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Neuropathy Hope

Hope through caring, support, research, education, and empowerment

A newsletter for members of Western Neuropathy Association (WNA)

WESTERN NEUROPATHY ASSOCIATION

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WESTERN NEUROPATHY ASSOCIATION
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GENE THERAPY REDUCES CHRONIC PAIN AND CHEMO-INDUCED PERIPHERAL NEUROPATHY IN MICE

Helen Floersh, fiercebiotech.com, July 31, 2023

(This was first reported in Neuropathy Hope in the March 2022 issue, page 4. Results of continuing research is detailed in this article.)

In a study published July 27 in Proceedings of the National Academy of Sciences, researchers from New York University (NYU) described how they developed a gene therapy that relieved chronic neuropathic pain in mice by regulating a previously uncharacterized part of the sodium ion channel NaV1.7. The treatment was also effective against chemotherapy-induced peripheral neuropathy, a type of pain experienced by some cancer patients who undergo chemo.

"Our study represents a major step forward in understanding the underlying biology of the NaV1.7 sodium ion channel, which can be harnessed to provide relief from chronic pain," Rajesh Khanna, Ph.D., the study's senior author and director of the NYU Pain Research Center, said in a press release.

Scientists have known since 2006 that the NaV1.7 sodium ion channel—found on the ends of pain-sensing nerve cells—is key to experiencing pain. But the pharma industry's attempts to drug it directly with small molecules have failed.

Khanna's former lab at the University of Arizona previously developed its own small molecule against NaV1.7, dubbed 194. The drug worked differently from its predecessors; rather than directly inhibiting NaV1.7, it inhibited a protein called CRMP2, which regulates the sodium ion channel's activity. After finding that 194 was effective in controlling chronic neuropathic pain in mice, the researchers licensed it out for development by Khanna's startup, Regulonix.

But Khanna still wondered why regulation by CRMP2 was specific to NaV1.7 and not to one of the other seven sodium ion channels of the same family. His lab at NYU addressed that question as part of their new study. Using a technique called peptide mapping, they discovered a unique binding domain for CRMP2 in NaV1.7 that wasn't present in other sodium ion channels. They also found that if they removed the binding domain, CRMP2 could no longer regulate NaV1.7.

Armed with this discovery, the researchers set out to see whether they could leverage it to relieve pain for the long run. They created an AAV9 viral vector that encoded a genetic sequence that would inhibit CRMP2, then injected it into male and female mice that already had sciatic nerve injury. The treatment appeared to reverse pain in the mice for the duration of the 30-day study period, compared to no pain relief in mice that received a control virus.

Next, the researchers tested whether the treatment could prevent chronic pain. In this case, they injected male and female mice with the gene therapy before performing spared nerve injury surgery, a technique used to induce sciatic nerve injury. None of the mice that received the therapy showed symptoms of pain following recovery, while the mice in the control group did.

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Katherine Stenzel
Editor

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PERIPHERAL NEUROPATHY SUPPORT GROUPS OCTOBER 2023 SCHEDULE

Encourage, inform, share, support, and hope.
Join a meeting to help others, learn something new, and/or share experiences.
In-person or virtual – connect to others with peripheral neuropathy

October 2 Auburn CA Support Group
11:00 am PST, Woodside Village Mobile Home Park, 12155 Luther Road
Guest speaker: Bev Anderson, founder of Western Neuropathy Association
Contact: Sharlene McCord (530) 878-8392, Kathy Clemens (916) 580-9449, kaclemens@earthlink.net

October 14 2nd Saturday Virtual Support Group
11:00am-1:00pm Pacific/1:00pm-3:00pm Central, Meeting ID: 856 7106 1474, Passcode: 114963
Host – Katherine Stenzel, klstenzel@hotmail.com, contact Katherine for Zoom link

October 18 3rd Wednesday Virtual Support Group
10:00am-noon Pacific/12:00pm-2:00pm Central, Meeting ID: 833 4473 0364 / Passcode: 341654
Host – Glenn Ribotsky, glenntaj@yahoo.com, contact Katherine for Zoom link

October 18 3rd Wednesday CIDP and Autoimmune Virtual Support Group
3:00pm-4:00pm Pacific, 5:00pm-6:00pm Central
Host - John Phillips, johnphillips.wna@gmail.com, contact John for Zoom link

October 28 4th Saturday Virtual Open Discussion
11:00am-1:00pm Pacific/1:00pm-3:00pm Central, Meeting ID: 851 7949 9276 / Passcode: 159827
Host – John Phillips, johnphillips.wna@gmail.com, contact Katherine for Zoom link

