Transcript of RELIEF podcast with Peter Grace:

RELIEF: Hello, and thanks for tuning in to RELIEF's podcast series, I'm Neil Andrews, editor of RELIEF. I'm thrilled to have the opportunity to chat today with Professor Peter Grace. Professor Grace is an assistant professor at the University of Texas MD Anderson Cancer Center. His research focuses on the contribution of inflammation in the nervous system to chronic pain. In that context he has done studies and is doing research now looking at the impact of cells called microglia, which will be the focus of our podcast today. Professor Grace, welcome to the podcast. Thanks so much for being here today.

Peter Grace: Thanks. It's a pleasure to talk with you.

RELIEF: Let's start at the top. What are microglia and what is their role in the nervous system?

Peter Grace: Microglia are immune cells that live in the central nervous system—that's the the brain and the spinal cord—and they actually account for around 10% of all of the cells in this system. They are widely known as playing a housekeeping role in the central nervous system. Ordinarily they maintain the healthy functioning of this system by scavenging cellular debris from cells that have been damaged as part of normal physiological processes, but then, also protecting the central nervous system from infections as well by attacking viruses and bacteria.

RELIEF: As a pain researcher, why did you become interested in studying microglia? What do they have to do with pain?

Peter Grace: I guess work in the early 90s was suggesting that microglia may be doing more than just performing this housekeeping function. Work from other fields began to show that they can release all sorts of mediators that actually activate neurons, suggesting then that they could act as a volume control, I guess, in pain pathways. So people then such as Linda Watkins, in Colorado, where I did my postdoctoral work, as well as other groups, have then shown that amazingly pain could be alleviated in animal models if microglia were deactivated. I have been interested then in how microglia are involved in pain and then how we might therapeutically target them to treat pain better.

RELIEF: Can you talk a little bit more about how researchers discovered in the first place that microglia contribute to pain, and what is the evidence, how solid is the evidence, that they do in fact play a role in pain?

Peter Grace: That case has really been building over time. At first, people noticed that after nerves were damaged that microglia were activated in the spinal cord. They did that by looking at very thin [tissue] sections and showing that the shape of these cells had changed, suggesting that they were actually becoming activated.

The next step then was to actually inhibit microglia or the immune signals that they released. They found that these strategies then produced pain relief in animals. This

general finding now has been repeated by many different researchers in different labs, for many different models of chronic pain, and that has been done all over the world. The evidence then is pretty strong, at least in animal models, but recently there has been some controversy over whether these findings actually apply to females as well.

Stepping now toward humans, there have been imaging studies done that are now revealing that microglia are also activated in the brains of people with chronic pain. That's actually very encouraging that we are on the right track as we study these effects in animals.

RELIEF: How exactly do microglia contribute to pain? What are the mechanisms at a cellular level and molecular level? Do they somehow affect neurons, are they sort of contributing themselves, how is that working?

Peter Grace: Yes, microglia are situated around neurons in pain pathways and particularly at the junctions where neurons send chemical signals to each other. At that site, microglia come along and they cut the brakes and then hit the gas in these pain pathways. So, they release cell signals, like those called cytokines, that activate neurons in pain pathways. But then these signals also dysregulate inhibitory signaling in the spinal cord, which basically means that the body's natural systems for turning off pain signaling are impaired.

RELIEF: So, it's really these microglia that sort of really rev up the pain system by interacting with neurons. Is that a way to look at it?

Peter Grace: Yes, exactly right. You know, if you imagine a car driving along, they are really hitting the accelerator and exacerbating that pain signaling by neurons that's already occurring.

RELIEF: In addition to the contribution of microglia to pain, you've done some work looking at the effects of opioids, like morphine, on these microglia cells. What led you to that line of research?

Peter Grace: In the early 2000s then researchers began to notice that microglia in the brain and spinal cord were becoming activated after opioid treatment. Much in the same way that these cells are activated after nerves are injured. This finding was really quite striking because it suggested then that microglia could be playing a role in the effects of opioids. Sure enough, researchers found then that blocking microglia or things like cytokines actually improved the level of pain relief from opioids.

Given that activated microglia caused pain, as I talked about a little bit earlier, and then that opioids and nerve injury both activate microglia, we started wondering whether treating pain from nerve injury with opioids might actually send these glial cells into overdrive and then make the pain much much worse.

RELIEF: Can you describe one of those studies in this area that you did? A year or so ago you published a paper looking at the microglia response to opioids. What were the main findings from this work, and how did you do the experiments?

Peter Grace: We set out to test the idea that opioids could make the pain worse. We did that in rat models of nerve injury. We injured the nerves of some rats while the controls then had no injury. And then once the pain was established in this model, we then administered morphine, which is a widely used opioid painkiller, or a salt water control for about five days.

The effect that we noticed was really quite profound. Morphine actually doubled the duration of nerve injury pain. Where the animals that were treated with the salt water recovered in about five weeks from that peripheral nerve injury, those animals that received morphine actually took about 10 weeks to recover.

We then implicated the role of microglia then in this process by showing that we could prevent this terrible effect of morphine on prolonging the pain if we inhibited these cells or the pathways that were then responsible for the production of cell signals that are released by microglia and then excite neurons in pain pathways.

