Perspectives on Neuropathic Pain
Imaging Neuroinflammation—An Important Advance for Pain Medicine
Talking with Mark Cooper, PhD

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In October, the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA) will host a translational research workshop on Imaging Neuroinflammation and Neuropathic Pain, which will be chaired by Mark Cooper, PhD, University of Washington; and Vince Clark, PhD and Erin Milligan, PhD, both from the University of New Mexico in Albuquerque. This invitation-only workshop will bring together basic researchers, clinicians, and biomedical industry representatives to examine neuroimaging methods and to further investigate neuroinflammation as a cause of neuropathic pain and associated co-morbidities. It will also help accelerate the development of imaging methods to diagnose neuroinflammation and to follow the timecourse of neuroinflammatory diseases, as they respond to medical treatments. Dr. Cooper, a member of RSDSA’s Board of Directors and of the Scientific Advisory Committee (SAC), talked with us about the importance of the new imaging technologies and their implications for people with neuropathic pain.

PP: How does this research change the way we look at neuropathic pain?
DR COOPER: The scientific and medical communities have concluded that neuropathic pain is frequently a neuroinflammatory disorder. Around 2000, Donald Manning, MD, PhD [a member of the RSDSA Board and SAC] emphasized that RSDSA should be looking at activated glia as a possible cause of Complex Regional Pain Syndrome (CRPS). This has become a central focus for RSDSA, and was the topic of our first translational research conference last October. (http://www.rsdsa.org/glial_workshop/glial_workshop.html)

PP: Can you explain how glial cells work?
DR COOPER: When the nervous system gets injured, chemical signals are sent out from injured neurons, which activate neighboring glial cells (Figure 1). In response, neighboring glial cells are triggered to produce neuroprotective reactions, which include the release of neurotrophins and cytokines. At the same time, leukocytes are often attracted to the injury site. In animals, and in humans, researchers can label leukocytes with magnetic nanoparticles and then image them as they infiltrate into injured nerves or injured brain tissue, using magnetic resonance imaging (MRI). Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) can be used to image the activation of microglia—resident immune cells in the nervous system. These are key cellular markers of neuroinflammatory processes. Imaging sites of activated microglia and infiltrating leukocytes in the nervous system is a huge advance for pain medicine.

PP: Why?
DR COOPER: Before this, doctors had no way of seeing what activated microglia and infiltrating leukocytes were doing in the live human nervous system. Nanoparticle-enhanced MRI imaging is rapidly expanding in clinical research, and the possibility of applying this technology to neuropathic pain diagnosis is on the near horizon.

PP: This has real practical applications.
DR COOPER: Absolutely. With this knowledge, doctors can make a variety of informed decisions. For example, once a medical team identifies sites of neuroinflammation, the team can decide how to treat them. One option is to calm the neuroinflammation with drugs aimed at activated glia, and therefore relieve one presumed cause for the pain.
An alternative option is to treat the disrupted neurophysiology of the patient with chronic pain by having the patient engage in physical therapy. Glial attenuators, however, open many important opportunities for the treatment of chronic pain. Consider for a moment the treatment of high fever. Fever is a normal defense process to help eliminate infections. However, if the fever becomes too high, it can cause brain damage or even kill a patient. In the late 1800s, aspirin was considered to be a wonder drug because it could calm fever-generating mechanisms. Physicians could suddenly control a life-threatening condition using an anti-inflammatory therapy. We are arriving at the same point with neuroinflammation. Glial attenuators (e.g., minocycline, (+) isomer of naloxone, naltrexone, ibudilast) have the potential of calming a key cellular generator of neuropathic pain—activated glia. However, to develop better glial attenuators, doctors and researchers will need to be able to see what is going on in the inflamed human nervous system, using new advances in cellular and molecular imaging.

**PP: You are looking at CRPS on the cellular level then?**

**DR COOPER:** Yes. Glial cell-neuron conversations are an important type of information processing that is taking place within the nervous system. In a chronic pain state that is produced by neuroinflammation, some neurons are being triggered into a survival mode because of signals sent to them by neighboring activated glial cells. During this period of social disruption, the neurons don’t process information normally. Consider this analogy. When data processing centers within a city or country start to malfunction, what happens? The whole economy can begin to collapse. Some processes are driven into overdrive, and other processes just don’t happen. You see that with CRPS, perhaps more than with any other neuropathic pain disorder. Data processing disruptions can potentially occur in almost every data processing center of the nervous system. Abnormal, and sometimes extreme, changes occur in target organs as a result.

