Activated Glia: Targets for the Treatment of Neuropathic Pain

Report from a recent translational research workshop that included clinicians, scientists, patient advocates, and industry representatives interested in the study and treatment of painful conditions.

By Peter A. Moskovitz, MD and Mark S. Cooper, PhD


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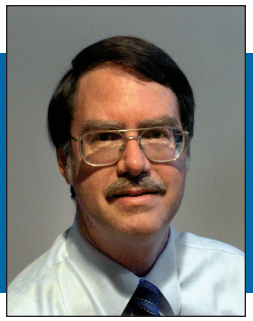
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Editor's note: Glia, originally called neuroglia, were so named by Dr. Rudolf Virchow, a German pathologist, in 1854. Virchow initially believed these cells weren't really cells at all but a "glue" or supporting structure for the neurons. Today, we know the glial matrix is comprised of specialized cells including astrocytes, oligodendrocytes, and microglia. These specialized cells have a myriad of connections and physiologic purposes. We now know that the glial cells aren't just "glue" but have a very key role in pain signal transmission, the encoding of chronic, constant pain, and the nervous system's response to opioids and other drugs. This article is an excellent primer for the pain practitioner as it brings us right up-to-date on the roles of the glial cells in chronic pain.
—Forest Tennant, MD

The workshop was organized by Mark S. Cooper, PhD (Univ. Washington); Donald C. Manning, MD, PhD (Shionogi USA, Inc.); and Kirk W. Johnson, PhD (MediciNova, Inc.). Additional information about the workshop, including a video of microglial activation from Michael Dailey (U. Iowa), is available on the workshop website at www.rsds.org/3/research/glia_workshop.

On October 8-9, 2010, a workshop in Chicago considered the role of activated glia in the neural mechanisms of chronic pain. The workshop, Activated Glia: Targets for the Treatment of Neuropathic Pain, was sponsored by the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA; www.rsds.org) and included clinicians, scientists, patient advocates, and industry representatives interested in the study and treatment of painful conditions. RSDSA is a not-for-profit organization that promotes awareness, provides access to resources, funds research, and gives support and information to people who suffer Complex Regional Pain Syndrome (CRPS). Although RSDSA's primary interest concerns CRPS, topics of the workshop pertained to other neuroinflammatory conditions, including Huntington's disease, fibromyalgia, spasmodic torticollis, and multiple sclerosis.

There is a growing body of science to persuade us to think of disparate neurologic, neuro-muscular and myofascial syndromes as a single class of diseases characterized by neuroinflammation. Clinicians have long known that there are central nervous system abnormalities in people who suffer chronic pain. In a bygone era, they thought that premorbid personality and characterologic predispositions were responsible for a broad range of behaviors associated with chronic pain. We now understand that "central sensitization"[1] is responsible for many of the sensory, mood and movement disorders observed in a variety of neuroinflammatory diseases. There is good reason to think that activated glia mediate such disorders and play a significant role in the onset and course of neuroinflammation and neurodegeneration that exacerbate nociception and the experience of pain.

There is a rich literature on the science of glia and how many diseases are caused and exacerbated by the activation of glia, however, much of this literature is unfamiliar to physicians and their patients. Yet, glia constitute 50% of the volume of our central nervous system (CNS).[2] The collected human nervous systems—central, peripheral and autonomic—could not function without them. While there are about 50 billion neurons in the CNS, glia in the CNS outnumber neurons 10:1.[3] In other words, 90% of cells in the CNS, or half a trillion of them, are glia.

"Glia" refers to a diverse set of specialized cell types that are found both in the peripheral nervous system (Schwann cells, satellite glia, perineural glia) and in the central nervous system (astrocytes, oligodendrocytes, microglia, and perivascular glia).[4] Glia are also genetically and immunologically active, and their up- or down-regulation has broad effects on neurons and neuronal pathways. The state of the science of glial activation, its role in the experience of pain, and its implication for potential treatment of chronic pain was the subject of this Chicago workshop.

