



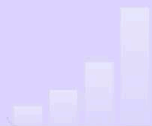
NEUROCARRUS

Treating Neurodegenerative Disease and Pain Without Addiction

Highlights

Regular Updates

Founders have a strong track record of investor updates.



1

Drug candidate N-001 provides relief from acute pain in animals caused by inflammation or surgery.

2

Neurocarrus has built a pipeline of drugs using the APOLLO targeting and delivery system.

3

- 3 N-001, NL-17, N-19a treat acute, migraine and chronic pain by sensory neuron targeting.
- 4 The APOLLO drugs use a unique manufacturing process to discourage competitors.
- 5 There is a massive market for the treatment of Neurodegenerative disease and pain around the world.
- 6 Neurocarrus has a strong track record of non-dilutive funding from federal and state government.
- 7 Founder has been working in the space for 25+ years trouble shooting commercial biologicals.
- 8 Patents issued and pending on exclusively licensed technology in both the U.S. and select countries.

Team



Paul Blum Co-founder/CEO

30+ years in cell engineering and microbiology, focused on protein drug development. Paul is full time CEO of Neurocarrus in Monterey, California. He is a serial inventor and was an endowed university professor.



Derek Allen Research Scientist

Ph.D. focused on protein drug development with emphasis on protein synthesis and purification. Also specialized in bioassays and potency studies.



Jianguo Cheng, MD, Ph.D Board Member

Professor and Director, Cleveland Clinic; Past President, American Academy of Pain Medicine. Highly active in research and pain medicine and strongly supported by NIH. Also an active editor in top pain journals.





Bruce McDonald, JD Board Member

Partner in the intellectual property group at Smith, Gambrell & Russell, LLP; member of the District of Columbia Bar. Specialized in trademark law and intellectual property litigation, particularly negotiation of licensing agreements.



Mark Blum, JD Board Member

Mark is an attorney licensed in California who practices law in California since 1986. For the past three years, he has continued his role as a shareholder, managing member and practicing attorney at Horan Lloyd.



Vicky Valverde Salas Board Member

Vicky attended MIT majoring in Mathematics, Physics and Biology. He earned an M.D. from the U. Madison Wisconsin Medical School and trained in Family Medicine at Case Western Reserve. For the past 20 years he ran his own medical Primary Care Clinic.

neurocarrus.com

Publications:


Neurocarrus top scientific publications:

[Animal efficacy and safety studies](#)

[Targeting, mechanism, and efficacy studies](#)

[Drug design and engineering studies](#)

NEUROCARRUS



***Treating
Neurodegenerative
Disease and Pain
Without Addiction***

Cell-targeted, Non-Opioid
Therapeutics

*For more information:
paul@neurocarrus.com*

Welcome to Neurocarrus!

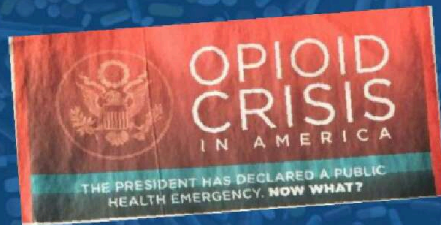
We are a drug development startup company making a new therapeutic to treat severe human pain without addiction.

Paul Blum our CEO, invented the drug while at the U Nebraska. After retiring from academia, he now works full time at Neurocarrus.

Together with chief scientist Derek Allen and other Neurocarrus staff, our team is highly motivated to bring our drug to market.

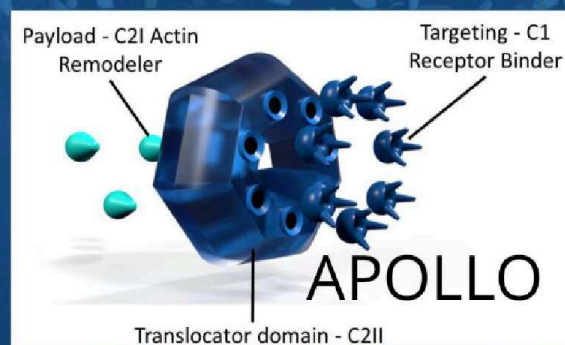
Help us fight the opioid epidemic and solve the human tragedy of widespread poorly managed severe pain.

Current drugs for neurodegenerative disease and severe pain can be addictive and toxic resulting in hundreds of thousands of deaths per year



By DAN REYNOLDS CBS NEWS March 6, 2018, 4:45 PM
CDC: Opioid overdoses kill almost 5 people every hour in the U.S.