To understand the physiological context of neuroinflammation, it is useful to think about cellular
interactions in terms of cellular sociology, particularly when it comes to the dynamics of wound repair. Injury to the nervous system stimulates microglia to transition from a surveillance mode into a highly neuroprotective mode. Microglia are like the National Guard being mobilized in a community during a natural disaster. Using microscopy, you can see what these activated microglia are doing—they surround injured neurons, providing chemical signals to keep the neurons alive, while the microglia are looking for pathogens because of the injury. The microglia are also there to destroy the bodies of dying neurons. They have to clean up the cellular debris of the injury. Imaging what’s going on in these neuroinflammatory states, and understanding the local cellular sociology in these locations, is where the basic researchers are headed. To understand persistent neuroinflammation, researchers are hoping to determine which molecules activate specific cellular behaviors. This type of inquiry is where new pharmacological therapeutics are likely to come from.

Physicians are able to look at the behavior of the whole organism, ie, the whole person, but they are often limited to looking at external signs and talking with the patient about how he or she feels in response to various stimuli. In the clinic, doctors can’t often see the sources of neuroinflammation-mediated pain; they must infer it using reasoning. That’s why there is a need for better diagnostic imaging tools, to find out about the cellular and molecular levels. From ongoing research on neuroinflammation, there is an exponential growth in information about these dynamics. The exciting thing is that imaging technologies are being rapidly developed to visualize molecular and cellular behaviors that underlie the neuroinflammatory process. These imaging technologies will help transform pain medicine. At the workshop next October, some of the world’s leading experts in neuroinflammation and neuroimaging will gather to exchange information, and hopefully form new collaborations. Clinicians at the workshop should be able to form novel partnerships with very talented neuroinflammation researchers. These types of interactions are what the FasterCures Foundation, a medical “action tank,” calls “partnering for cures.”

RSDSA’s goal is not only to make this happen in the CRPS community, but to foster partnerships between other groups to make neuroimaging advances happen faster for all neuroinflammatory and neuropathic pain disorders. That is the motivation behind forming an International Neuroinflammation Knowledge Consortium—to foster new collaborations among basic researchers, patient advocacy groups, and the biomedical industry, as well as clinicians working on neuroinflammatory disorders.

Imaging neuroinflammation can help in the study and treatment of many neurological disorders—ALS, Alzheimer’s disease, autism, multiple sclerosis, and Parkinson’s disease, for example. The CRPS community is not in this alone. We are using a vast amount of knowledge that has been generated from all of these communities. That’s why RSDSA is gathering people who are associated with more than 40 separate patient organizations and medical research foundations, which are concerned with neuroinflammatory and/or autoimmune disorders.

These workshops are extremely useful because they allow RSDSA to interface with all of these other organizations and to be able to synthesize and project this knowledge to key stakeholder communities including patient organizations, compensation organizations, government officials, and physicians. It is a very important to get expert pain practitioners, with their extensive clinical experience, to interact closely with basic researchers. This is the “bench-to bedside-and back” concept in action. RSDSA’s private and corporate sponsors are generously supporting this effort.

PP: How does the neuroimaging of neuroinflammation translate from the research bench to the office visit?

DR COOPER: There are two steps. One is to get research from the bench into clinical research. Then these technologies have to be taken from clinical research into clinical practice. Those two goals are central to what the Imaging Neuroinflammation and Neuropathic Pain meeting is about. We are bringing in people who have developed new technologies from basic research, like Dr. Ralph James, a Group Leader and Senior Scientist at the Brookhaven National Laboratory, and Mr. Terry Lall, President of Hybrydine Imaging Technologies. Brookhaven and Hybrydine have worked cooperatively to develop a novel high-spatial-resolution SPECT gamma-ray camera for screening prostate cancer. At RSDSA’s first translational research workshop in Chicago last year, we learned about these types of gamma cameras from Dr. Richard Banati (University of Sydney). We then contacted Brookhaven and Hybrydine and asked them to
consider uses of their compact, hand-held gamma camera for investigating neurological disorders. They are now working with Dr. Erin Milligan and her collaborators at the University of New Mexico to study neuroinflammation in the spinal cord. I think that this is a very important outcome from the Activated Glia workshop that was held last year. It is also an excellent example of how quickly translational research workshops can help foster new partnerships and move R&D from the bench into clinically relevant research. By forming a network of partners, the RDSMA/CRPS community is gaining tremendous intellectual resources, as well as being able to share the knowledge that we have accumulated about CRPS. This is how our organization can help catalyze advances for many neuroinflammatory disorders, including CRPS.