Santa Cruz CA Support Group will meet in November
Host - Mary Ann Leer, (831) 477-1239

ADAPTIVE CLOTHING FOR THOSE WITH PHYSICAL CHALLENGES

Kimberly Blaker, Pittsburgh Beaver County Senior News, September 3, 2021
(submitted by Helaine Greenburg, Reno, NV)

Alternative Fasteners
Traditional clothes fasteners like buttons and zippers can be difficult to easily secure clothing. It takes a lot of fine motor control and hand and finger strength to grab and manipulate small parts to fasten clothing together. Common alternatives include Velcro and magnet fasteners along the seam.

- **Tommy Hilfiger** has an adaptive line with many features, including a whole section for easy closures like magnets, Velcro and one-handed zippers.
- **Buck & Buck** is an adaptive clothing line that includes shirts for men that look like button-ups but uses Velcro in the front and Velcro cuffs.
- **Target** has adaptive clothing, such as the Velcro Side Fastener Bra with front closure for ease.

Workaround Medical Devices
Some adults may require specific medical devices like braces, monitors or wheelchairs, which may interfere with their clothing. Some clothes are explicitly designed to work around wearable devices.

- **Silverts** has wheelchair-specific clothing like the Wheelchair Gabardine Pants for Men. These allow you to dress from a seated position and are designed to keep everything covered while sitting.
- **Elder Wear and Aids** has a wheelchair-friendly adaptive clothing section with pants, dresses, shirts and more.

Adaptive Footwear
Whether you need outdoor shoes for leaving the house or slippers to prevent falls indoors, proper

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FROM THE PRESIDENT Pam Hart, WNA President

At the time I write this article, I wonder - will we have a fall? Will the summer last longer than normal, or will we be plunged into winter before we are ready? I have faith that October will be beautiful and that the chill in the air will inspire us to get outdoors and explore a bit.

We usually think of Halloween for the month of October ---well, the stores already think of it in August!! I guess that means that we should prepare for large hordes of children descending upon us dressed in remarkable costumes. In fact, there are a number of other things to celebrate in October (see calendar below). How fun would it be to actually try to celebrate each of these days in some way. It gives an otherwise ordinary day some pizazz! When we have fun events to plan for and think about, it helps us to forget the daily grind of our 'pain'.

Maybe this would be a good time to reach out to a neighbor or friend and surprise them with a treat on one of these special days. It could develop into an annual celebration – who knew that celebrating National Fossil Day could be so rewarding!

Please let us know if you intend to celebrate one of these days, and how you will do it. It may be the inspiration needed for someone in our support groups. Until then – enjoy that Pumpkin Spice latte, or whatever favorite foods you have during this season. Just in case you are inspired to make one at home – The Best Homemade Pumpkin Spice Latte (inspiredtaste.net).

Please be sure to join us for the October webinar featuring a compounding pharmacist discussing Low Dose Naltrexone.
Cheers,
Pam

Adaptive Clothing For Those With Physical Challenges – Continued from page 2

footwear is essential. Shoes should have a wide opening to be easy to get on and off and have a simple fastener. They should also have enough room for potential swelling, be stable and non-slip, padded to reduce foot stress, easy to walk in, and fit around braces or any other devices around the foot.

- **Nike** has an adaptive sneaker line called Flyease that is easy to put on with one hand.
- **Zappos** has a section on its website where you can filter for all the adaptive shoe brands they offer in one place.

Health Care Challenges Websites
(updated)

SHIPs
State Health Insurance Assistance Programs
www.shiphelp.org
(877) 839-2675

Help for navigating the complexities of Medicare. Search the website for your specific state program.

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Medicare Rights Center
www.medicarerights.org
(800) 333-4114

Non-profit that works to ensure access to affordable health care for older adults and people with disabilities.

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Medicare
www.medicare.org
(800) MEDICARE
(800) 633-4227

Get started with Medicare, options, news.

———

Benefits and Insurance for People with Disabilities
www.usa.gov/disability-benefits-insurance
(844) USAGOV1
(844) 872-4681

For those with a disability, learn how government programs and services can help in your daily life.

Gene Therapy Reduces Chronic Pain And Chemo-Induced Peripheral Neuropathy In Mice

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"Collectively, these findings reveal that the [CRMP2 binding domain] can be targeted to prevent the initiation and maintenance of chronic neuropathic pain in both male and female mice," the scientists wrote in their paper. "Therefore, the [treatment] could be used as a genetic therapy to provide long-lasting pain relief."

