Akelos Inc.

First-in-class HCN1 selective inhibitors for the management of neuropathic pain

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NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some of the information in this slide deck contains forward-looking statements within the meaning of the federal securities laws. Forward-looking statements typically are identified by the use of terms such as “anticipates,” “believes,” “can,” “continue,” “could,” “estimates,” “expects,” “intends,” “may,” “plans,” “potential,” “predicts,” “should,” or the negative of these terms, although some forward-looking statements are expressed differently.

These statements include, among others, those related to:

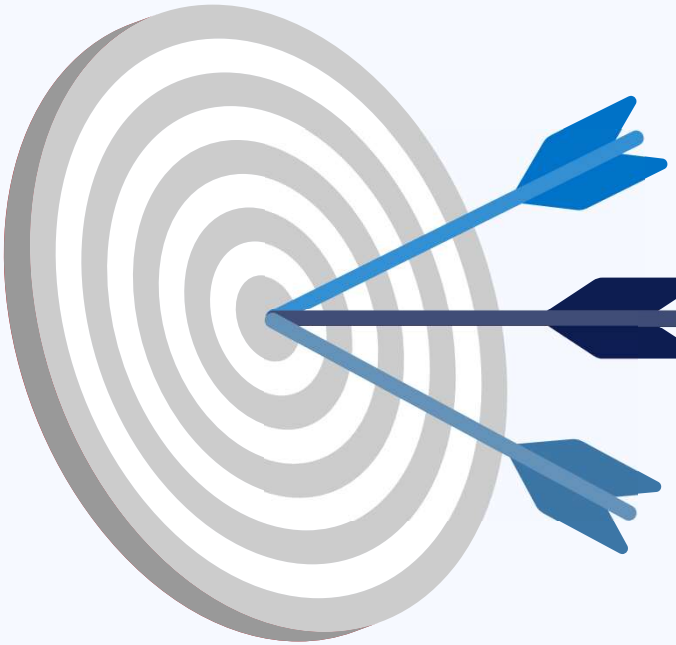
The results of research and development activities	Uncertainties relating to preclinical and clinical testing	The cost, timing and outcome of the regulatory development and approval process	Our budgets, expenditures and financing plans	Our need for substantial additional funds	Patent and intellectual property matters	Our dependence on third parties, including contract research and contract clinical trial organizations	Market opportunity and competition

You should be aware that our business is subject to risks and uncertainties, including the foregoing, that could cause actual results to differ materially from those contained in the forward-looking statements. Readers are cautioned not to place undue reliance on forward-looking statements, which speak only as of the date thereof. We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances on which any such statement is based.

This slide deck also contains projections and forecasts that have been prepared by Akelos for internal use and are based on assumptions about conditions and courses of action that management believes are reasonably possible, but not necessarily probable. Projections or forecasts compiled on the basis of a set of different conditions and courses of action could differ substantially from those included herein. Readers of these projections and forecasts should be aware that some of the conditions and courses of action in management’s assumptions inevitably will not materialize and unanticipated events and circumstances may occur. Therefore, the actual results achieved during the projections or forecasts period will vary from the projections and forecasts, and the variations may be material.

Mission

To support the growing number of patients who suffer from **neuropathic pain**, a taxing condition with limited treatment options.



First in class non-opiate, anti-hyperalgesic therapy specifically for the treatment of neuropathic pain

Active preclinical development program with defined endpoints and outcomes

Experienced team with a track record of launch success

Neuropathic pain is a chronic condition, with substantial risks tied to current treatment options

Treatment Options Plagued with **Side Effects** and **Limited Efficacy**[1]

Gabapentinoids	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Tricyclic antidepressants (TCAs)
Opioids	Topical treatment	Neurotoxin

Based on the clinical evidence review conducted by the CDC[2]

"…long-term opioid use for chronic pain is associated with serious risks including increased risk for opioid use disorder, overdose, myocardial infarction, and motor vehicle injury."

Source: 1. Cavalli et al. *Int J Immunopathol Pharmacol*. 2019. 2. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016.

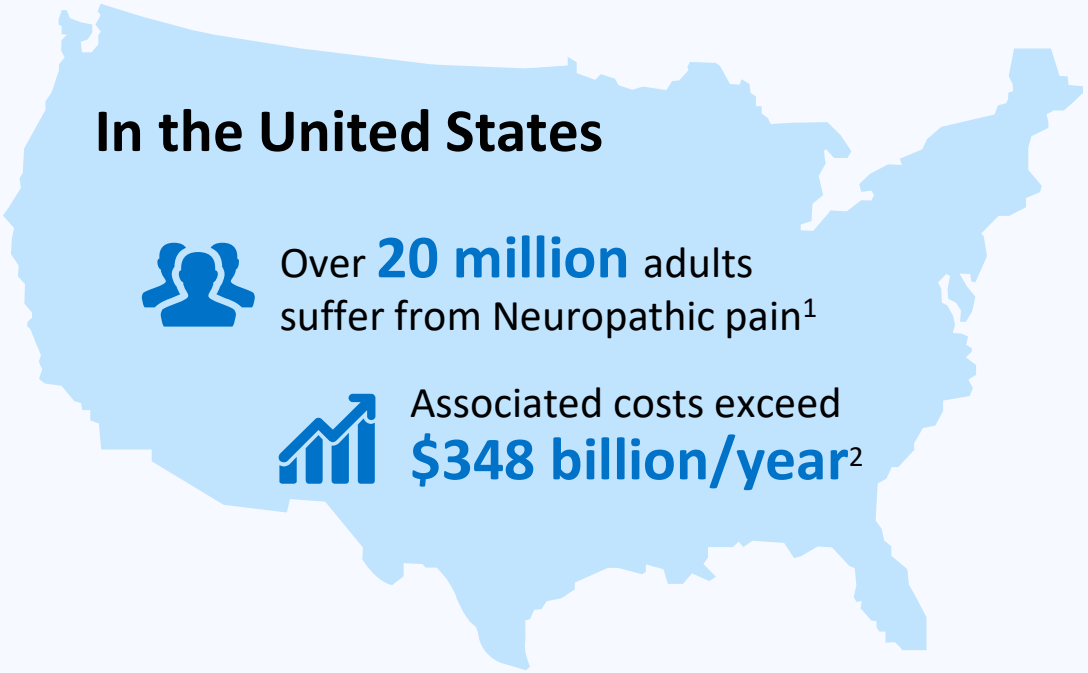
Treatment Guidelines: Poor Risk-Benefit Profile

