Neurological disorders can wreak havoc upon the carefully tuned processes of our brain that allow us to function and thrive. Among these disorders are migraine and cluster headaches, whose intense pain affects millions of people per year, decreasing their ability to work effectively, creating mental health issues, requiring bedrest for many and incurring billions of dollars in health care costs (Rozen and Fishman, 2012; Lipton et al, 2001).

Despite ongoing documentation of headaches for over two thousand years (the Egyptians described migraine-like headaches in 1200 B.C.), and ongoing research in the modern era, the last major breakthrough in headache treatment was in the 1990s. The introduction of a class of drugs called triptans in the ‘90s brought promise for abortive medications which could offer acute treatment. Now, however, after a dearth of research for almost a decade, a new breakthrough is on the horizon. In the past 5 years, promising new drugs and devices started entering the research pipeline resulting in exponential growth in headache knowledge.

Eager to be a part of this cutting-edge science, Dr. Cori Millen of Summit Headache and Neurologic Institute, turned to CNI for research collaboration. A renowned headache specialist and neurologist, Dr. Millen teamed with CNI to launch the Research Department’s first head pain trials. Dr. Millen has now served as Principal Investigator on 14 Phase 3 head pain studies over the last five years and is a star recruiter with over 100 patients enrolled. Her research includes non-invasive treatment for cluster headaches (see Research Impact page 5) and the new hot molecules targeting the calcitonin gene-related peptide (cGRP) pathway for treatment of migraine and cluster headaches.

Implication of cGRP in migraine and cluster pathways has taken many years and different paths (Edvinsson et al, 2017). One approach has been to generate monoclonal antibodies to the cGRP peptide – a 37-amino acid neuropeptide that can cause potent vasodilation when it binds to a cGRP receptor. The antibody prevents cGRP binding, thus blocking vasodilation, inflammation and the subsequent pain generated by aggravation of the trigeminal nerve. Two such cGRP antibodies, fremanezumab and galcanezumab, have been the focus of 11 studies coordinated by CNI for patients with migraine and cluster headache, with a special emphasis on chronic and episodic populations and long-term treatment. These double-blind, placebo-controlled studies look at the reduction of headache days, safety and efficacy of the molecules given, as well as long term safety of administration of the molecule. Enrollment is currently open for cluster headache trials (see Enrolling Studies page 4).

Another approach used to target the cGRP pathway is a receptor-antagonist molecule that binds to the cGRP receptor but does not cause its activation. Dr. Millen and CNI have been a site for two studies examining the use of a receptor-antagonist called ubrogepant in the acute treatment of migraines. These studies have looked at the efficacy of pain reduction, optimal dosing and safety.

Many of these studies have either recently closed enrollment or will be doing so soon, with the hopes of rapid FDA-approval and release to patients who currently have no other options. The next step will be post-approval, Phase 4 studies to explore long-term efficacy and safety for these and similar molecules. Keep your eyes on CNI’s Neuro News monthly e-newsletter for the latest on cGRP approvals and new studies. Read more about migraine and cluster headaches on page 3
It’s All About Attitude
A Patient’s Perspective

Dennis Babiniec knew something was wrong when he started having trouble with his memory. He hesitated going to the doctor despite increasing confusion, aphasia, headaches, dizziness, and lethargy. In May 2017, Dennis decided he needed answers, and went to his primary care physician who ordered a CT image of his head. Only 40 minutes after the CT, he received a phone call and was told to go to the Emergency Room where he was diagnosed with a large left hemisphere glioblastoma (GBM). GBMs are the most common grade IV brain cancer. They are fast-growing, aggressive, and the most malignant of glial tumors, as well as the hardest to treat.

Three days later, Dennis underwent a craniotomy to resect the tumor. “I wasn’t ready. I didn’t know what was happening,” he recollects. His wife Katherine remembers, “I didn’t know what glioblastoma was, but they gave me a lot of information. They tried, but it was a difficult time.” After tumor resection, Dennis was treated according to the standard of care for GMB: chemotherapy and radiation.

Dennis made it through his rapid diagnosis and surgery with the love and support of his wife and two sons. Originally from Illinois, Katherine recalls, “37 years ago we jumped into the car with $250 and moved west.” The Babiniecs made a home for themselves in Colorado, joining a local church and raising their family. Dennis established his own law firm, where he practices family law.

