Maiarù, OB Morgan, T Mao, M Breitsamer, H Bamber, M Pöhlmann, MV Schmidt, G Winter, F Hausch, SM Géranton. The stress regulator FKBP51: a novel and promising druggable target for the treatment of persistent pain states across sexes. (*Pain*, in press; accepted 14th February 2018; doi: 10.1097/j.pain.0000000000001204).

The data has also been and will be discussed at various meetings:

- Talent Innovation Pain, La Spezia, Italy; 20th-21st of April 2017.
- Neuroscience Symposium, UCL, London (UK), 17th of June 2017.
- Royal Society of Psychiatry, London, UK, October 2017.
- Neuroscience 2017 (SfN), Washington, DC, 11th-15th November 2017.
- Instituto Butantan, Sao Paulo, Brazil, November 2017.
- 2018 International Congress of the Royal College of Psychiatrists, Birmingham, UK, April 2018.
- 17th World Congress on Pain (IASP), Boston (USA), 12th-16th September 2018.