**PP:** How would a Neuroinflammation Knowledge Consortium help those working on integrated pain management?

**DR COOPER:** Every academy and organization concerned with neuroinflammation is working on the development and dissemination of new knowledge. However, you must find ways to bring together people from these diverse groups who are eager to work together on solving key questions. And you need the financial support to make things happen. RDSMA, the Trauma Related Neuronal Dysfunction (TRENDD) knowledge consortium in The Netherlands, CRPS researchers in the UK, and members of the German Research Network for Neuropathic Pain have recently united efforts to study the rehabilitation of patients with CRPS. This type of focused international cooperation needs to be replicated for a wide range of issues. At the workshop, RDSMA will be fostering the formation of Focus Groups, to address specific issues, such as methods to image neuroinflammation, neurogenic visceral pain, neuroinflammation-mediated movement disorders, and immunotherapies for neuroinflammation, as well as medical education about neuroinflammation. A given Focus Group will assess the current status of the problem, formulate a set of directions and goals, and communicate them to the rest of the Neuroinflammation Knowledge Consortium. RDSMA anticipates that CRPS will become a very instructive disorder for the Neuroinflammation Knowledge Consortium, because

**Figure 2A**

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**Figure 2B**

Remote neuroimmune activation following peripheral nerve injury (Banati et al, NeuroReport, 2000). A. Schematic Diagram: A peripheral nerve injury induces a transsynaptic activation of microglia in the projection area of the second-order neuron. B. Experimental Evidence for the Model: No structural changes can be detected in the brain of a patient with chronic pain, 36 months after amputation of the forearm (volumetric T1-weighted MRI). In contrast, [(1)C] (R)-PK11195 PET (a marker for activated microglia) superimposed onto the patient’s MRI reveals a significant regional increase in [(1)C] (R)-PK11195 binding, signifying the presence of persistent activated microglial cells in the left ventral posterolateral nucleus of the thalamus (white arrow), contralateral to the peripheral nerve injury (reproduced with permission from Lippincott, Williams & Wilkins, publisher of NeuroReport).
so many sensory, autonomic, motor, limbic, and somatovisceral co-morbidities are associated with it. The ability of physicians and basic researchers to dialog about the comorbidities of CRPS is likely to help everyone understand the etiologies and mechanisms of similar symptoms in other neuroinflammatory disorders.

**PP: What type of issues could be answered with neuroinflammation imaging technologies?**

**DR COOPER:** Here is an example of such a problem. In 2001, Dr. Richard Banati and his colleagues published a paper (1) showing that activated microglia were present in the contralateral thalamus of individuals with chronic pain who had experienced unilateral peripheral nerve injury (Figure 2). In one case, the thalamic inflammation was present up to two decades after the peripheral nerve injury had healed. In a series of papers, Banati and colleagues showed evidence that neuroinflammation could spread through the nervous system, along axonal projections, through a process that they called “transsynaptic activation of microglia.” This process is now generally referred to as “remote neuroimmune activation.” Pain practitioners must become very familiar with this knowledge and integrate it into their practice. The concept of “remote neuroimmune activation” should also be integrated into medical school curricula right away. This knowledge also must be disseminated widely to the public, so that people with neuropathic pain know that it is possible for neuroinflammation to spread from site-to-site within their nervous system.

This is where the Imaging Neuroinflammation and Neuropathic Pain workshop can help. We have built a website for the workshop. Published papers of the workshop participants are archived there. The talks of the workshop will be filmed and disseminated on the website. Dr. Carl Saab from Brown University School of Medicine, who has coauthored an excellent review on Remote Neuroimmune Activation (2), will give a keynote address on this topic, and related issues. We are making this information available online, so that everyone can gain access to it. This is a cost-effective way to projecting this knowledge to key stakeholder groups, as well as to people in chronic pain. The Imaging Neuroinflammation and Neuropathic Pain workshop is built around the concept of interlinking the scientific and medical expertise of patient organizations with academic, industrial, governmental, and philanthropic partners and making this knowledge widely available.

Within one year of the upcoming workshop, we hope that the first SPECT images of activated microglia in the human spinal cord will be obtained. This information is currently lacking for patients with presumed spinal neuroinflammation. This is the type of research goal that can be achieved through a concerted community effort. Expertise, imaging technologies, and funding all must be aligned to achieve this. This is one example of what the Neuroinflammation Knowledge Consortium could do through its partnering abilities.

**PP: How is the study and treatment of neuroinflammation likely to impact society?**

**DR COOPER:** In the late 1800s, when scientists and doctors first realized that infectious diseases were caused by microbes, medicine rapidly advanced. Vaccines were then developed in a systematic way, sterile surgical theaters were created, and public sanitation efforts were accelerated. All of these occurred because better imaging (eg, microscopy) and biotechnologies (eg, bacterial culturing) had produced better hypothesis testing, and a fundamental shift in thinking about the causes of infectious disease. The societal outcomes of this research were an increase in life expectancy, as well as economic growth. The field of neuroimmunology is currently producing a similar paradigm shift in medicine. Realizing that many neurological diseases are actually neuroinflammatory disorders is a great conceptual advance for science and medicine. Controlling neuroinflammation is the path to restoring and reintegrating into society millions of people disabled with neuropathic pain and other neuroinflammatory disorders. You can see that the potential social and economic benefits of rehabling individuals with neuroinflammatory disorders are immense. Right now, the tools to effectively image and treat neuroinflammation are currently being developed and they will very likely change the way that neuropathic pain is treated.

**REFERENCES**