For this discussion, we define "pain" as the experience of the neural representation of the transduction, transmission, encoding and storage of actual or simulated tissue damage.[5] The simulation may be either peripheral, as in the subcutaneous injection of capsaicin, or central, as in the stimulation of central projecting spinal pathways or cortical somatic maps. "Good pain," derived from the definitions of Lippe, is an experience that does not last long and enhances the quality of life by being corrective, instructive and adaptive.[6] Lippe's "bad pain," on the other hand, is an experience of suffering that degrades the quality of life. Such is the pain of CRPS, diabetic polyneuropathy and fibromyalgia, among many other diseases. From a clinical perspective, the role of activated glia in "bad pain," such as neuropathic or neuroinflammatory pain, is currently hypothetical but probably will not be so for long.

We can divide the Chicago workshop presentations into four general subjects:

A. The clinical diagnosis and course of neuropathic pain, particularly CRPS,
B. The science of glia and their activation,
C. The detection of activated glia, and
D. Possible targets for pain treatment based on the science of activated glia.

As we discuss each group of presentations, the reader will

easily consider the implications of the knowledge they contain to the original and remarkably prescient description of CRPS by Silas Weir Mitchell (1829-1914), an American Civil War neurologist. In 1872, Dr. Silas Weir Mitchell published a neurological text entitled: *Injuries of Nerves and Their Consequences*.[7] Mitchell described an intense burning pain in soldiers who had suffered nerve injuries:

"Long after every other trace of the effects of a wound has gone, these neuralgic symptoms are apt to linger, and too many carry [with] them throughout the long years this final reminder of the battlefield."

One of Dr. Mitchell's patients, David Schievely (age 17), was wounded in the Battle of Gettysburg on July 2, 1863, when a bullet shattered his right clavicle and exited the posterior part of his right arm. Six months after the battle, Mitchell writes:

"…The burning in the right hand is intense and constant…. Both hands are kept covered with loose cotton gloves, which he wets at brief intervals. He is especially fearful of having the right hand touched; is nervous and hysterical to such a degree that his relatives suppose him to be partially insane. It is difficult to even examine him properly on account of his timidity, and his whole appearance exhibits the effects of pain…"

Mitchell expressed his belief that this unbearable burning pain, which he termed causalgia, was caused by a combination of (a) inflammation within the injured nerve, (b) physiological changes in the terminals of nerves, and (c) abnormal actions originating from the spinal cord.[7] Current knowledge about glia cell activation in the injured nerve, as well as in the spinal cord, appears to validate Mitchell's insights.

The Chicago Workshop: Activated Glia and Neuropathic Pain

Donald Manning (Shionogi, USA) opened the program by declaring "Knowledge defines our possibilities, but philosophy (disease concept) defines our goals." He further stated that a paradigm shift is currently in progress and which will lead us away from understanding pain in terms of neuronal function only.[8,9] A neuronal model of CRPS does not work. The "non-anatomic" features of CRPS symptoms and signs are not adequately explained by a neuronal, somatotopic model alone, and this error leads clinicians to the false conclusion that the signs and symptoms are "non-organic" and psychogenic. The same can be said for fibromyalgia and other diseases.

We are now "looking through the glial glass" to examine the immunologic and inflammatory reactions to injuries that affect the peripheral, central, and sympathetic nervous systems. The multi-dimensional model that includes glial activation explains the phenomena of CRPS, including the observations of rapid remission of CRPS reported by Mitchell in some Civil War soldiers.[7]

Manning further declared that, ultimately, clinicians must begin by listening to their patients, by trusting their reports of their experience of pain—for in the story of illness is the key to an understanding of the phenomenon of central sensitization of pain. For each specific disease we must seek new knowledge of (a) biomarkers of the disease, (b) a refined classification of the symptoms and signs, (c) assessment instruments to objectify diagnostic criteria and (d) markers of disease progress to assess treatments. A tantalizing question presents itself: Are glial markers the "Holy Grail" of this quest?