Low/inconsistent efficacy paired with side-effects

Treatments for Neuropathic Pain		Drugs	Adverse Effect
First Line Therapy	Gabapentinoids	Gabapentin (Gralise®) Pregabalin (Lyrica®)	Lethargy, vertigo, peripheral swelling, blurred vision, increased body weight
	Tricyclic antidepressants (TCAs)	Amitriptyline	Anticholinergic effects, QT prolongation (arrhythmia), suicide risk, urinary retention
	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Duloxetine (Cymbalta®) Venlafaxine (Effexor®)	Nausea, lethargy, constipation, ataxia, dry mouth, vertigo, hyperhidrosis, hypertension
Second Line Therapy	Opioids	Tramadol (Ultram®) Tapentadol (Nucynta®)	Nausea/vomiting, constipation, lethargy, seizures, ataxia
	Topical treatment	Lidocaine, Capsaicin	Local erythema, itching and rash, pain, rare cases of high blood pressure
Third-line therapy	Strong opioids	Morphine, Oxycodone	Nausea, vomiting, constipation, dizziness and lethargy, respiratory depression
	Neurotoxin	Botulinum toxin	Pain at injection site

Source: Cavalli et al. *Int J Immunopathol Pharmacol*. 2019.

Akelos is developing solutions to treat neuropathic pain: a prevalent, costly condition



Worldwide

Valued at **$7.7** billion[3]

$7.7 bn

6.5% CAGR[3]

$7.7bn (2022) → $13bn (2032)

Expected to reach $13.3 billion by 2032[3]

Source: 1. National Institute of Health Fact Sheet, 2022. 2. Vertex Pharmaceuticals, Economic Burden of Treating Chronic Peripheral Neuropathic Pain in the United States: National Estimates From 2022 Data3. Maximize Market Research, December 2023 (Forecast Period 2022-2032)

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage

Major types of pain[1]

Acute Pain	Functional Pain	Chronic Pain	Inflammatory Pain	Neuropathic Pain
Pain that occurs immediately in response to tissue injury. It serves a biologically important function and although unpleasant, is not pathologic.	Pain without obvious origin. Examples include fibromyalgia and irritable bowel syndrome	Any pain lasting longer than 3 months	Inflammation caused by an inappropriate immune system response. Conditions include gout and rheumatoid arthritis	Pain caused by injury to neurons - can arise from injured cells in central nervous system (ex., post-stroke) or peripheral nervous system (ex., sensory nerve transection)

Neuropathic Pain[2]

Derives from numerous conditions and diseases, including:

- Chemotherapy-induced peripheral neuropathy
- Diabetes
- Multiple sclerosis
- Strok
- Limb Amputation

Often chronic

Source: 1. *Journal of Pain & Relief*, Accessed 10-15-20; 2. Brain & Spine Foundation, Accessed 10/2/20

CIPN

Chemotherapy Induced Peripheral Neuropathy

Progressive, enduring, and often irreversible condition: pain, numbness, tingling and sensitivity to cold in the hands and feet (can progress to the arms/legs)

30% of chemotherapy patients and 93% of those receiving platins develop CIPN – common treatment for solid tumors

Often so unbearable that patients discontinue treatment despite increased risk of death

Source: Wolf et al. *Eur J Cancer* 2008; Hall et al. BMC Fam Practice 2008; Freynhagen & Bennett, *BMJ* 2009 ; von Hehn et al., *Neuron* 2012; Colvin L, Rice A. Progress in Pain Medicine. British Journal of Anesthesia 2019.

CIPN is a global problem

2015

17.5 million cancer cases worldwide ▲(33% compared to 2005)[1]

2017

24.5 million cancer cases worldwide (▲40% in two years)[1]

2022

New cancer cases in US 1.9 million[2]

World Health Organization estimates new cancer cases to rise by ▲70% over the next two decades[1]

Depending on chemotherapeutic class, CIPN occurs in up to 90% of patients[1]

No meaningful prevention

No effective therapy

Attractive regulatory path

Source: 1. Aromolaran & Goldstein, Mol Pain 2016Global Burden of Disease Cancer Collaboration, JAMA Oncology 2016, 2019 https://www.marketwatch.com/press-release/cancer-biological-therapy-market-industry-growth-analysis-forecast-by-2025-2019-09-30; 2. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html#:~:text=The%20Facts%20%26%20Figures%20annual%20report,deaths%20in%20the%20United%20States.)

Market Opportunity

PERSISTENCE MARKET RESEARCH

The neuropathic pain market is expected to grow to US$ 9.5 Bn between 2021 and 2031.

The neuropathic pain market, in the last 5 years (2015 and 2020), witnessed a CAGR of 5.5%.

COHERENT MARKET INSIGHTS

The Global Neuropathic Pain Market is estimated to be valued at US$ 7.56 Billion in 2023 and is expected to exhibit a CAGR of 6.2% during the forecast period (2023-2030).

Allied Market Research®

"The overall demand for therapeutic drugs, including neuropathic pain medicines, remains relatively stable during economic downturns due to their essential role in treating health conditions."