RELIEF: Some people who are listening to the podcast might be surprised that opioids like morphine can actually lead to pain, increased pain, over time, and so the results from this study are really very relevant to that problem that patients face in the clinic. Is that correct?

Peter Grace: Yes. A number of different groups have shown that opioids tend to stop working over time and that in some patients, as well, that can then actually lead to increased pain sensitivity. What we are showing here is that this effect lasts for a really, really long time after morphine has stopped being administered, and [this] suggests then that perhaps opioids could be contributing to chronic pain itself rather than being an appropriate treatment for it.

RELIEF: Interesting. What studies are you doing right now on microglia? What studies do you have planned long-term?

Peter Grace: Do other opioids beyond morphine, things like oxycodone and fentanyl, actually do the same thing and exacerbate the pain? We want to know whether the timing matters—how long can we give the opioids for? And then also whether it applies to other conditions as well beyond neuropathic pain—something like postoperative pain or inflammatory pain.

Then looking at the question of which pain conditions then that microglia are involved in, we are using animal models to address this question, because it's becoming evident that microglia aren't activated in every pain condition. For example, pain can develop during chemotherapy treatment, which is a big problem for cancer patients and oncologists, but in our animal models it really doesn't look like microglia are doing very much.

Right now, we are trying to understand why microglia activate after nerve injury, but then on the other hand, they don't activate after chemotherapy, despite the fact that the pain looks pretty comparable. Trying to understand these differences then could provide some important insights into the specific pathways that microglia recruit to promote pain. Then on the flipside, it could then reveal which pathways we should be targeting to then develop new treatments for pain.

RELIEF: Can you say a little bit more about that? How do you move from observations that you and others have made and will make about microglia in the lab to coming up with better treatments for pain? Is the idea, as you mentioned, to target signaling pathways that microglia affect? Is it to target the microglia directly? How do you move from observations in the lab to treatments for patients?

Peter Grace: Firstly, all of the pain treatments that we have available right now just target neurons. They are not targeting the inflammatory mechanisms and that could be an important key as to why the pain treatments that we have really don't work very well. They are actually missing a key component of the signaling cascade that is responsible for chronic pain.

There are a couple of different strategies that are being developed. One is to try and understand why microglia are becoming activated in the first place. What's being released, causing them to become activated? Then, can we block that in particular? There are some drugs that are being developed to target that.

Another approach then is to try and suppress the inflammatory products that are released by microglia. Something that has been developed in Linda Watkins' lab, as I said where I did my postdoctoral work, is to promote expression of this anti-inflammatory cytokine for interleukin-10. That suppresses excitatory signaling on neurons and it returns the activated glial cells back to a more normal state. In animal models, beyond rats as well, looking at pet dogs and horses, we are actually seeing amazing pain relief using this strategy. So there's a couple of ways that we can really go here.

RELIEF: What are the most important questions that remain about the role of microglia in pain and also their role in the response to opioids, and I'm thinking both in terms of basic science—the science that people do in the lab—what are the questions that remain, and also for patients in the clinic, what are the key outstanding questions?

Peter Grace: I think there's a basic science question that I alluded to earlier, which is, do microglia contribute equally to pain in both males and females? Right now, that's a point of contention among pain researchers and I think more work needs to be done in that particular arena.

I think the big question though is a clinical one, and that's, does the knowledge that we've gleaned from animal models actually apply to chronic pain in humans and can we target microglia for pain relief and to improve the action of opioids?

RELIEF: Finally, are you optimistic that researchers are going to find answers to each of these questions, and why or why not?

Peter Grace: I am optimistic. If I wasn't, I guess, I'd probably be working in a different field. I guess looking at the first question, regarding sex differences, I think there we just need more experimental work to be done. I think that's important as it could then form the clinical work that we do when we're trying to treat chronic pain by targeting microglia.

I think the clinical question is perhaps more complex, especially as there have been rather lackluster results in some clinical trials for drugs that target these inflammatory mechanisms. Sadly, though, this is sort of generally true for many pain drugs, not just those targeting microglia and inflammation. However, as I alluded to before, there are better experimental drugs that are coming through the pipeline such as interleukin-10 gene therapy. And through these trials, I guess, we have also gained a more nuanced understanding of which pain conditions might be relevant for microglia and then which ones to avoid.

Finally, I guess, I'm really encouraged by the recent imaging studies that have identified glial cell activation in the brains of chronic pain patients. Not only because it suggests that these cells might play a role in chronic pain, as has been predicted from our animal models, but because we've also got a readout now for our experimental drugs. We should be able to show in clinical trials what the drugs are doing, which is as we hoped, that they are deactivating microglia.

RELIEF: Great. It sounds like there's lots of reason for optimism then. I think that's a great note to end on. Peter, thank you so much for being here today. It's been great to chat with you, to learn more about these very interesting cells, these microglia, and their role in chronic pain, and in the response to opioids, and I'm sure the audience will really look forward to following your research in this area in the future. Thank you so much.

Peter Grace: Thanks very much, Neil.