Neurocarrus designed APOLLO as a novel drug delivery platform for treatment of diverse neurodegenerative disease without addiction, toxicity or off-target effects



Neurodegeneration and Pain:

Neurodegeneration damages neurons and often causes pain (called sensory neurons) that lie outside the central nervous system and brain. Therefore the Neurocarrus drug, N-001, designed using the APOLLO targeting and delivery system finds and attaches to such neurons located only in the body's peripheral regions (not brain) and then calms their excessive activity. This strategy avoids addiction because it avoids the central nervous system (brain).

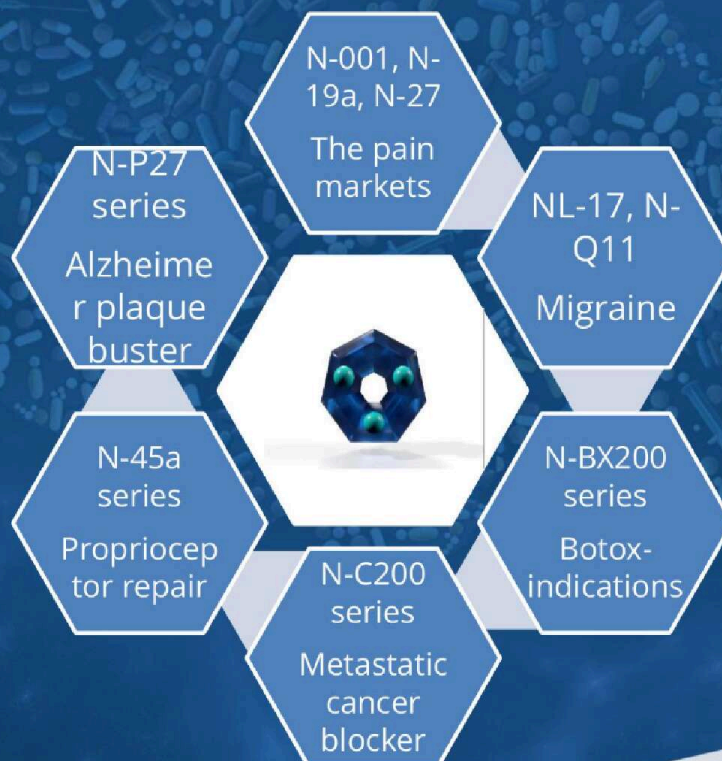
To target sensory neurons and and treat pain, N-001 had to be multi-functional. N-001 is targeted to sensory neurons not motor neurons and therefore has no effect on muscles. It is only active once it goes inside sensory neurons. Together these two functions limit side effects and

distinguishes N-001 from all other pain drugs. Once inside the sensory neuron, N-001 modifies the internal actin-based skeleton to reduce neural signaling.

The Neurocarrus drug acts like a dimmer switch on neurons without blocking sensation. Importantly N-001 is reversible.

NEUROCARRUS

Apollo: A pipeline of targeted therapeutics for delivery to selected tissues and cells



5

A pipeline of new therapeutics :

Using the APOLLO targeting and delivery system, a deep tech invention unparalleled in pharmaceutical science, Neurocarrus has built a series of candidate therapeutics.

N-001 treats acute pain
NL-17 treats migraine
N-19a treats chronic pain

Each of these biologics (proteins) have unique medical uses for specific populations providing important value propositions.

NEUROCARRUS

Leading Drug Products are Efficacious, Safe and Valuable

Main Indications

Acute Pain asset N-001: at a price point of \$500 per dose (estimate based on competitor anesthesia) this is market entry at **\$250M revenue** with capacity to expand 100 fold and **net profit of \$200 per dose.**

Chronic pain asset N-19a: 1% market entry (670K patients) dosed monthly **\$4.02B revenue** per year.

Migraine Prevention asset NL-17: 1% market entry (66K patients) dosed monthly is **\$396M revenue** per year.