Allied Market Research®

Neuropathic pain market is expected to reach **$13.3 Billion** in 2032

Growing at a **CAGR of 5.6% (2022-2032)**

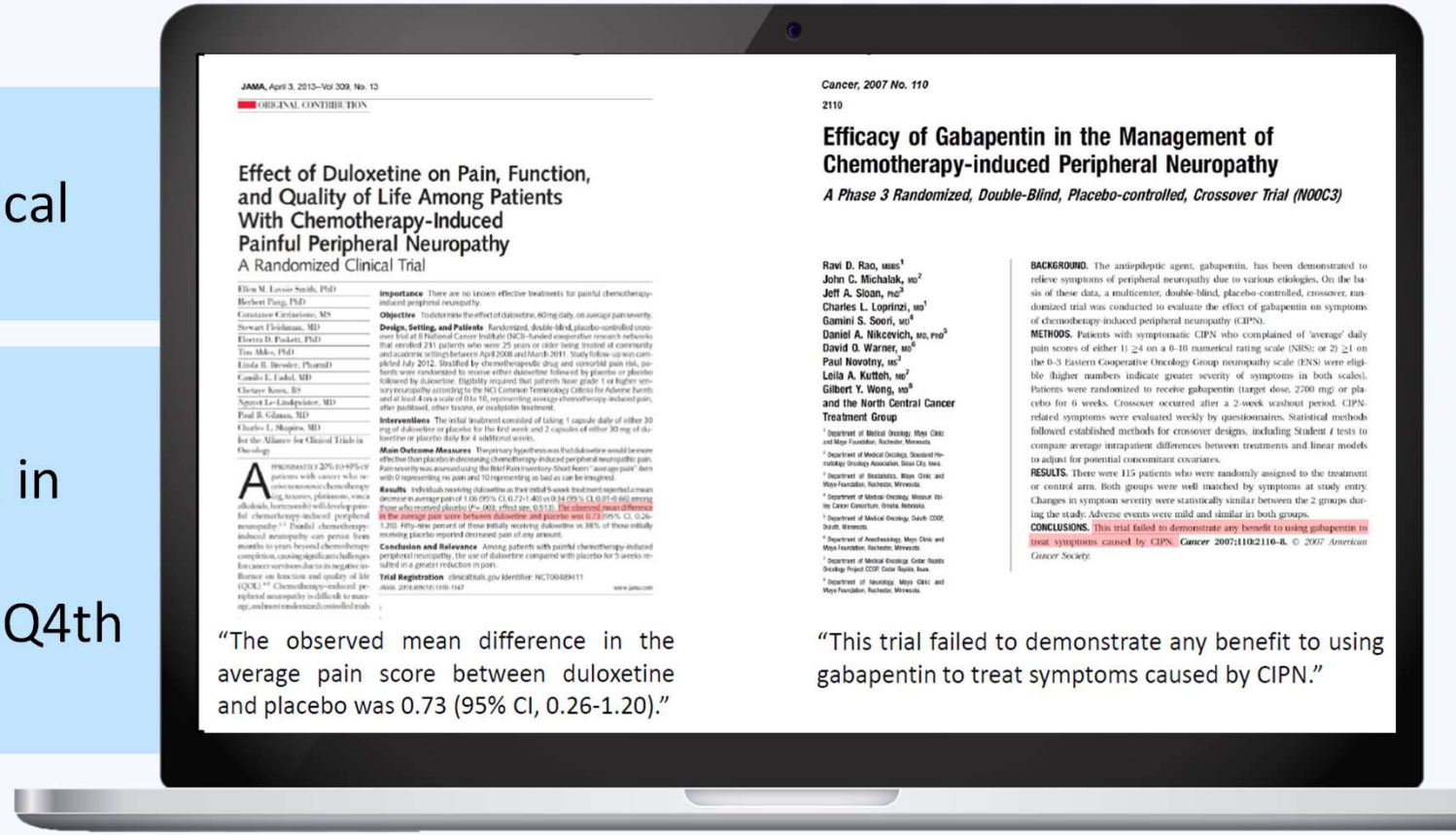
TRANSPARENCY MARKET RESEARCH

"By indication ... chemotherapy induced peripheral neuropathy is projected for most prominent growth rate."

Few Effective Treatments for CIPN Patients

Physicians resort to treatments lacking clinical evidence[1]

Duloxetine resulted in minimal pain reduction in patients with CIPN[2] (Cymbalta®; Lilly, 2018 Q4th sales US$ 184.5M)



JAMA, April 3, 2013—Vol 309, No. 13

ORIGINAL CONTRIBUTION

Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy
A Randomized Clinical Trial

"The observed mean difference in the average pain score between duloxetine and placebo was 0.73 (95% CI, 0.26-1.20)."

Cancer, 2007 No. 110

2110

Efficacy of Gabapentin in the Management of Chemotherapy-induced Peripheral Neuropathy
A Phase 3 Randomized, Double-Blind, Placebo-controlled, Crossover Trial (N00C3)

Ravi D. Rao, MBBS[1]
John C. Michalak, MD[2]
Jeff A. Sloan, PhD[3]
Charles L. Loprinzi, MD[1]
Gamini S. Soori, MD[4]
Daniel A. Nikcevich, MD, PhD[5]
David O. Warner, MD[6]
Paul Novotny, MS[3]
Leila A. Kutteh, MD[7]
Gilbert Y. Wong, MD[8]
and the North Central Cancer Treatment Group

"This trial failed to demonstrate any benefit to using gabapentin to treat symptoms caused by CIPN."

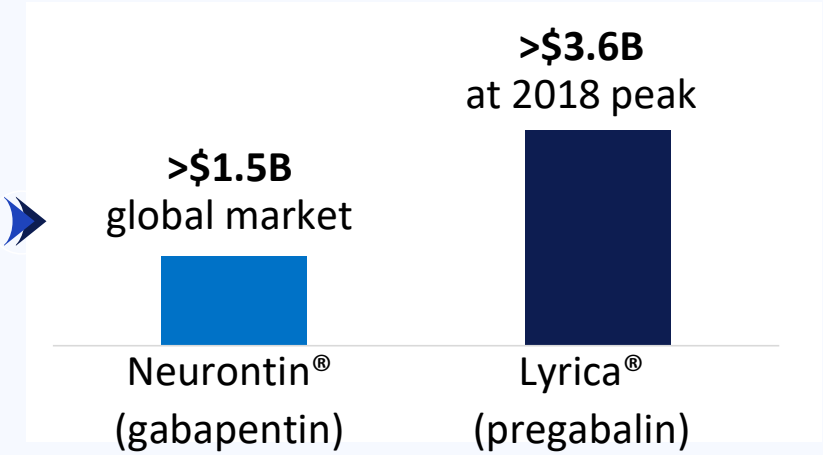
Source: 1. Smith et al. JAMA, 2013. 2. Rao et al. Cancer 2007

Blockbuster Treatments; Limited Efficacy

Patients report unsatisfactory pain relief[1]