In their next set of experiments, the researchers investigated whether the therapy could be used to treat chemotherapy-induced peripheral neuropathy. They injected male and female mice with a chemo drug called paclitaxel, most commonly known as Taxol, and assessed their pain responses seven days later. On Day 8 following the treatment, they also tested whether the animals were hypersensitive to cold, another symptom of chemotherapy-induced peripheral neuropathy.

After confirming that the mice had developed both heightened pain and hypersensitivity to cold, the researchers injected one group of them with the treatment and another with a control virus. Fourteen, 16 or 21 days after treatment, they assessed the mice's pain responses again; on Days 15, 17 and 22, they tested their cold sensitivity.

By Days 16 and 21, the treatment had reversed pain levels in the mice. It worked even sooner on cold hypersensitivity, which dropped by Day 15. The researchers noted that in both the studies on sciatic nerve injury and chemotherapy-induced peripheral neuropathy, motor function remained intact, with no signs of off-target effects.

Going a step further, the researchers studied the gene therapy's effects on spinal cord neurons from macaque monkeys, which are genetically similar to the same type of cell in humans. Their findings showed that the treatment reduced NaV1.7 function, suggesting it might work against pain in nonhuman primates—and perhaps in humans—as well.

The study has some limitations. For one, CRMP2 may not be the only protein that interacts with the newly identified receptor binding domain, the researchers pointed out. Furthermore, they know that other proteins do get involved when CRMP2's interaction with NaV1.7 is inhibited; exactly what those proteins are and how they exert their effects remains unknown. And, of course, mice aren't men—indeed, studies have shown that the NaV1.7-mediated pain responses in the two species aren't exactly the same.

Finally, there are drawbacks to gene therapy, the scientists noted. Some reports have suggested the possibility of sensory neuron toxicity from AAV9 vectors like the one used in the study. Long-term NaV1.7 suppression might have deleterious side effects that weren't apparent in the new study, they wrote.

Still, the team said they "expect that the targeting of the [CRMP2 binding] domain can be used as a viable strategy for developing future therapeutics that are highly specific and safe for treating chronic pain." The long-term goal is to take the gene therapy to the clinic, Khanna said in the press release.

The findings are the latest to validate gene therapy as a potential solution for chronic pain. In 2021, a team from startup Navega, a spinout from the University of California, San Diego, reported that it had successfully used CRISPR and zinc fingers—both gene editing techniques—to completely suppress the gene that encodes NaV1.7 in mice. Before it shuttered in March, Coda Biotherapeutics was developing an approach that involved shutting down neuronal pain circuits by combining gene therapy with an oral small-molecule agonist.

"Always remind yourself that your track record of making it through the bad days is perfect."

74-YEARS-YOUNG ATHLETE (with Peripheral Neuropathy) SERVES AS INSPIRATION FOR SENIORS

Bill White, www.highlandernews.com, Friday, July 7, 2023

(Check out the November 2022 issue of Neuropathy Hope, page 4, for Dana's journey with peripheral neuropathy.)

In her late 50s, Dana Delgado embraced sports and quickly found that basketball was her passion. Previously an Army captain who served in the Vietnam War, she now battles Peripheral Neuropathy from Agent Orange exposure. However, through basketball, Dana manages her health and is alleviating symptoms from her disease and other complications.

While training for this year's National Senior Games, Dana suffered an unexpected injury that will prevent her from competing, but it won't prevent her from cheering on her team, looking forward to the next National Senior Games, and encouraging others to live life to the fullest.

Dana is one of more than 11,000 athletes competing in the 2023 National Senior Games – the world's largest multisport event for seniors – in Pittsburgh from July 7-18. Dana also has been chosen as a Humana Game Changer, a national recognition of outstanding athletes who exemplify active aging and provide encouragement, motivation and inspiration for people of all ages to pursue lifelong health.

Dana's passion for basketball is proof age isn't an obstacle to engaging in activities that bring joy and promote well-being. While not everyone has a desire to compete, I think Dana can inspire us all to change the game for active aging and challenge society's expectations of what it means to be a senior. It's a fact, staying active can help prevent or delay many common health problems as we age.