At another level of abstraction, both basic scientists and clinicians must work together to build testable models that explain (a) the onset of neuropathic pain, (b) the progression of neuropathic pain, and (c) the remission of neuropathic pain. For example, we know that a child with CRPS can experience the remission of pain within a short period after the initiation of physical therapy. Is the anti-nociceptive effect of physical therapy mediated by the attenuation of activated glia? Is the attenuation of glial activation a normal "healing" mechanism after neurotrauma and neuroinflammation and what is its time-course?

A. The Clinical Diagnosis and Course of Neuropathic Pain, Particularly CRPS

The symptoms and signs that constitute CRPS are well known among pain management practitioners.[10] Few clinicians have been as instrumental in refining the diagnostic criteria for CRPS as Norman Harden (Chicago Rehabilitation Institute), who described the syndrome.[11] Briefly, CRPS occurs after trauma and is characterized by intense, chronic pain. Although CRPS is officially classified as a "rare disorder" (USA prevalence of less than 200,000), recent epidemiological studies report an annual incidence of new CRPS-I cases at more than 50,000.[12] CRPS is poorly understood, under-diagnosed and undertreated. There is usually a long delay of three months to more than 12 months between the onset of symptoms and the diagnosis of CRPS.[10]

CRPS pain is usually intense and is described as "excruciating," "intolerable" and "insufferable." It is commonly accompanied by swelling, abnormal skin texture (too thick or too thin), skin discoloration and mottling, changes in temperature, abnormal hair and nail growth, and movement disorders.[13] The syndrome frequently progresses and spreads to involve adjacent, and even distant, parts of the body. People with CRPS are often unable to tolerate even the light touch of garments or bedclothes.

The experience of neuropathic pain is further exacerbated by associated conditions, such as traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Post-traumatic neuropathic pain is, itself, a cause of PTSD thus creating a vicious cycle of pain and suffering. Remissions and relapses of CRPS are common. Note that the intense neuropathic pain of CRPS is far beyond normal experience. In the words of one person who is living with CRPS: "... the CRPS spread throughout my entire body, leaving me bedridden and screaming in pain for nearly a

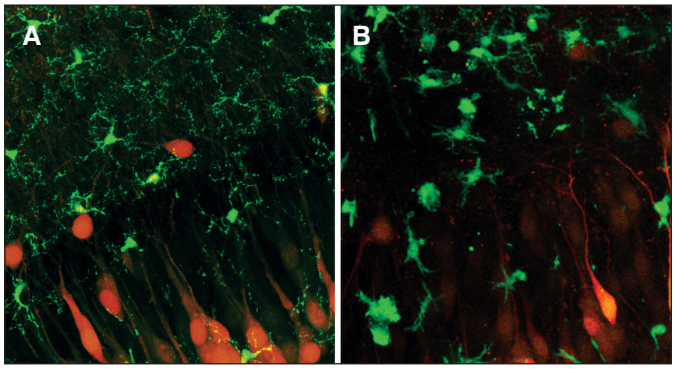

FIGURE 1. *Before and after activation of microglia. A. Quiescent GFP-labeled (green) microglia in mouse cortex have ramified morphologies. B. After tissue injury, microglia withdraw their extended processes and become migratory, phagocytic cells. This ramified-to-amoeboid transition is a key morphological biomarker for neuroimmune activation. Neurons are fluorescently labeled orange. (Confocal micrographs courtesy of Michael Dailey, University of Iowa)*

decade—a pain that felt as if I had been doused with gasoline and lit on fire."[14] Physicians, family, friends, and medical insurance providers often do not comprehend the scale of suffering experienced by CRPS patients.