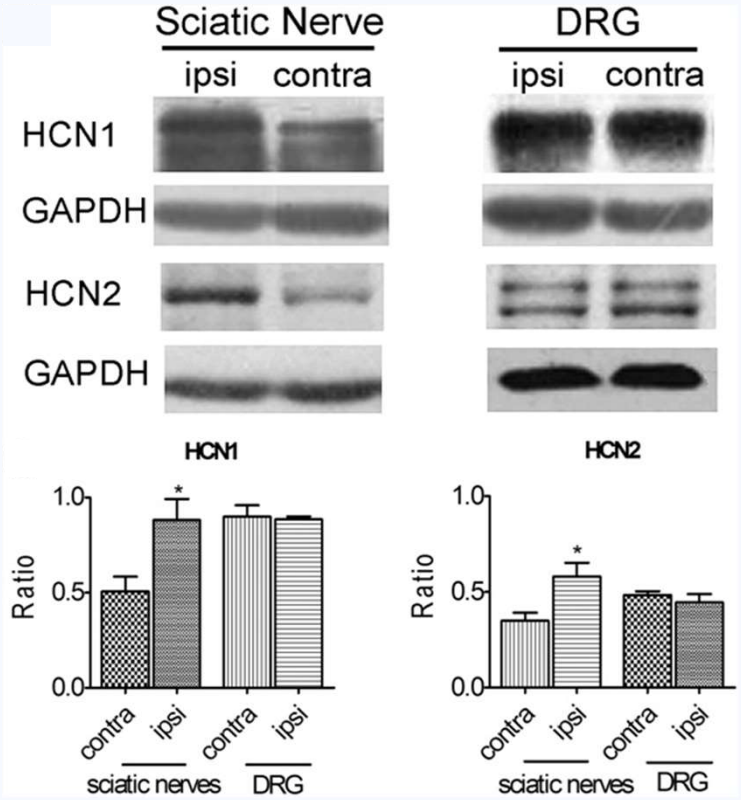
- Complex regimen – wide range of effectiveness
- Burden of trial-and-error therapy regimens
- Forced to choose between benefits and adverse effects

Limited efficacy with gabapentinoids for neuropathic pain despite widespread use[2]



Source: 1. FDA Voice of the Patient, 2016 ; 2. Goodman C, Brett A. *JAMA Intern Med* 2019 3. Gabapentin Market Forecast, 2022 MarketWatch; 4. Fierce Pharma, 2019

HCN1 Expression – Post Peripheral Nerve Injury



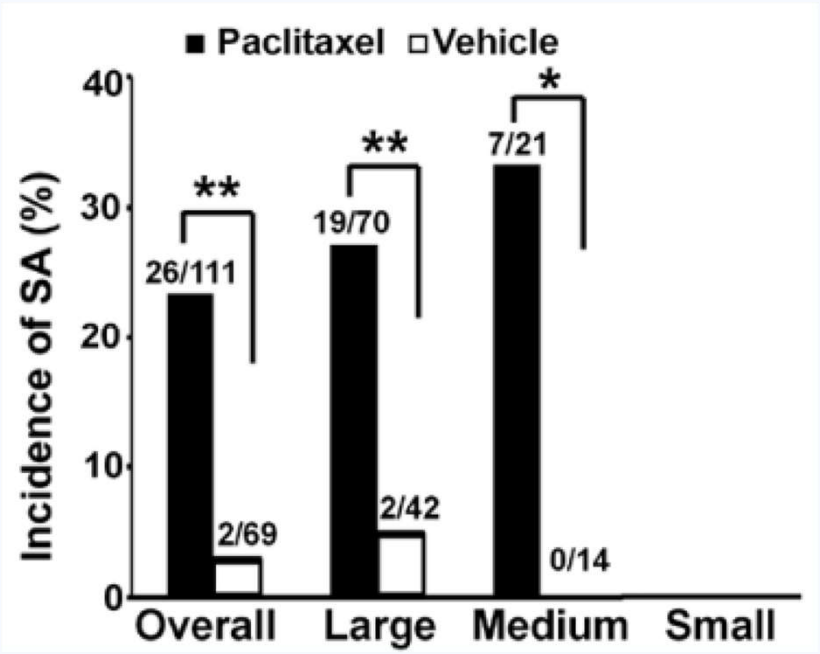
Rat chronic constriction injury model

- Following nerve injury (chronic constriction), HCN1 expression markedly increases in the injured sciatic nerve, but not in the uninjured nerve (contralateral hind limb)
- HCN2 increases as well, but much less than for HCN1

Source: Jiang *et al*. Pain 2008

Paclitaxel Increases Spontaneous Activity in Sensory Neurons*

Significantly increases HCN1 gene expression by ~1.8-fold



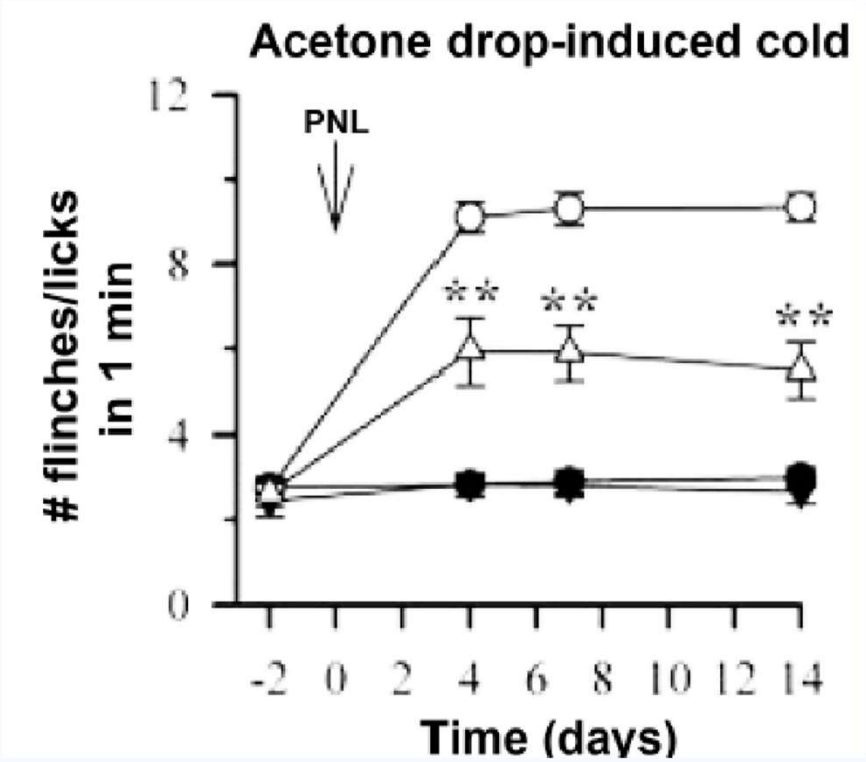
*action potential firing in rat DRG neurons