Preclinical PAIN Trial Metrics*

Eliminates inflammatory, surgical, chronic, and migraine pain

Acts longer than anesthetics AND narcotics

High safety. After multiple dosing; no toxicity, adverse histochemistry, cytology, or physiology and no neutralizing ADAs

*Independently confirmed by CROs and Stanford University using double blinded procedures

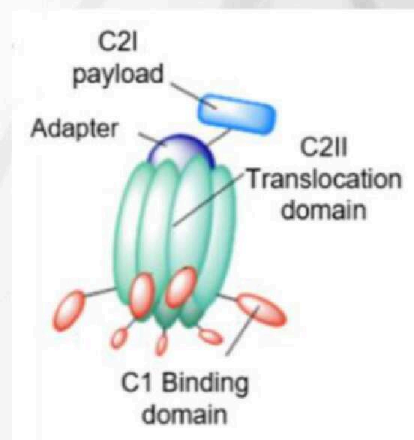
Alternatives and Competitors

N-001 is first-in-class

	N-001	Opioids (OxyContin)	Over-the-counter (Tylenol, Ibuprofen)	Anesthesia (Amytal)	Long Lasting Anesthesia (Exparel)
Severe Pain Surgical	X	X		X	X
Non-addictive	X		X	X	X
Long lasting	X				X
Targeted	X				

N-001 Profile

- A rationally designed multifunctional biological (protein) that targets sensory neurons and is active only inside them.
- Cell targeting combined with intracellular activity minimizes side effects and improves likelihood of positive clinical trial outcomes.
- Locally administered at the site of pain, by injection or patch or nerve block, not systemic no CNS effect.
- Preclinical tests measuring efficacy and safety are promising.



The market opportunity and human health:

With an estimated 30% of the population worldwide affected, pain is one the most prevalent health problems in the world. Pain is affecting 56% of American adults, more than diabetes, heart disease, and cancer combined.

Acute pain due to injuries, accidents, labor, and childbirth, or surgeries represents a significant concern for 67.5% of patients admitted to hospitals. There are nearly 50 million surgeries in the US per year that involve pain management.

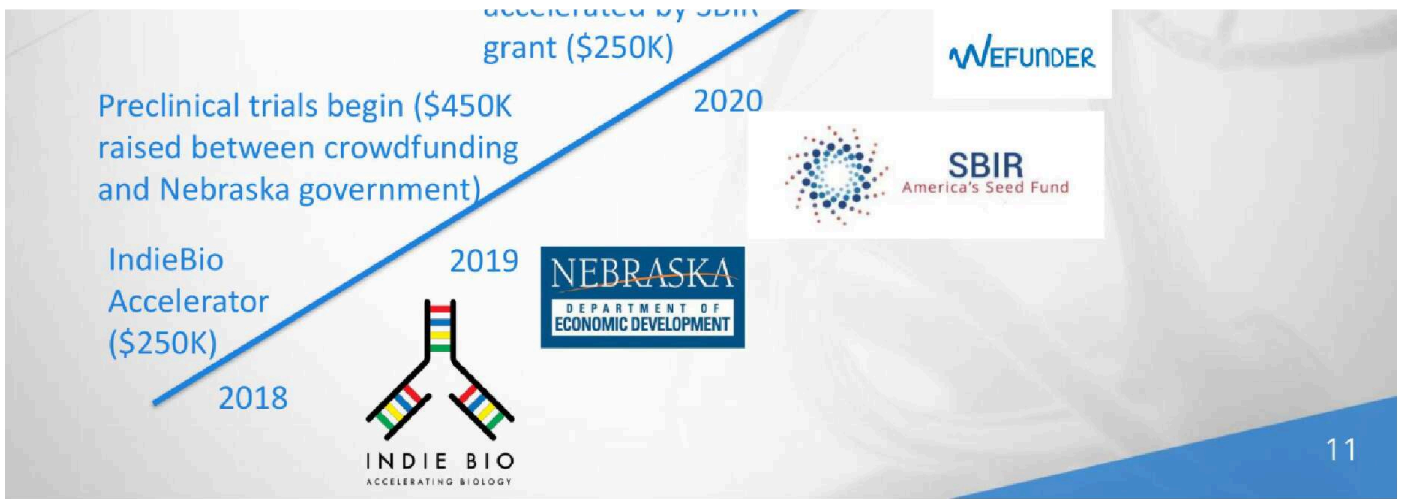
Unrelieved acute pain is one of the risk factors in the development of chronic pain, with 10% - 50% of patients developing persistent pain after different operations. Specifically, there are over a million orthopedic surgeries performed each year in the US. Total hip and knee arthroplasties are common surgeries in orthopedics with more than 300,000 hip replacements and 600,000 knee replacements performed each year.

NEUROCARRUS

Progress

Neurocarrus progress is accelerating





A history of strong funding:

Neurocarrus has received considerable non dilutive investment (\$3,321,000). These federal and state awards result from confidential reviews by pain experts and business executives coordinated by the awarding sources. They prove that Neurocarrus is highly competitive within the landscape of the US medical establishment. The company has received \$600,000 in private investment resulting in a very promising ratio of 5.6 non-dilutive to dilutive funding for future investors. This means that their investment leverages the much larger federal and state commitments which dictate valuation.