Dr. Harden's concern for his patients has taken on a new urgency from evolving evidence that at both ends of the perceptual apparatus there is loss of neurological tissue that may be permanent, not unlike the chronic changes that are seen in multiple sclerosis and other neurodegenerative diseases. Microscopic examination of CRPS-affected skin reveals C-fiber loss or "dropout."[15] There is MRI evidence of volume loss in areas of the midbrain and cortex.[16] Executive decision functions, as revealed in the Bechara gambling task, are impaired. These features are seen in other chronic pain disorders, such as fibromyalgia and chronic low back pain. Realistic hope emerges from data that indicate that aggressive medical treatment can reverse volumetric changes seen in MRI scans.[17] Guillermo Alexander (Drexel University) described observations in the human spinal cord showing somatotopic and non-dermatomal glial activation and neurodegeneration in the spinal cord of a patient with long-standing CRPS.[18]

Michael Ossipov (Univ. Arizona) reported that 40% to 50% of Americans will suffer chronic pain at some point with continuous pain for three months out of any six month period. Among Europeans, 40% say that "chronic pain [makes them] feel helpless" and 30% think their loved ones do not believe them. One fifth think others, including physicians, are insensitive to their pain; 16% report having had suicidal thoughts. In a recent Internet-based, patient survey performed at Johns Hopkins, 47% of CRPS patients reported suicide ideation and 15% reported attempting suicide.[12]

Dr. Ossipov described how inflammatory foot injury in an animal model results in the activation of microglia and astrocytes in the rostroventromedial medulla (RVM). This is a key center for the generation of antinociceptive drive to spinal nociceptive circuits and is also a major site of opioid action.[19] Based on these findings, clinicians, when treating a person with neuropathic pain, must appreciate that neuroinflammation may be simultaneously present in both spinal and supraspinal sites. The differential diagnosis of non-anatomic and potentially confusing symptoms may come into clearer focus using these concepts, even though our ability to measure neuroinflammation is in its infancy.

Ken Price (National Spasmodic Torticollis Association), who suffers from cervical dystonia, described new evidence that neuromechanical trauma to branches of the trigeminal nerve can cause cervical dystonia along with widespread movement and gait disorders. He presented video demonstrations that an oral orthotic appliance that repositions the temporomandibular joints completely normalizes posture and gait in some dystonia and Tourette's syndrome sufferers.[20,21]

Roberto Perez (VU University Medical Center) came to the workshop to report on his work as a principal investigator of the TREND knowledge consortium (Trauma RElated Neuronal Dysfunction).[21-24] TREND was originally funded by the Dutch government with 21 million Euros. The population-adjusted equivalent in the United States is more than $500 million. In the Netherlands, a densely populated nation of 16.5 million persons, the annual incidence of CRPS is 26.2 per 100,000, which is equivalent to between 75,000 and 80,000 new cases of CRPS-1 in the United States each year. Following the lead of Dr. Harden who declared that CRPS is all about cytokines, Dr. Perez reported TREND's work in identifying the peripheral cytokines that appear to be responsible for peripheral and widespread neuroinflammation. Among them are adenosine triphosphate (ATP), tissue necrosis factor alpha (TNF-alpha), Interleukin-6 (IL-6), Substance P, calcitonin gene-related peptide (CGRP), bradykinin, and angiotensin converting enzyme (ACE).

Dr. Perez echoed the discussion by Robert Knobler (KIND Clinic) who emphasized the similarities between apparently different neuroinflammatory diseases: CRPS and MS. Both are characterized by neuroimmune impairments that have a genetic predisposition and an environmental trigger. Similar comparisons have been made between rheumatoid arthritis and CRPS.

Phenomenological similarities among neuroinflammatory diseases extend to their biology, as described by Thomas Möller (Univ. Washington), who discussed his work on the cellular biology of Huntington's disease.[25] The pattern of similarities among many diseases strongly implies the shared role of activated glia in the cause and course of neuropathic pain.

B. The Science of Glia and Their Activation

Dr. Möller sounded a cautionary note: Neuroinflammation is a normal and necessary process. In the acute phase after injury, neuroinflammation is tightly controlled. In its chronic phase or when directed against normal tissue (in an autoimmune response), neuroinflammation is detrimental as occurs in MS, ALS, various sorts of dementia, Huntington's disease, and other diseases.[25-28] Microglia are monocyte derivatives that respond to a variety of cytokines. They release cytokines, migrate, proliferate, and destroy the cells they chemically target (phagocytosis). Failure of microglia to release neuroprotective agents (e.g., Brain-Derived Neurotrophic Factor, BDNF) may underlie the neurodegeneration that occurs in Huntington's disease.