Gene	Ion Channel	Mean Fold Change	SEM	*P* Value
Accn2	Amiloride-sensitive cation channel 2, neuronal	1.210	0.167	0.335
Cacna1d	$Ca_v1.3$	1.232	0.348	0.573
Cacna1i	$Ca_v3.3$	1.278	0.238	0.363
Hcn1	HCN1	1.758**	0.064	0.007
Kcna2	$K_v1.2$	1.566*	0.066	0.013
Kcna5	$K_v1.5$	0.689	0.116	0.115
Kcnab2	$K_v\beta2$	1.206	0.160	0.327
Kcnd2	$K_v4.2$	1.327	0.078	0.053
Kcnh1	$K_v10.1$	1.260	0.136	0.195
Kcnh7	$K_v11.3$	1.452*	0.077	0.028
Kcnj1	$K_v1.1$	0.730*	0.048	0.031
Kcnj13	$K_v1.4$	1.449	0.218	0.175
Kcnj15	$K_v4.2$	1.646	0.211	0.092
Kcnj16	$K_v5.1$	1.252	0.482	0.653
Kcnj3	$K_v3.1$	1.356*	0.036	0.011
Kcnj5	$K_v3.4$	0.655*	0.051	0.030
Kcnk1	$K_{2p}1.1$	0.752*	0.046	0.033
Kcnn2	$K_{Ca}2.2$	1.233	0.058	0.119
Kcnq1	$K_v7.1$	2.010	0.386	0.120
Kcnq3	$K_v7.3$	1.248	0.126	0.192
Ryr3	Brain ryanodine receptor-calcium release channel	1.528*	0.089	0.027
Scn1a	$Na_v1.1$	1.326	0.268	0.375
Scn1b	$Na_v\beta1$	1.299	0.331	0.481
Scn8a	$Na_v1.6$	1.205	0.223	0.455
Scn9a	$Na_v1.7$	1.258**	0.017	0.004
Slc12a5	KCC2	1.287	0.277	0.409
Trpm1	TRPM1	0.733	0.094	0.105
Trpm6	TRPM6	1.382	0.111	0.075
Trpm8	TRPM8	1.210	0.133	0.254
Trpv1	TRPV1	1.215	0.079	0.113
Trpv3	TRPV3	1.997*	0.140	0.019

Data are expressed as fold change (paclitaxel/vehicle).*P < 0.05, **P < 0.01, one-sample t test (n = 3/gene), without Bonferroni correction.

Source: Zhang & Dougherty Anesthesiology 2014

HCN1 Contributes to Cold Allodynia



** P < 0.01

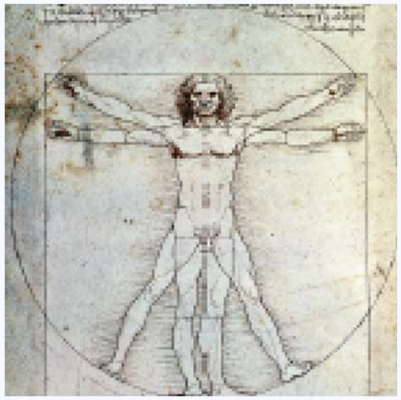
Source: Momin et al. J Physiol 2008

Target engagement HCN1 in human sensory neurons

In humans, HCN1 mRNA is present in a larger proportion of DRG neurons than is HCN2 (~2.1-fold). In mice, HCN2 mRNA-positive and HCN1 mRNA-positive DRG neurons are seen with the same frequency[1]

In humans, HCN1 mRNA is present at twice the level of that for HCN2, and ~11-fold and ~29-fold than that for HCN3 and HCN4, respectively[2]

Functional (electrophysiologic) analysis suggests that HCN1 is the primary isoform in human sensory neurons[3]



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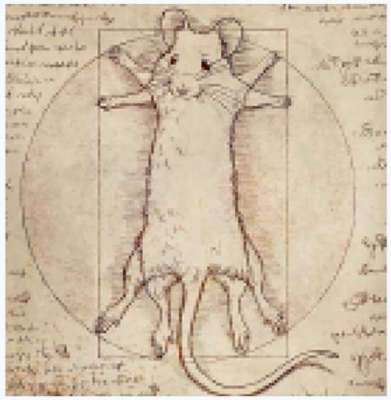


Source: 1. Shiers et al. Pain 2020 2. North et al. Brain 2019 3. Young et al. *Mol Ther* 2014

Additional evidence identified in key journals

nature

Article | Published: 31 July 2024

Propofol rescues voltage-dependent gating of HCN1 channel epilepsy mutants

Elizabeth D. Kim, Xiaoan Wu, Sangyun Lee, Gareth R. Tibbs, Kevin P. Cunningham, Eleonora Di Zanni, Marta E. Perez, Peter A. Goldstein, Alessio Accardi, H. Peter Larsson & Crina M. Nimigean

Nature **632**, 451–459 (2024) | Cite this article

Further defining the underlying mechanism of action of propofol[1]

Identified the binding site for a clinically important class of molecules that target the human HCN1 ion channel. These findings will guide efforts for novel drug development for poorly treated neurologic disorders in which HCN1 channels play a role.

Cell Chemical Biology

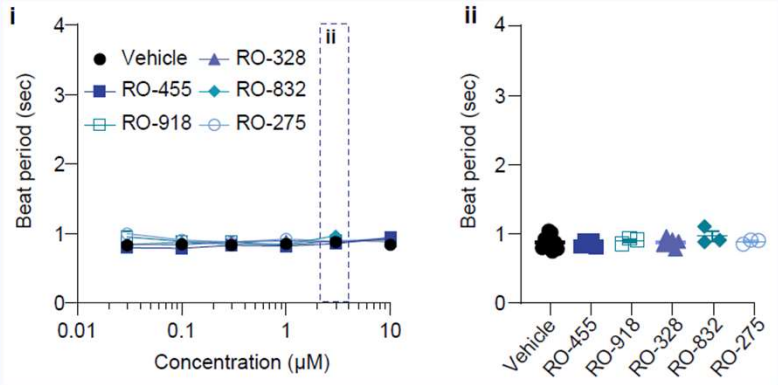
Volume 31, Issue 3, 21 March 2024, Pages 577-592.e23

Article

Selective and brain-penetrant HCN1 inhibitors reveal links between synaptic integration, cortical function, and working memory

Demonstrated that selective HCN1 inhibition does not affect electrophysiological properties of human inducible pluripotent stem-cell-derived atrial-like cardiomyocytes.[2]

Concordant with data indicating that HCN2 and HCN4 are the primary isoforms present in human cardiac tissues.