A well developed commercialization plan:

Our current Phase II NIH SBIR award of \$2,780,000 depended on development of a highly detailed commercialization plan that was reviewed and vetted by reviewers. This plan includes near and long term strategies to develop N-001 within the structure of the federal approval process and to fund the development by strategic partnerships.

And now opportunities to out-license pipeline drugs for revenue generation

Accomplishments Since Our Last Wefunder Raise

NEUROCARRUS

Before Wefunder Raise After Wefunder Raise

IndieBio Incubator Class 6

Public Dissemination: First publication:
<https://doi.org/10.1038/srep23707>

\$100K non dilutive funding awarded by
Nebraska Department of Economic
Development.

2020:

\$250K non dilutive funding awarded by the US NIH Phase I SBIR
program

\$91K non dilutive funding awarded by Nebraska Department of
Economic Development

Partnered with Stanford Medical School and Veterans
Administration in Palo Alto CA

First U.S. patent issued

Public Dissemination: Second publication:
<https://doi.org/10.1038/s41598-020-69612-9>

2021:

Accepted into the United States NIH Preclinical Screening Platform
for Pain

Second U.S. patent issued

2023:

\$2.78M non dilutive funding awarded by the NIH Phase II SBIR
program

\$100K non dilutive funding awarded by Nebraska Department of
Economic Development

Public Transparency: Third publication:
<https://doi.org/10.1038/s41598-020-69612-9>

13

NEUROCARRUS

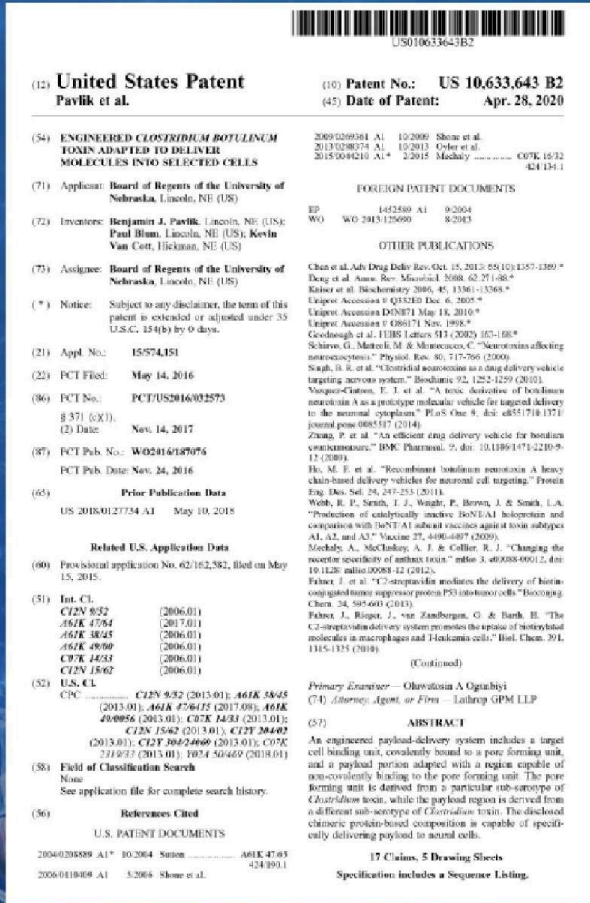
Investor Opportunity and Exit Strategies

Wefunder investors receive a SAFE in exchange for their investment using a contract between the investor and Wefunder. A SAFE is a Simple Agreement for Future Equity and is like a convertible note but less complicated. When conditions are met such as an Equity Financing of preferred stock, SAFEs convert to preferred stock.

Investors have several potential strategies to make money. Neurocarrus may be acquired and the investor's shares would be bought out at an increased valuation in exchange for cash, or potentially exchanged for shares in the purchasing company. Alternatively, Neurocarrus may go public and undergo an initial public offering (IPO) allowing investor shares to be publically traded and sold.

14

Intellectual Property



- Patent No. 10,633,643 issued by USPTO on April 28, 2020 (priority date in 2015)
- Follow on divisional Patent No. 11,118,170 issued May 19, 2021
- Neurocarrus exclusively licensed these patents for all-fields-of-use along with a sublicense option.
- PCT US 1632573 has issued in Japan 2017-559588 (6-17-21) and EU and is pending in Canada, Israel, and South Korea.
- [Provisional 63/695,737 filed September 2024 for treatment of Migraine – extends IP sales protection to 2044](#)
- [Provisional filing anticipated 2025 for treatment of chronic pain](#)

What does success look like?