Joyce DeLeo (Dartmouth School of Medicine) and Linda Watkins (Univ. Colorado) set the stage for our understanding of the neurobiology of glia by describing the evolving model of the synapse—the electro-biochemical switching station that is responsible for "passing on" (or for inhibiting) the transmission of a transduced stimulus of actual or simulated tissue damage.[29-33] We used to think of the synapse as having two cellular components: a presynaptic neuron and a postsynaptic neuron. Neuroscientists have now added an astrocyte and a microglia to create a "quadripartite model" of the synapse. Perivascular microglia may serve a separate function to make it a "quintipartite model."[34-36] Dr. Möller described the normal spectrum of microglia from M1 excitatory cells to M2 inhibitory cells. So it is not a scientific question of whether microglia are involved, but how they alter the function of neuronal circuits and when and where they do it.

Like all immune competent cells, glia have a myriad of receptors on their cell surface membranes. Speakers at the Chicago workshop described their work to understand the biology and immunochemistry of a number of these glial-activating receptors and ligands. Part of this research is summarized in Table 1.

Each of these scientists is actively working to characterize the biology and neurochemistry of glia with the various goals of identifying and locating activated glia, modifying the effect of activated microglia on the transmission and experience of pain, or simply understanding how these necessary and exceedingly complex cells do their work in health and disease.

The picture that emerged during the workshop is one of a

Table 1. Continuing Investigation of the Biology and Immunochemistry of Glial Activators

Presenter	Banati	Deleo	T. Price	Möller	Stella	Watkins
Molecules of Interest:						
PK11195	X					
PBBS	X					
TSPO	X				X	
IL-4		X				
IL-12		X				
IFN-g		X				
TLR-4		X				X
CB-2		X			X	X
BDNF			X			
IL-6			X			
NGF			X			
NKCC1			X			
C68				X		
OX42				X		
Ibal-F4				X		
Alarmins				X		
LPS				X		
STT-1					X	
WIN					X	
A-2A						X
IL-10						X
Opioids						X

Legend:	
PK11195	An isoquinolone carboxamide
PBBS	Peripheral Benzodiazepine Binding Site
TSPO	18kD Translocator Protein
IL-X	Interleukin-X
IFN-gamma	InterFeroN-gamma
TLR-4	Toll-Like Receptor-4
CB-2	Cannabinoid
BDNF	Brain-Derived Neurotrophic Factor
NGF	Nerve Growth Factor
NKCC1	Na-K-Cl Cotransporter
Iba 1-F4	Ionized calcium Binding Adaptor molecule 1
LPS	LipoPolySaccharide-binding protein
STT-1	STaurosporine- and Temperature-sensitive
A-2A	Adenosine 2A

cascade of events that begins with neurotrauma that releases an excess of neurotransmitters and pro-inflammatory cytokines. Glia can be activated at many levels of the peripheral and central nervous system. There follows the up- or down-regulation of cytokines and neurotransmitters whose release alters the excitatory-inhibitory balance of the synapse. Microglia contract, migrate, and become phagocytic. An increase of transmission of the "painful" signal (bottom up effect), or a loss of inhibition of the signal from higher centers (top down effect) results.

Ingenious experimental models and research designs, neuroimmunology and multidimensional neurophysiology present new complexity for the clinician. Nonetheless, this model of "central sensitization" of pain well explains many of the clinical phenomena of chronic pain that have been obscure to former generations of clinicians, or simply ascribed to amorphous psychological or "predispositional" causes. Multiple lines of research, presented to the workshop, suggest that activated glia are responsible for these previously misunderstood phenomena.