Source: 1. Kim, E.D., Wu, X., Lee, S. et al. Propofol rescues voltage-dependent gating of HCN1 channel epilepsy mutants. *Nature* 632, 451–459 (2024). https://doi.org/10.1038/s41586-024-07743-z
2. Harde E, Hierl M,Weber M, et al. Selective and brain-penetrant HCN1 inhibitors reveal links between synaptic integration, cortical function, and working memory, *Cell Chemical Biology* 3, 577-592 (2024). https://doi.org/10.1016/j.chembiol.2023.11.004

Akelos' anchor-tethered warhead concept

Structural Concepts

AKE-1018
Small Molecule (SM)

ANCHOR

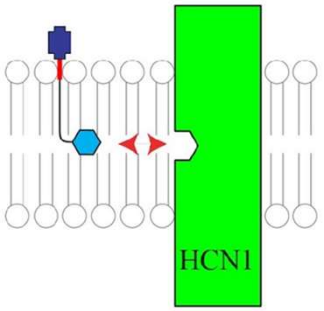
COUPLING
Hydrophilic chemistry with length to reach from anchor attachment to the hydrophobic aspect of the plasma membrane

LINKER
Hydrophobic chemistry with length and geometry to optimize reach and orientation of the pharmacophore

PHARMACOPHORE
Tethered analgesic 26DTB-P or analogue with enhanced anti-HCN1 potency/selectivity

Mechanistic Concepts

AKE-1018
Hydrophilic anchor retained in the extracellular space

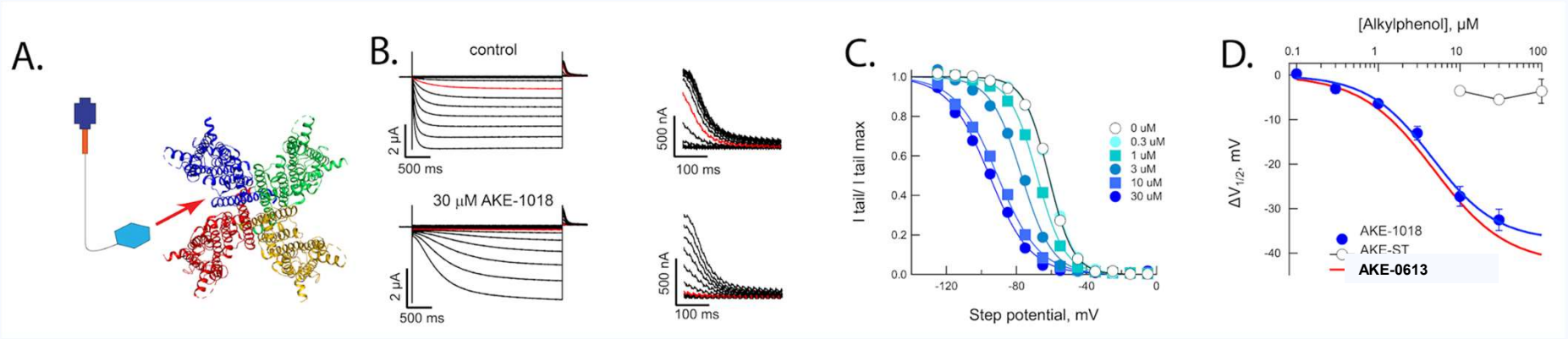


ORAL

Concentrating activity at the site of action to improve safety and efficacy

AKE-1018: Efficacy against target

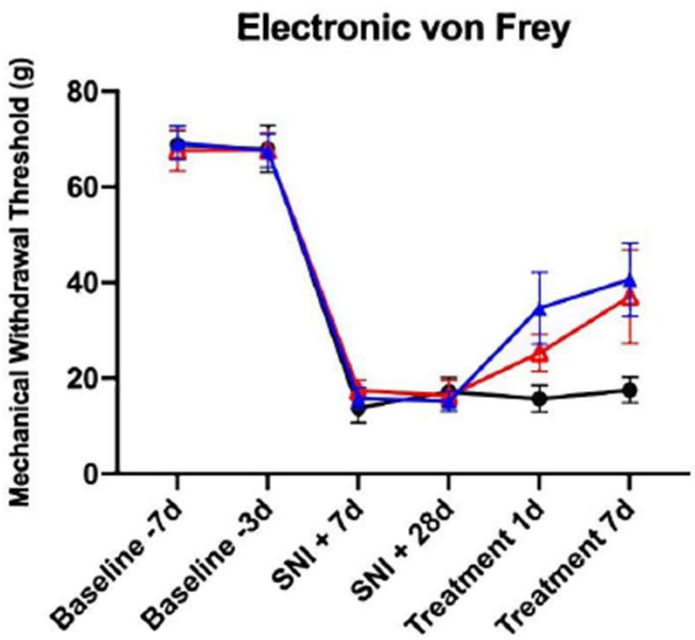
Inhibits HCN1 Function in a Concentration- Dependent Manner