Here are just a few ways physical activity plays a vital role in health:

- Brain health: Physical activity sharpens thinking skills and can lower the risk of anxiety and depression. It helps you sleep better, too!
- Disease risk: Staying active helps reduce a whole host of ailments, like high blood pressure, high cholesterol levels and arthritis pain, and helps reduce the risk of type 2 diabetes, cardiovascular disease and several types of cancer.
- Stronger bones and muscles: With healthy muscles and bones, you reduce the risk of falls and are more likely to keep up with your grandkids longer and check off more adventures on your bucket list.
- For adults aged 65 and older, the Centers for Disease Control and Prevention recommend at least 2.5 hours of moderate-intensity activity per week, activities that help improve balance, and at least two days per week of strength training.

I know I am personally inspired by Dana as one of just 28 Game Changers Humana is recognizing and celebrating nationwide this year. As she has clearly demonstrated, being a senior can be about leveling up, not settling down. Good luck to Dana and all the athletes from Texas heading to compete at the Games!

HYLAND RESTFUL LEGS LOTION FOR LEGS AND FEET

Karen Hewitt, Rossmoor, CA, former Walnut Creek PN Support Group leader

Hyland's Restful Legs helps to calm my legs and feet, and can be found at CVS. If I wake up and can't get back to sleep because my feet are going crazy, I go out on my balcony and rock with purpose in my rocking chair. It always helps. (I have been afflicted with this "crappy disease" for 20 years.)

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CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY TREATMENTS (Part 2 - SCS and DRG stimulation)

Aranke M, Kolcun G, Huh B, Javed S. *Chemotherapy-Induced Peripheral Neuropathy Treatments*. Practical Pain Management. 2023 January/February;23(1).

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) affects between 40% and 70% of individuals undergoing chemotherapy and may significantly affect quality of life by worsening symptomatic clusters, such as psychological distress, fatigue-related pain, and abdominal discomfort.

A host of treatment and prevention modalities have been studied for CIPN, but there is still no clear preventive or treatment option. A majority of current treatment modalities center on pharmaceutical regimens rooted in duloxetine and opioids, which come with their own well-known variety of adverse effects (Part 1 – *Medications* – Neuropathy Hope, September issue). Although conservative management with multimodal pain control and physical therapy serves a purpose as first-line therapy, a growing body of evidence supports the use of spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation both as an adjuvant treatment to conservative management and as second-line therapy for treatment-resistant CIPN.

This section of the literature review summarizes the emerging role of neuromodulation.

SPINAL CORD STIMULATION FOR CIPN

Spinal cord stimulation (SCS) works at the level of the dorsal columns and activates both spinal and supraspinal neurophysiologic mechanisms to inhibit pain. SCS can acutely inhibit wind-up (short-form neuronal sensitization) and long-term potentiation at the level of the dorsal columns and dorsal horns. This mechanism of action suggests that SCS might have preventive effects, as well as a therapeutic benefit, for people living with CIPN.

Technically speaking, SCS is considered one of the most challenging procedures in interventional pain management. Although still a minimally invasive procedure and performed in the outpatient setting, it requires multiple steps to achieve successful placement. Under fluoroscopy, a lead is first sterilely introduced into the epidural space and then directed to its target location. For instance, lower extremity CIPN SCS leads enter the epidural space at the T12-L1 level, yet the leads are typically placed at the T6-7 level.

After its placement, there is a trial stimulation period where electrical activity is sent through the lead with the goal to mask the painful sensation ailing the patient. If the stimulation is successful in overriding the patient's pain, then the leads must be anchored and connected to a permanent implantable pulse generator or radiofrequency unit, often implanted in the gluteal or abdominal area.

SCS in the Literature

While our search turned up no human subject RCTs for the use of SCS and only one animal model study for electroacupunture in the treatment of chemotherapy-induced peripheral neuropathy, we did come across multiple case reports. The case reports and series from this literature review highlight a successful outcome of SCS for CIPN at long-term follow-up. Additionally, the single animal model RCT studying electroacupuncture showed significant therapeutic benefit in rats, providing a potential molecular mechanism of action for SCS in CIPN.

Notably, there were no negative outcomes reported, such as failure of SCS to improve pain, adverse effects, or unintended complications. Given the nature of these types of studies, there is likely a reporting bias. Additionally, due to the small number of patients in each of these reports and varying variables – such as medication use or degree of neuropathy – more structured research is needed to solidify SCS as a valid treatment option for CIPN.

DORSAL ROOT GANGLION STIMULATION FOR CIPN

Dorsal root ganglion stimulation is a more selective form of neuromodulation that targets the dorsal root ganglion. It is currently FDA-approved for the treatment of complex regional pain syndrome (CRPS) but has gained increasing traction in the treatment of neuropathic pain conditions, including CIPN. Compared with SCS, DRG stimulation may offer a more

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targeted approach to CIPN. CIPN is thought to disproportionately affect neurons at the DRG since the DRG is not protected by the blood-brain barrier.