Eight months after the first surgery, the Babiniecs heard words they hoped they'd never hear – there was tumor progression. According to Dennis, “Dr Michael Pearlman, Neuro-oncologist, called me that night and told me he wanted to see me the next day.” Dennis learned about the Tocagen research trial at that visit with Dr. Pearlman, who collaborates with CNI as the study’s Principal Investigator. Toca 511 (an injected virus) and Toca FC (an oral tablet) are an investigational combination product being developed by Tocagen to treat recurrent high-grade gliomas such as GBM. Dennis reports, “I was concerned about participating in a research trial, but when I compared it to everything else, there wasn’t anything that had better results.”

The current study is a Phase 3, randomized, open-label treatment with 1:1 assignment to the study drug versus control arms for patients undergoing planned resection. Toca 511 is administered during surgery by injection, while Toca FC is given orally several weeks later. “I trusted God—I trusted that he would take care of me,” Dennis said. “I didn’t know what that would mean—whether I got the drug or didn’t get the drug.” Dennis received the Toca 511 virus during his second tumor resection in January 2018. His surgery went well, with neurosurgeon and Sub-Investigator Benjamin Rubin, M.D. removing most of the tumor. “I did so well [this time] they didn’t know what to do with me,” Dennis said. In fact, just four days after his surgery Dennis was discharged home, and by the next weekend he was shoveling snow after a large winter storm with the help of family and neighbors.

“It’s all about attitude – if your recovery takes 22 ½ days or 4 ½ days, which would you rather have? I had to learn about the process. When I noticed something different or wrong, I told them about it so they could fix it and have a better recovery time,” Dennis says. “That way you have people working with you. When you don’t, all they can do is check the machines. If the patient can contribute, the outcome will be better. It takes being willing.” When asked about his participation in the Tocagen research trial, Dennis reports, “Drawing on our faith has brought us strength and peace. What happens from here – I’m excited about it. I don’t know what it is, but I’m excited.” The clinical research trial is currently open to enrollment and subjects are being randomized at over 80 clinical sites around the globe, including at CNI.
Migraines and “Suicide” Headaches

Migraine and cluster headaches are complex neurological disorders. While the cGRP pathway has been implicated in both migraine and cluster headaches, they are distinct classes of headaches. Migraines are recurrent, throbbing headaches that are often unilateral, and may be accompanied by sensory disturbances and nausea. They can last 4 hours to few days. Women are three times as likely to have migraines as men. Worldwide, an estimated 10% of the population suffers from migraines.

Cluster headaches are a much less common headache characterized by short, intense headaches (15 to 180 minutes) that occur repeatedly in clusters, lasting from weeks to months. The headaches often stop during a period of remission which can be months or years. In addition to some of the sensory disturbances that migraineurs experience, cluster headaches can also be accompanied by drooping eyelids, nasal congestion, facial sweating and excessive tearing. This headache type is more common in men and has been described as so severe as to earn the nickname “suicide headache.”

If you know someone suffering from these types of headaches, reach out for help. CNI is here to assist in connecting you with resources and research.

AREAS OF RESEARCH AT CNI
35 clinical trials conducted in 2017

Enrolling Studies at CNI
Highlights from recent studies

Toca5 Toca 511 & Toca FC versus standard of care in patients with recurrent high-grade glioma (anaplastic astrocytoma or glioblastoma). Principal Investigator (PI) Michael Pearlman, M.D., Ph.D.

Stellar Study to evaluate efomithine and lomustine versus lomustine in recurrent anaplastic astrocytoma patients. PI Michael Pearlman, M.D., Ph.D.

Perc Nucleus percutaneous contour advance clinical study. PI David Kelsall, M.D.

CMS Evaluation of revised indications for cochlear implant candidacy for the adult CMS population. PI David Kelsall, M.D.

Enforce (1) A study comparing the efficacy and safety of TEV-48125 (Fremanezumab) for the prevention of chronic cluster headache. PI Cori Millen, D.O.