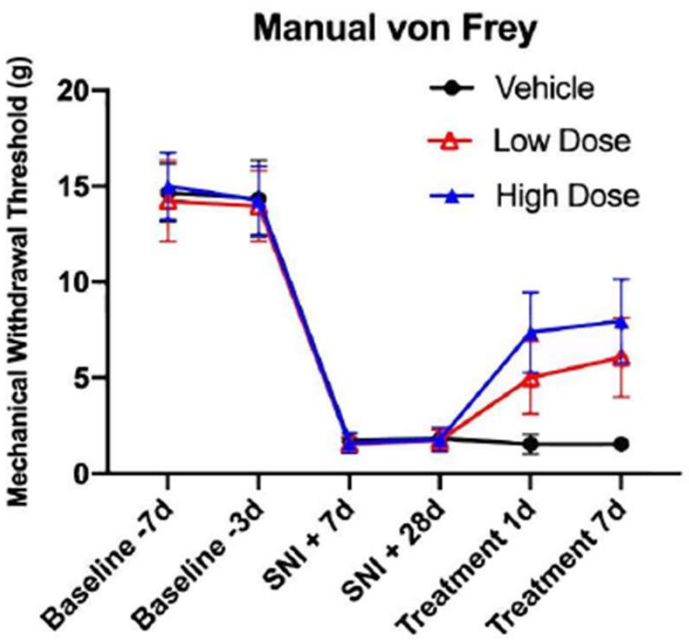


Two-electrode voltage clamp recordings from Xenopus oocytes expressing HCN1

AK-1018: Antihyperalgesic efficacy in Rat Nerve-Injury Model

Relieves nerve injury-induced mechanical allodynia, dose-dependent





Statistically significant efficacy

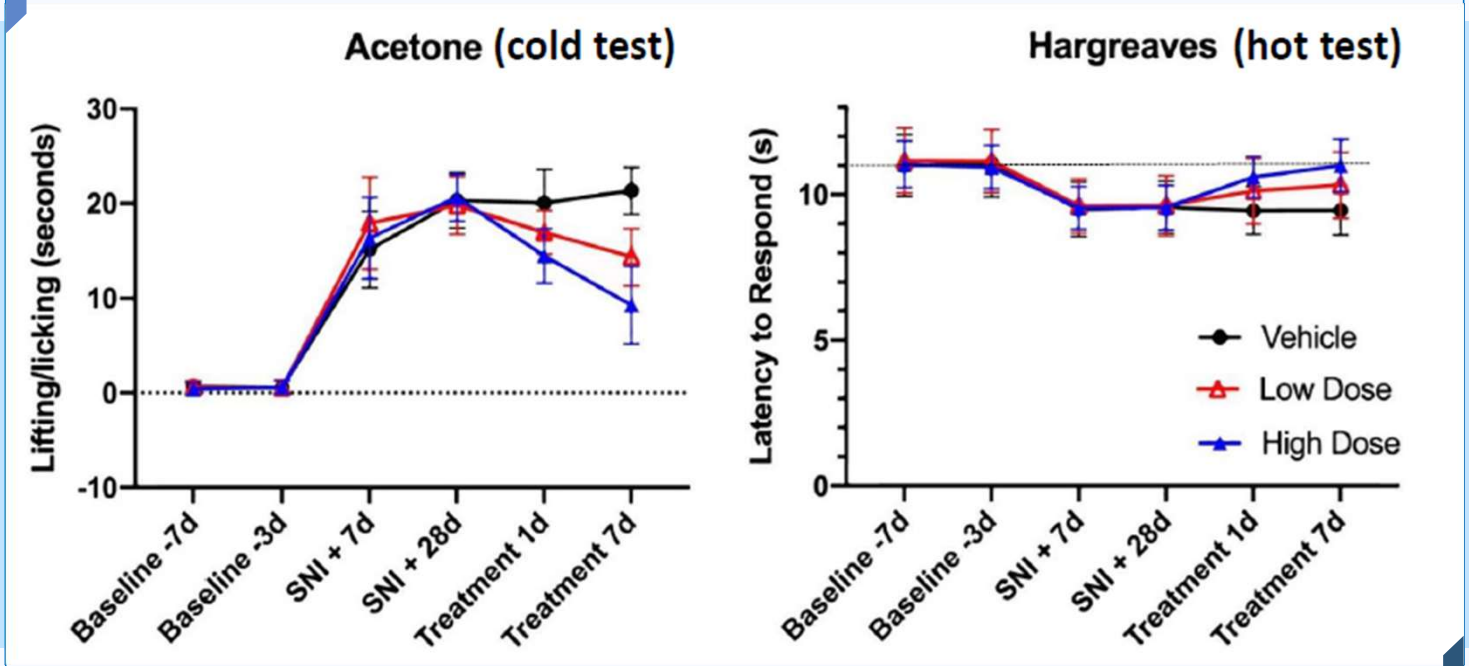
Reductions in probability of response to mechanical and thermal stimulation following nerve injury

N = 12 animals (male rats) per group total # groups 3. Comparable results observed in females. Low dose 0.58 mmole/kg; high dose 1.74 mmole/kg.

Tibbs et al. Br J Anaesth. 2023 Aug 9;131(4):745–763

AK-1018: Antihyperalgesic efficacy in Rat Nerve-Injury Model

Relieves nerve injury-induced thermal hyperalgesia in a dose-dependent manner



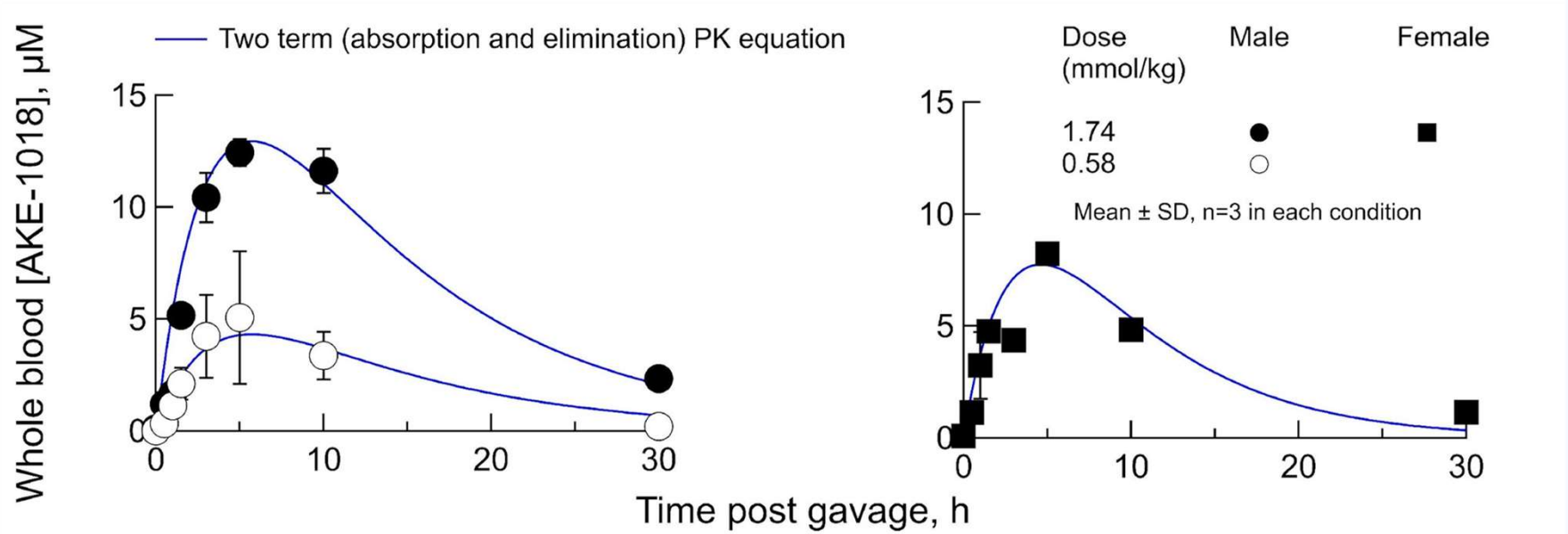
Statistically significant efficacy

Reductions in time of response to thermal stimulation following nerve injury

N = 12 animals (male rats) per group total # groups 3. Comparable results observed in females. Low dose 0.58 mmole/kg; high dose 1.74 mmole/kg.