C. The Detection of Activated Glia

If scientists and clinicians are ever to understand how activated glia increase the experience of pain and to use that knowledge to decrease the suffering of chronic pain, they must be able to mark activated glia for identification by imaging instruments. Accurate imaging of activated glia will permit the monitoring of the effectiveness of therapies designed to moderate, modulate and deactivate glial function. Several speakers described their work on "tagging" and visualizing activated glia in the living state.

Dr. Ossipov (Univ. Arizona) presented microscopic evidence of increased populations of activated glia in the rostroventromedial medulla of his experimental animal model of neuropathic pain.[21,37] Michael Dailey (Univ. Iowa) uses time-lapse microscopy of multiphoton fluorescence from resting glia and after activation by chemical, mechanical and thermal injury (see Figure 1). He studies glia in cell culture, tissue slice culture, and in whole animal preparations. By manipulating the chemistry of the preparations and their genetic strains, Dailey is parsing out the effects of various glial activators.[38,39] But optical microscopy in the visible spectrum usually requires either a pathological specimen or a surgical preparation. Can activated glia be observed in the intact, living, human patient?

Diana Martinez (Columbia Univ.) and Richard Banati (Univ. Sydney) described their work with positron emission tomography (PET) and presented hauntingly beautiful images of normal and abnormal states. Dr. Martinez's interest is the imaging of the neurochemistry of drug abuse—particularly the dopamine circuits, networks and systems of the brain.[40,41] Dr. Banati uses labeled PK11195, PBBS and TSPO receptor ligands to map glial activation with increasing accuracy. His data suggest that after injury, glial responses occur even in normal-appearing regions of the brain.[42-46] Banati proposes that chemical signals can be transmitted through axons (e.g., axonal transport), allowing neuroinflammation to spread from site to site within the neuraxis. The premise implies retrograde, anterograde, and transsynaptic spread of neuroinflammation.[46] Banati's concepts, which are supported by PET imaging, have important implications for understanding the apparently non-dermatomal spread of neurological symptoms in patients with neuropathic pain.

D. Possible Targets for Pain Treatment Based on the Science of Activated Glia

Several attendees presented their ongoing work on therapeutic agents that target activated glia, whether in development in animal models,

in preparation for human trials, or in clinical research. Table 2 summarizes some of this work on therapeutic agents.

In his opening remarks to the Chicago workshop, Donald Manning observed that new therapeutic agents have and will continue to come from basic research. None has yet proven effective against chronic, neuropathic pain. Experience tells us that a single agent is unlikely to be successful and agents that held great promise in the laboratory have not proven themselves in the clinic. Effective medications are "dirty" and their adverse effects limit their utility. Glial activation is necessary for neural repair after stroke and seizure, trauma and infection. How can we attenuate "bad" glial activation, which provokes and aggravates neuropathic pain, without destroying the infrastructure of innate mechanisms of injury and disease control and repair? Immunomodulation must suppress pro-inflammatory cytokines and augment anti-inflammatory ones. Antagonists to glial membrane surface receptors must inhibit unwanted activation without immobilizing critical neuroprotective functions of glia. Success will be hard won.

For example, in his keynote address to the workshop participants, James Campbell (Johns Hopkins Hospital)[47,48] described his personal experience advancing new medical treatments for neuropathic pain. He recounted the steps of the path through the maze of laboratory, academic, corporate, regulatory and clinical enterprises. But, such a journey is the cost of the development of mechanism-based therapies as opposed to the development of symptom-based therapies. The discovery of glial attenuators is an example of the first of many steps in the development of new mechanism-based therapies for the treatment of neuropathic pain.

Kirk Johnson's (MediciNova) discussion of his experience with ibudilast illustrates some of the promises and challenges of treatment of neuropathic pain using agents that target glial activation.[49-51] Ibudilast appears to be protective in a neural "storm." After stroke, it appears to be anti-inflammatory and neuroprotective in humans. In the laboratory, ibudilast does not affect many normal enzyme systems and is selective for several neuroactive PDE (phosphodiesterase) systems. It appears to inhibit macrophage migration, a desirable trait when selective. In the initial double-blinded clinical trials for neuropathic pain, patients taking ibudilast were found to voluntarily use a lower amount of opioids for pain control than individuals given a placebo.[49] As a safe and well-tolerated pharmaceutical, ibudilast holds promise and Johnson anticipated a more extensive clinical trial for patients with neuropathic pain.