Enforce (2) A study comparing the efficacy and safety of TEV-48125 (Fremanezumab) for the prevention of episodic cluster headache. PI Cori Millen, D.O.

Enforce (3) A study to explore the long-term safety of TEV-48125 (Fremanezumab) for the prevention of cluster headache. PI Cori Millen, D.O.

IMPAX Efficacy and Safety of Zomig nasal spray for acute migraine treatment in subjects 6 to 11 years old, with open label extension. PI Michael Pearlman, M.D., Ph.D.

Patient-Driven Research

Donor funding enables CNI to give patients with neurological conditions the ability to get cutting-edge treatment through clinical research trials. As a non-profit organization dedicated to Improving the Lives of Patients Living with Neurological Conditions, our focus is our patients. Pharmaceutical sponsors fund some of our research, however much of our research is funded by donors like you.

Consider helping CNI to continue providing life changing research and new advances in our understanding of neurological conditions. Donations may be designated to a specific disease research line, or to the Research Department generally. For more information, contact Sheila Kutzer at 720-974-4094 or skutzer@thecni.org
Financial support for non-profit organizations often comes from those who believe in the organization's mission and the impact it is having. There are also supporters who champion an organization because they are intimately connected to the cause, and choose to back that with financial support. Suzanne Birkans, manager at the Ralph L. Smith Foundation, supports CNI for both of these reasons. The Ralph L. Smith Foundation was started by successful lumberman, farmer and philanthropist, Ralph Leftwich Smith in 1952. Today the foundation continues the work of its founder supporting education, health care, and human services through the dedication and management of Ralph’s family.

Suzanne, the great granddaughter of Ralph. L. Smith, has been an advocate and supporter of CNI’s ALS research and ALS Clinic over the past two years, gifting $36,000 in honor of her late father, Edward (Marsh) Douthat III. Having recently lost her father to ALS, Suzanne understands the important work CNI is doing to improve the quality of life for those living with this neurological disease. When Suzanne was asked why she selected CNI as the organization to support, she said, “I choose to give to CNI because, as the daughter of a former ALS patient, it can feel like you are constantly helpless in the battle with this disease. However, supporting the ALS clinic at CNI helps you feel like you can make even a small impact on the current ALS patients and their families, particularly because Tami (CNI Executive Director Tami Lack) is so clear and decisive with the current research and patient priorities and their funding requirements.”

Unfortunately, Suzanne is not alone in her struggle as an ALS caregiver and family member. The ALS Association statistics cite an average of 15 people are newly diagnosed with ALS each day—more than 5,600 people per year. As many as 30,000 Americans may currently be affected by ALS. Annually, ALS is responsible for two deaths per 100,000 people. The average life expectancy of a person with ALS is two to five years from time of diagnosis. These are daunting statistics and bleak outcomes. CNI’s mission of Improving the Quality of Life for People Living with Neurological Conditions means that we are working hard every day to help people live well for as long as possible.

Thanks to financial support from friends like Suzanne and her family’s Ralph. L. Smith foundation, CNI is able to continue our rehabilitation, clinical research, and supportive services to improve the lives of people with ALS, proudly doing so in honor of great men like Edward Marsh Douthat III and Ralph L. Smith.

Amyotrophic Lateral Sclerosis (ALS), often called Lou Gehrig’s disease, is a degenerative neuromuscular disease affecting the nerve cells of the brain and spinal cord. CNI is an Amyotrophic Lateral Sclerosis Association (ALSA) Recognized Treatment Center. In partnership with The ALS Association Rocky Mountain Chapter, CNI offers a comprehensive monthly clinic at the Vollbracht NeuroHealth and Wellness Center in Englewood, Colorado. To learn more about supporting the ALS Clinic or any of CNI’s programs or research efforts, contact Sheila Kutzer at (720) 974-4094 skutzer@thenci.org
2018 marks CNI's 30th year as a non-profit 501(c)(3) organization. Over these years, our mission has not changed, however we have become increasingly community-focused, moving away from a hospital-based model. Our mission areas continue to be neurological rehabilitation, clinical research, and supportive services. We are here to improve the quality of life for people living with neurological conditions, and those who love them.