Solving severe pain without addiction is its own reward. Financial benefit to early investors will result in part from the ongoing protection of intellectual property.

Neurocarrus has two issued US patents invented by CEO Paul Blum and coworkers. The company continues to pursue protection of its intellectual property by patent protection in other countries. These countries were selected by their current manufacturing ability to make protein drugs. Fortunately, the Covid epidemic revealed and reinforced as highly strategic, the selection of countries made by Neurocarrus.

Neurocarrus recently filed a new patent about migraine

Neurocarrus recently filed a new patent about migraine treatment using NL-17, extending the period of protected drug sales and increasing interest by long term investors.

Neurocarrus will continue its aggressive IP strategy to extend protection of its inventions.

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN **Retargeting the *Clostridium botulinum* C2 toxin to the neuronal cytosol**

Benjamin J. Pavlik^{1,2}, Elizabeth J. Huska¹, Kevin E. Van Cott¹ & Paul H. Blum^{1,2}

Many biological toxins are known to attach specific cell types, delivering their enzymatic payload to the cytosol. This process can be manipulated by molecular engineering of clinical toxins. Using toxins with naturally unlinked components as a starting point is advantageous because it allows for the development of payloads separate from the binding and activation components. Here the *Clostridium botulinum* C2 binding/activation domain was targeted to neural cell populations by deleting its non-specific binding domain and replacing with a C. botulinum neuraminidase binding domain. This fusion protein was used to deliver fluorescently labeled payload to Neuro-2a cells. Intracellular delivery was quantified by flow cytometry and found to be dependent on artificial attachment of cells with the polyglutamine receptor G73. Visualization by confocal microscopy showed a dissociation of payload from the early endosome indicating translocation of the clinical toxin. The natural *Clostridium botulinum* C2 toxin was then delivered to human glioblastoma U87 and postionized HeLa cells. In the presence of the fusion protein, active cytosolic enzymatic activity of the enzyme was

Received: 29 November 2023
Accepted: 18 March 2024
Published: 18 March 2024

SCIENTIFIC REPORTS
nature research

OPEN **Intracellular G-actin targeting of peripheral sensory neurons by the multifunctional engineered protein C2C confers relief from inflammatory pain**

Devak Allen^{1,2}, You Zhou¹, Audrey Whitehead¹ & Paul Blum^{1,2}

The engineered multifunctional protein C2C was tested for central afferent neuron activity by targeted G-actin modification. C2C consists of the heparanase, collagenase, C2/C1, and the neurotoxic chondroitinase. C2C treatment of sensory neurons and DRG-DVY cultures demonstrated actin and reduced calcium influx in a peripheral mouse. C2C prepared viable fluorescently labeled C2C chondroitinase in vitro C2C delivery to sensory neurons receptor but not motor neurons. Delivery was dependent on presence of both C2C subunits and blocked by receptor competition. Transmembrane delivery of mice treated separately with C2C showed minimal action of interest. C2C with G-actin positive sensory neurons and fibers but not with G-actin positive motor neurons and fibers. The significance of sensory neuron targeting was assessed intraperitoneally by testing C2C activity in the formalin-inflammatory mouse pain model. Subcutaneous C2C demonstrated robust pain-like behaviors by 30% relative to untreated control 6 hours treatment and similar to the opioid buprenorphine. C2C effects were dose-dependent, equally potent in female and male animals and did not change gross motor function. One dose was effective in 2h and lasted 3 weeks. Administration of C2C chondroitinase did not reduce pain-like behavior indicating its intracellular delivery was required for behavioral effect.