Tibbs et al. Br J Anaesth. 2023 Aug 9;131(4):745–763

AKE-1018: Orally bioavailable



Following a single bolus, LC-MS/MS analysis shows AKE-1018 blood concentration persistently exceeds the IC_{50} for inhibition of HCN1 (5 µM)

Tibbs et al. Br J Anaesth. 2023 Aug 9;131(4):745–763

AKE-1018: Designed exclusion from the CNS

PREDICTION:	A CNS MPO score below 4 predicts CNS exclusion The CNS MPO score for AKE-1018 is 2.25
OBSERVATION:	AKE-1018 was gavaged at 1.74 mmol/kg on 7 consecutive days Tissue distribution was determined by LC-MS/MS following acetonitrile extraction AKE-1018 in Brain << AKE-1018 in Peripheral Tissues 100-fold
SIGNIFICANCE:	Precludes inhibition of central HCN1 Minimizes risk of adverse CNS side effects

CNS MPO: Central Nervous System Multiparameter Optimization.

THE LEAD NCE – AKE-1018

Effective

- Orally bioavailable
- Potent and efficacious inhibitor of HCN1
- Effectively anchored to the lipid membrane extracellular leaflet *in silico*
- Effectively relieves mechanical and thermal hypersensitivity in male and female rats
- Excluded from the CNS as designed

Safe –
at doses > 10X the lowest efficacious dose

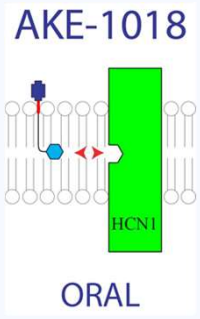
⚠ Does not produce changes in heart rate or blood pressure

⚠ Does not produce changes in motor strength/coordination or activity (non-sedating)

⚠ Does not show potential for abuse/addiction – a hallmark of opioids

AKE-1018 – Cost through Phase I

Value proposition



Exclusive license to IP

Partnership (sponsored research) with Cornell to develop HCN1 inhibitors

Efficacy and safety

Demonstrated in lead compounds in extensive preclinical testing

Grant-funded research

$8 million prior academic research funding for Goldstein Lab

$1.7 million research grant from the NIH to Cornell team working with Akelos

$3.69 million Phase I/II Fast-Track Small Business Technology Transfer (STTR) grant from the National Institute of Neurological Disorders and Stroke (NINDS).

Next Steps

Akelos is seeking an $14 million dollar investment

Fund pre-clinical drug development and IND enabling studies for their two lead programs

Build out R&D and regulatory teams in anticipation of Phase 1 trials

Team

Peter Goldstein, MD

Scientific Advisory Board & Scientific Co-Founder

Principal Investigator in the C.V. Starr Laboratory for Molecular Neuropharmacology, Weill Cornell Medical College

18+ years in the Department of Anesthesiology at Weill Cornell Medical Center

Steven R. Fox, DDS

President & Chief Executive Officer

20+ years of success as an entrepreneur
Medal of Freedom recipient
Ernst & Young Entrepreneur of the Year
Former CEO of public oral care company
40 years as Doctor of Dental Surgery
Chairman, The Rebel Group
Former Faculty of Harvard University & New York University

Gareth Tibbs, PhD

Scientific Advisory Board & Scientific Co-Founder

Leading authority on HCN channel function

Leading authority with deep domain expertise in biophysics of HCN channel function

B.A. and Ph.D. from University College, London; London and Dundee University in Scotland

Robert Benson, PhD

IP Advisor

Over 20 years of experience in licensing and intellectual property
Principal of South Shaker Associates
Former department head of Harvard University
Former supervisor at the National Institute of Health

Peter Hutt, JD

FDA Counsel

50+ years as a food and drug law specialist
Former Chief Counsel, Food and Drug Administration
Senior Counsel, Covington & Burling LLP, specializing in Food and Drug law
Faculty member, Harvard Law School

Strategic Advisors

Cyrus Arman, PhD, MBA

Head of Business Development

Tenured experience in corporate, clinical, and commercial strategy for biotechnology companies including Amgen, Nimble Therapeutics, and NEUVOGEN, Inc.
Former President and Principal Operating Executive for CytoDyn, Inc.
MBA, PhD and MS in from the University of Southern California and a BS in from the University of California San Diego

Senator Thomas Daschle

Strategic Healthcare Advisor

Serves on the Health Policy and Management Executive Council at the Harvard School of Public Health
Member of the Council on Governance for Sustainability at the World Economic Forum & the Federal Advisory Board of Accenture
Chair of the DuPont Advisory Committee on Agriculture Innovation and Productivity

Distinguished Scientific Advisory Board

Darryle D. Schoepp, Ph.D
Strategic Advisor
30+ years in Pharmaceutical Research and Drug Discovery
Former SVP, Neuroscience Research Head at Merck; VP, Neuroscience Delivery Research at Eli Lilly and Co.
Over 200 publications.,19,000 citations., and 15 US patents

Michael Levitt, PhD
Acclaimed Biophysicist
Robert W. & Vivian K. Cahill Professor in Cancer Research in the Stanford School of Medicine
Recipient of the 2013 Nobel Prize in Chemistry

Dianna Willis, PhD
Prominent Pain Researcher
Head, Laboratory for Axonal and RNA Biology, Director of the Center for Pain Research, and Associate Director at the Burke Neurological Institute
Assistant Professor of Neuroscience at Weill Cornell Medicine
Director, Burke-Blythedale Program in Pediatric Clinical Neuroscience

J. David Warren, PhD
Biochemistry Expert and Team Leader
Staff Scientist in the Yale Center for Molecular Discovery
Adjunct Professor of Biochemistry at Weill Cornell Medicine
Former member and team leader, the Sandra and Edward Meyer Cancer Center
Co-founder and Scientific Advisory Board member of Unii Therapeutics

Charles Berde, MD PhD
Principal Investigator and KOL
Sara Page Mayo Chair in Pediatric Pain Medicine and Director Pain Treatment Services, Boston Children's Hospital
Professor of Anesthesia (Pediatrics) at Harvard Medical School

Scott L. Dax, MS, PhD
Research and Development Champion
Former Chief Scientific Officer at CerSci Therapeutics
Analgesics research team leader at Johnson & Johnson
Inventor of over 100 issued patents worldwide; over 100 abstracts/publications

Vision for the future – Disruptive Therapeutics

Akelos is developing first-in-class, novel mechanism of action, therapeutics

For Neuropathic Pain

- Poor treatment options
- Market projected to grow
- It is the right time

As a Generalizable Platform

Akelos is seeking:

$14 million dollars for AKE-1018

- Fund preclinical drug development and IND enabling studies for their two lead programs
- Build out R&D and Regulatory teams in anticipation of Phase 1 trials

$1.5 million dollars for AKE-XG

- Novel platform technology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