CNI began as a collaboration between three hospitals, two of which later became for-profit entities. CNI acquired Centers of Excellence status in almost every major neuro disease line, and became well known throughout the Rocky Mountain region as an institute without the constraints of a university setting. As we grew and achieved, changes were occurring in the health care environment, and hospitals were becoming more competitive. CNI leadership realized two things: 1) There was a need for CNI to diversify and not remain tied to any one health system; and 2) Hospitals were becoming more in-patient focused, and CNI would have to meet the need for out-patient services. As a non-profit community entity, CNI knew we had the expertise and constituents to build a strong network of donors and supporters to leverage these out-patient services.

At CNI, we now have 70 physician and research associates, over 40 ongoing clinical trials, and the Vollbracht NeuroHealth & Wellness Center offering out-patient physical, occupational, and speech therapy, counseling, cognitive driving assessments, specialty clinics and more. We are a Huntington's Disease Center of Excellence and are working to become an ALS Center of Excellence. We receive referrals from neurologists and primary care physicians across the region.

With a solid foundation under us, we are looking to 2018 for innovation. We are launching expanded initiatives that will move us into a nationwide service area under the title CNI: Center for Neurological Innovation. We are building a unique national model for outpatient neurological education, support, rehab, and wellness. Our research endeavors continue to offer physicians and patients an opportunity to be involved in clinical trials and investigator-initiated projects outside of a university setting.

As we move into the next 30 years, we remain the only non-profit entity of our kind. We are proud of the amazing work we do and the incredible support we have from our physician partners and researchers who put patient needs above all else.

### Celebrating 30 years of Service

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### Research Impact

The outcome of these CNI trials led to FDA or industry approval for new devices, drugs, or medical procedures:

**DBS** The Intrepid trial tested a new Deep Brain Stimulation (DBS) device for treatment of Parkinson's disease (VerciseTM Deep Brain Stimulation System-Boston Scientific). Principal Investigator (PI) Monique Giroux, M.D. Co-Investigator Adam Hebb, M.D.

**Headache** GammaCore® from electrocore, LLC, a device tested for non-invasive treatment of cluster headaches, was approved for episodic cluster and later migraine headache treatment. PI Cori Millen, D.O.

**Stroke** The Escape trial, to examine the benefit of rapid endovascular treatment when added to early stroke care, proved value in adding clot removal to standard of care stroke treatment. PI Donald Frei, M.D.

**Neurosurgery** The Adherus® AutoSpray Dural Sealant (Hyperbranch Medical Technology) was approved for sealing the brain dura after neurosurgery. PI Alexander West, M.D., Ph.D.

**Multiple Sclerosis** A new monoclonal antibody drug was recently approved for treatment in Relapsing Remitting Multiple Sclerosis (Ocrelizumab–Genentech). PI Allen Bowling, M.D., Ph.D.

For more information on our programs, services, events, or innovations, contact us at (303) 788-4010, visit us at www.thecni.org or follow us on social media at @coloradoneurologicalinstitute @CONeuro
Become a CNI Physician Associate or Research Associate

CNI partners with clinicians in private practice and researchers engaged in neuroscience projects throughout the community, to better serve individuals with neurological conditions.

The Opportunities

- Work on research projects and publish your findings, with support from seasoned CNI researchers.
- Plan and implement community education programs and supportive services with resource assistance from CNI, including the opportunity to obtain donations and offer tax-deductible contributions to donors.
- Network with other physicians, researchers and neuroscience service providers in a non-competitive environment.
- Market your association with CNI on letterhead, business cards, and CV.
- Act as an advisor for programs and services for neurological patients in our region.
- Receive promotion on CNI website and marketing materials, as a CNI Physician Associate.

The Requirements

- Currently engaged in a clinical practice or research related to the neurosciences, and hold a doctoral degree.
- Demonstrate patient first practices and behaviors.
- Must submit current CV and update it annually.
- Agree to attend two CNI events per year.
- Give back through research, clinic support, or educational support to the patient and professional community.
- Able to sign a statement of ethical conduct.
- Submit two professional references.
- Receive approval by the CNI Medical Advisory Council.

For more information or to obtain an application, contact
Lorre Gibson, Physician and Donor Relations Coordinator  lgibson@thecni.org     (303) 806-7420