Acute peripheral pain can be treated with analgesics which inhibit ion channels¹ and thereby formation or propagation of an action potential required for neuronal signaling. However, side effects (vomiting,² fatigue, sedation, dizziness,³ and loss of appetite⁴) have led to the use of calcium channel blockers as additional pain relief perception because actin potentially prevents membrane depolarization leading to calcium influx. In neurons, calcium channel depolarization opens other channels, calcium neurotransmission⁵ and acts as a second messenger in neuronal signaling.⁶ These channels include ligand-gated ion channels activated by high voltage calcium current (low voltage calcium channels), L-type and R-type voltage-dependent calcium channels, and play a major role in neurotransmitter release in neuronal cells.⁷ They transmit pain signals from peripheral neurons through secondary neurons to the central nervous system. For the human skeletal muscle, calcium channel blockers are used to treat hypertension, angina, and arrhythmias.⁸

Calcium channel blockers are dependent on the conformational protein actin. Actin occurs as monomeric subunits (G-actin) or as polymerized form (F-actin) in the human cell body, arms and dendrites. Inhibiting the polymerization that maintains and reinforces F-actin through addition and removal of G-actin inhibition of the process using actin inhibitors can modulate formation of actin protrusions through inhibition of cellular influx.⁹ In addition, the modulation of actin polymerization has been shown to inhibit neuronal influx,¹⁰ inhibition of actin polymerization is a novel pain reliever because it can block peripheral neuronal signaling.¹¹ However, all known actin inhibitors are small molecules and moderate soluble molecules that lack cell type specificity.¹² Thus, an actin inhibitor was developed because of its ability to cause drug to overcome widespread, low-affinity binding preventing irreversible inhibition of actin polymerization.¹³

¹School of Biological Sciences, University of Nebraska—E233 Brandt Center, Lincoln, NE 68583, USA. ²Center for Biotechnology, University of Nebraska, E233 Brandt Center, Lincoln, NE 68583, USA. ³email: paulh@unl.edu

SCIENTIFIC REPORTS | (2024) 14:10000 | https://doi.org/10.1038/s41598-024-59012-9

Current Topics in Peptide & Protein Research

REVIEW ARTICLE

REPURPOSED BACTERIAL TOXINS FOR HUMAN THERAPEUTICS

Benjamin J. Pavlik¹, Kevin E. Van Cott¹ & Paul H. Blum^{1,2}

¹Department of Chemical and Biomolecular Engineering, 207 Othmer Hall, University of Nebraska—Lincoln, Lincoln, NE 68583-0643; ²School of Biological Sciences, 1901 Vine Street, University of Nebraska—Lincoln, Lincoln, NE 68583-0665, USA.

ABSTRACT

Pathogenic bacterial toxins can be repurposed as therapeutic. Binary bacterial toxins are macromolecular complexes that use a current focus of therapeutic development. These proteins bind to surfaces of specific human cell populations and transport enzymes across membranes. Basic research has characterized bacterial toxin mechanisms and structure so that protein domains can be “tailored” for a variety of applications. This approach delivers an already characterized enzyme in new cell types, target, enter, and disrupt the biological structures and processes of cells. Many reviews are sophisticated membrane-associated proteins with high aqueous solubility, capable of targeted molecular transport to specific human cell types and intracellular locations. Treatments for cancer and neurological disorders have been the focus of several clinical trials [1–4], but only two have been approved for therapeutic use: Clostridium botulinum neurotoxin serotypes A and B (Botox[®], Dysport[®], Xeomin[®], Myobloc[®]) can be purified directly from the microorganisms and are

REVIEW ARTICLE

Preclinical characterization of the efficacy and safety of biologic N-001 as a novel pain analgesic for post-operative acute pain treatment

Devak Allen^{1,2}, Ganeshwar Rajaganathan¹, Rylie McDonnell¹, Karan-Ananda Irwin¹, Payton Saliba¹, David Clark^{1,2} & Paul Blum^{1,2,3,4}

Inhibition of actin remodeling in nerves modulates action potential propagation and therefore could be used to treat acute pain. N-001 is a novel protein analog engineered from avian C. botulinum toxin. N-001 targets sensory neurons through ganglioside G73 binding and ADP-ribosylation G-actin reducing actin remodeling. The activity and efficacy of N-001 was evaluated preclinically in vitro and in a mouse inflammatory pain model. To assess the efficacy of N-001 for treatment of acute post-operative pain, the current study evaluated the efficacy of N-001 in a mouse hind paw incision model by peripheral and peripheral nerve block administration combined with mechanical testing. N-001 provided relief of pain-like behavior over 8 days longer than the standard long-acting analgesic buprenorphine. Preclinical safety studies of N-001 indicated that drug parameters for use in a human neurological procedure over multiple doses were safe. These results combined with past behavioral results encourage further investigation of N-001 as an analgesic for post-operative pain management with the potential to function as a differential receptor specific nerve block.