Although the exact mechanism of DRG stimulation remains unknown, the leading theory is that DRG stimulation exerts its analgesic effect through multiple pathways:

- post-synaptic activation of pain-gating circuitry in the dorsal horn and possibly the DRG itself
- augmentation of the low pass filtering of painful signals at the T-junction of nociceptive neurons
- reduction of the intrinsic excitability of DRG neurons

Further research is needed to determine the degree to which each of these theories contribute to the overall analgesic effects of DRG stimulation. Delineation of its method may then guide a provider to recommend DRG stimulation over SCS for certain patients.

An understanding of the anatomy of the DRG is essential to discussing proper placement technique. There are bilateral pairs of dermatomal DRGs at each vertebral level, and these are encased by the meninges. As described by Graham et al, "during the implantation of a DRG [stimulator] system, electrode lead bodies are percutaneously inserted using a Touhy needle, guided through the epidural space of the spinal column using x-ray fluoroscopy, and routed into the intra-foraminal space where the array of electrode contacts are placed along the dorsal side of the DRG. The electrode leads are connected to an implanted pulse generator, which resides in a body cavity usually around the posterior lateral flank." The anatomy of the DRG neurons, particularly their location in the DRG relative to the stimulating electrodes, has a major impact on which cells are being stimulated by the DRG stimulation leads.

DRG in the Literature

The aforementioned 47-year-old patient with CIPN secondary to oxaliplatin therapy for rectal adenocarcinoma described by Finney et al elected to trial dorsal root ganglion stimulation with bilateral placement at the DRG of S1 and S2, resulting in successful relief of paresthesia in his feet bilaterally.

Additionally, Grabnar et al reported success after DRG stimulation in a patient with bilateral lower extremity CIPN who had previously failed conservative therapies. Similarly, another female patient with thalidomide-induced CIPN reported significant improvement after placement of bilateral S1 DRG leads.

DRG Discussion

Of the four case reports included for DRG stimulation, three described significant relief in otherwise treatment-resistant CIPN. One of these three patients had previously failed a SCS trial, suggesting some utility for DRG stimulation as a potential alternative. Although most of the literature highlights positive outcomes from neuromodulation, it is important to recognize that these techniques are technically challenging procedures with a moderate risk of complications.

Overall, DRG stimulation may present a more targeted neuromodulation approach, and it is hoped that these examples will stimulate further investigation of the technique.

PRACTICAL TAKEAWAYS

The literature discussed in this review supports neuromodulation as a long-term treatment option for chemotherapy-induced peripheral neuropathy that is refractory to medication management. Based on the favorable outcomes of the reviewed case reports, there is strong evidence that both SCS and DRG-S may play a beneficial role in the treatment of cancer-related neuropathic pain syndromes.

While spinal cord stimulation presents a promising method to treat chronic neuropathic pain, its technique is not without limitations. It is not uncommon for SCS electrodes to migrate, which may lead to unpredictable results. DRG stimulation may improve these outcomes by targeting focused regions of pain. Limitations notwithstanding, both techniques serve as valuable adjuncts to the current mainstay of CIPN treatment. Further studies with RCT would be required to establish these procedures in the treatment paradigm of CIPN.

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IN THIS ISSUE

A heartfelt *'Thank you'* to those who responded to my question on the focus of this newsletter. Everyone said they read the issues from 'cover to cover' and that the articles did give them hope. All of your comments touched me and give me enough motivation to continue editing the newsletter. And I also met more WNA members and heard about their neuropathy journeys. Page 7 has a short article on how one member calms her feet and legs at night.

Sharing our experiences with others – our success and our problems – is how we create this community of those who suffer from peripheral neuropathy. Sharing through Neuropathy Hope, sharing through support groups both virtual and in-person, and sharing through our website gives everyone information that helps us cope…cope with the pain, cope with the numbness, cope with the sleepless nights, cope with the anxiety and depression. Let's all be there for each other.

Otherwise, enjoy this issue! The front-page article is long and detailed but gives insight into the use of gene therapy for neuropathic pain. And the article on chemotherapy-induced peripheral neuropathy treatments includes a good explanation of dorsal root ganglion stimulation.

..Katherine
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Our mission is to provide support, information and referral to people with neuropathy and to those who care about them, to inform and connect with the health care community, and to support research.

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