Joyce DeLeo's (Dartmouth School of Medicine) narrative of her experience with propentofylline was even more cautionary. The clinical trial of propentofylline may have failed for a variety of reasons: (a) the drug might not have reached its target in the CNS, (b) rodent and human glia may have important differences in their surface markers (e.g., varicella virus does not replicate in rodents), (c) the target disease may have been wrong (postherpetic neuropathy) and the drug might be more effective for posttraumatic neuropathy. Dr. DeLeo emphasized that the case for neuroimmune "activation" causing pain in humans is still hypothetical. More work is needed to "…define how neuroimmune 'activation' can actually cause enhanced neuronal firing or decreased thresholds to firing and, therefore, produce heightened responses to noxious and non-noxious stimuli." Despite the disappointing clinical trial outcome of propentofylline, Dr. DeLeo still believes in the promise of neuromodulation of chronic pain through the control and attenuation of glial activities, which have been so convincingly demonstrated in animal models of neuropathic pain.

The clinicians attending the Chicago workshop were not surprised at such experiences. Years of development and testing for narrow, but clinically significant, margins of efficacy were required in the immune-modulation treatment of such diseases as multiple sclerosis and rheumatoid arthritis. All three of the foregoing narratives demonstrate that success will be hard won. Nonetheless, the stories of treatments for rheumatoid arthritis and multiple sclerosis give everyone hope.

During the Chicago workshop, there was great interest in Linda Watkins' (Univ. Colorado) work with stereoisomers of naloxone. The common form of naloxone is the minus (-) form.

Table 2. Ongoing Work on Therapeutic Agents That Target Activated Glia

Speaker	Therapeutic opportunity	Effect
J. DeLeo	Propentofylline (Inhibits glial markers. Prevents opioid tolerance. Can be intrathecal – abolishes pain behavior response. cAMP inhibitor, enhances GABA transmission)	Positive in animal model Negative in human trial
K. Johnson	Ibudilast (in use in Japan for asthma and cerebrovascular disorders, attenuates glial activation)	In human trial
T. Price	Acetozolamide and Midazolam (intrathecal (IT) in animal model)	Positive
	Metformin (AMP Kinase regulation)	Proposed
	Topirimate	Limited success clinically as a single agent
N. Stella	Endocannabinoid 2-arachidonylglycerol (2-AG)	Proposed
L. Watkins	ATL313 (Adenosine receptor target) once per month IT	Positive in animal model
	IL-10, non viral DNA gene therapy (drives anti-inflammatory balance) via a microparticle slow release vehicle	Positive in animal model
	Stereoisomers of naloxone (TLR-4 target)	Positive in animal model
	Dietary control of saturated fatty acids (soy diet)	Positive in animal model

It has the effect of activating glia, which exacerbates pain and has inhibitory effects on gut motility, producing the common adverse reactions of nausea and constipation with opioid therapy. The plus (+) isomer of naloxone reacts with opioid receptors but neither activates glia nor affects gut motility. This appears to be the basis of "very low dose naloxone" (VLDN) therapy as an adjunct to morphine derivative treatment through "patient-controlled analgesia" by an intravenous route after surgery. It has enough of the effects of (+) naloxone without too much opioid antagonism that makes patients ill. The differential affinity for the TLR-4 receptor appears to explain the differences in clinical response to the two isomers. The (+) isomer would not be dose limited as is the (–) isomer in VLDN therapy.

The workshop participants immediately saw potential diagnostic and therapeutic applications for pain control based on the work of Nephi Stella (Univ. Washington) and referred to in Table 1. Dr. Stella spoke about his laboratory's work on the cannabinoid CB-2 receptor and its effect on glial activation.[52-54] He noted with surprise that he was not receiving the usual jokes about "pot-head glia," an indicator of the serious enthusiasm of the audience. CB-2 receptors are upregulated in activated microglia and so opens important opportunities to visualize them using radiolabeled[53] or fluorescently-labeled CB-2 receptor ligands. Pharmacological agents that bind the CB-2 receptor may be able to produce potent relief of neuropathic pain.