Post-operative pain is defined as the pain present in a subject after surgery.¹ Poorly managed post-operative pain can lead to prolonged hospital stay, complications and poor quality of life.² The can lead to chronic pain like acute pain is prolonged and can reduce the quality of life.³ The use of opioid analgesics to manage the post-operative pain management⁴ and has led to concerns of opioid abuse and addiction.⁵ In addition, chronic pain is a leading cause of disability in the United States.⁶ There are over 125 chronic drug-resistant pain syndromes that are common in chronic disease.⁷ The global population is rapidly aging and the number of people with chronic pain is increasing.⁸ The need for new pain management strategies is increasing.⁹

Protein based therapeutics are stable alternatives to conventional opioids and may help address the opioid crisis.¹⁰ There is a growing need to study the target and its role in the development of receptor agonists/antagonists receptor potentialities with TRPV1 and different non-opioid protein coupled receptors (GPCRs).¹¹ The current challenge with these drugs is the lack of specificity leading to off-target effects combined with a limited effect due to rapid clearance.¹² A key component of pain management is a combination actin of actin with sensory neurons which is an actin and filamentous protein.¹³ Actin polymerization is a key component in the signaling and remodeling of the cytoskeleton. Actin is a central element in cell function and is involved in a wide range of cellular processes. Actin is a central element in cell function and is involved in a wide range of cellular processes. Actin is a central element in cell function and is involved in a wide range of cellular processes.

¹Neurocarrus Inc, Matthews, CA, USA. ²Microbiology and Biomaterials Technology, University of California Santa Cruz, Santa Cruz, CA, USA. ³School of Biological Sciences, University of Nebraska—Lincoln, NE, USA. ⁴School of Biomedical Sciences, University of California, Davis, CA, USA. ⁵Neurocarrus Inc, Matthews, CA, USA. ⁶email: paulh@unl.edu

SCIENTIFIC REPORTS | (2024) 14:10000 | https://doi.org/10.1038/s41598-024-59012-9

NEUROCARRUS

Publications

Allen et al 2023 Sci Rep
PMID: 37479740

Allen et al 2020 Sci Rep 10,
12789 PMID: 32732905

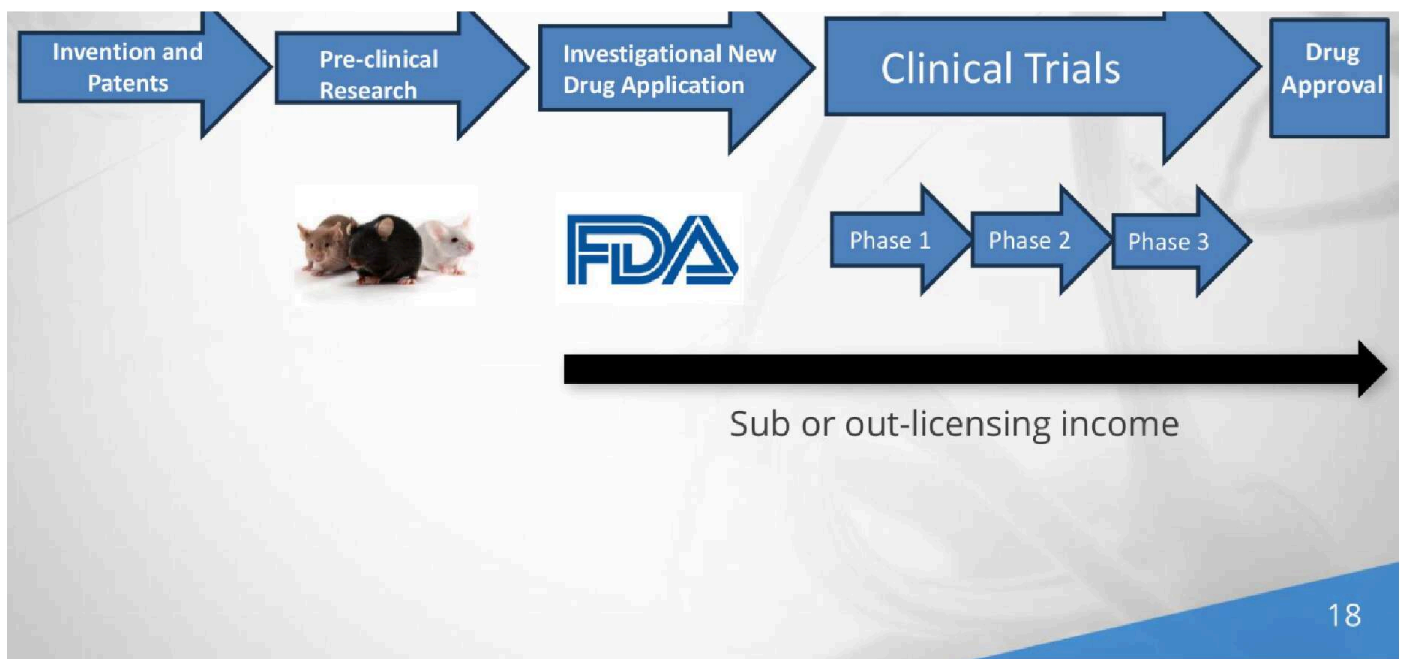
Pavlik et al 2017 Current
Topics in Peptide and
Protein Research 2017
18:1-15