Finally, the attendees of the Chicago workshop were fascinated and no less enthralled by Miqin Zhang's (Univ. Washington) description of her production of nanoparticles of ferrous oxide and their use in labeling and treating an experimental neuromalignancy in an animal model.[55-57] The tiny particles, 6 to 12 nanometers in diameter, cross the blood-brain barrier and can be "tagged" with either an imaging compound or a therapeutic agent, or both, along with the ligand that will attach it to the target cells' surface receptors. Dr. Zhang thought it entirely plausible to tag nanoparticles with glia-specific ligands—say for the CB2 receptor (perhaps not the best example since it also exists peripherally as well as in the CNS)—even though this is not presently within the scope of her own work.

Immediate Implications for Medical Therapies

The workshop participants explored several areas of research from which new therapies may be drawn. For example, studies that have successfully used minocycline as a glial attenuator[57,58] lead researchers to wonder if this tetracycline-class antibiotic can be used as a prophylactic agent to prevent new sites of microglial activation in neuropathic pain patients who are facing a stressful intervention such as elective surgery, chemotherapy or radiation therapy. Might a glial attenuator prevent the terrible neuropathic pain that sometimes follows radiation for colorectal or pelvic cancer?

The possibility of direct application of preclinical research to the relief of pain was also discussed by Ted Price (U. Arizona). Transmembrane chloride gradients are compromised in spinal nociceptive projection neurons by neighboring activated microglia, leading to a loss of the projection neurons' GABAergic and glycinergic inhibitory tone.[59,60] Functionally, this results in a loss of "pain gating" in the spinal cord. Can benzodiazepines and acetozolamide be used in combination to close opened pain gates and block "breakthrough pain" in patients? Pre-clinical work by Dr. Price in an animal model suggests that this is indeed possible.[60]

Richard Banati has found persistent glial activation in the thalamus of seven patients with chronic neuropathic pain.[44] Can activated microglia be imaged in the brainstem or spinal cord of patients with neuropathic pain? A new handheld PET imaging device, ProxiScan (Hybridyne), may provide a new avenue to image activated microglia in these regions. Using such a device, a clinician could monitor the effects of alternative treatment modalities over time.

Concluding Observations

It is difficult in a journal article, remote from the place and moment, to describe the enthusiasm and anticipation shared by this heterogeneous group of clinicians, basic scientists, patients, and advocates. Naturally, distinct groups have distinct interests. Basic scientists need funding that gives them the freedom to pursue fruitful lines of research, rather than being restricted to topics for which there is readily available funding. Clinicians need therapeutic modalities and the tools to establish their efficacy and safety. In the matter of funding, the patient advocates, particularly Rae Marie Gleason and Jan Chambers from the National Fibromyalgia Association, and James Broatch from RSDSA, were helpful in providing contacts for networking and funding of research in the field of chronic pain and activated glia. Regarding the development and testing of therapeutic agents, a new network of stakeholders from among the workshop attendees is bound to expand. Its members will share their knowledge and experience. They will coordinate research goals and share resources and protocols that can only hasten the advent of new treatments for chronic pain.

In the end it was Rae Marie Gleason, from the National Fibromyalgia Association, who best characterized the assembled group, as well as those who will join it in the future: A network that represents a "partnership among patients, practitioners, and the scientific community" to promote and effect the study, understanding and treatment of people who are disabled by painful conditions. ■

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References and Notes

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5. This definition is a subtle variation on the definition proposed by the IASP, familiar to all. The reader will soon appreciate that the present definition draws a bright line between the objectively measurable features of transduction, transmission encoding and storage of a stimulus and the subjective and immeasurable experience of "pain." The difference is useful in the present discussion of the proposed central sensitization of pain by activated glia.

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