Pavlik et al 2016 Nature Sci
Reports 6:23707 PMID:
27025362

17

NEUROCARRUS

Drug Development



Neurocarrus is early stage in its drug development process:

The company’s studies are “pre-clinical” meaning before testing in humans. Some of these studies are described in our publications and many more are underway. The Phase II SBIR award indicates the company has made very significant progress and intends to pursue clinical trials at the end of the funding period.

Preclinical testing uses animals to ensure drug benefit and safety before human testing. While the company regrets the dependence on using animals there are no alternatives. However, all attempts are made to minimize this testing and federal guidelines are followed closely in these efforts.

After pre-clinical development and approval of an IND (application for investigative drug), human testing, called clinical trials occur. They are divided into three stages, phase I, II and III. Each of these trials focus on specific outcomes, safety then benefit then more safety and benefit. Clinical trials are expensive. Funding will be pursued from multiple sources including the federal government by grants, from private investors and from strategic partnerships.

Finally, approval for distribution and sales of N-001 will be pursued in concert with pharmaceutical companies to benefit from their marketing and distribution networks.



Paul Blum, Ph.D.
CEO U Nebraska-
 Lincoln and UC Santa
 Cruz, 33 years
 protein engineering

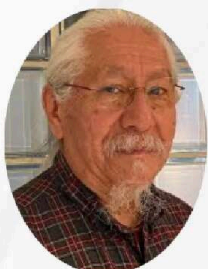


Derek Allen, Ph.D.,
Research Scientist
 University of Nebraska-
 Lincoln

Board



Jianguo Cheng, M.D., Ph.D.
 Professor of Anesthesiology
 Cleveland Clinic, Former
 President of American
 Academy of Pain Medicine



Vicky Valverde-Salas, MD
 M.D. from the U. Madison
 Wisconsin Medical
 School
 twenty years experience
 in running his own private
 practice and Medical
 Primary Care Clinic



Mark Blum, JD
 Attorney licensed in California.
 A 1986 graduate of University of
 California College of the Law, San
 Francisco



Bruce McDonald, JD
 Partner in the intellectual property
 group at Smith, Gambrell &
 Russell, LLP
 Member of the District of
 Columbia Bar

The Neurocarrus team:

Paul Blum, CEO of the company has over 30 years of research experience in protein engineering and microbiology. He leads a multidisciplinary team of investigators including chief scientist Derek Allen, with complementary expertise in pain physiology, protein biochemistry, pharmacology, microscopy, and commercial preclinical drug development.

Continuing efforts to establish drug benefit are led by Stanford University's Dr. David Clark, an expert in post-traumatic chronic pain and pain relief pathways. In addition, the company benefits from widespread interest among scientists and the public in the improvement of pain management.

The Neurocarrus advisory board currently includes doctors and lawyers with a history of interest in human pain and the development of Neurocarrus. Additional members of the company include other scientists and lawyers. Pending new federal funding may add a salaried CFO to the Neurocarrus team to raise private

may also be involved in raising additional venture capital and to coordinate strategic deals.

Advisors and collaborators

NEUROCARRUS



David Clark, MD., Ph.D. Pain Specialist Advisor and Collaborator Director of pain relief service, VAPHCS; Professor of anesthesiology, perioperative, and pain medicine at Stanford Medical Center; Member of Bio-X, Member of Wu Tsai Neurosciences Institute; 30 years' experience in pain research.



Rebecca Wachs, Ph.D., M.Eng. Chronic Pain Specialist Advisor and Collaborator Assistant Professor of Biological Systems Engineering Graduate Chair University of Nebraska-Lincoln



You Zhou, Ph.D. Microscopy Advisor and Collaborator Research Professor University of Nebraska-Lincoln; Director of UNL microscopy research core facility

Government



Business

Neurocarrus Partners

Academic



Legal

