Developing Novel Non-Opioid Treatments for Pain:
An Overview of Xenon's Nav1.7 and Kv7 Programs

OCTOBER 6, 2025

Forward Looking Statement/Safe Harbor

This slide presentation and the accompanying oral commentary contain forward-looking statements that involve risks, uncertainties and assumptions. If the risks or uncertainties ever materialize or the assumptions prove incorrect, our results may differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact could be deemed forward-looking and include statements regarding the timing of and potential results from clinical trials; the potential efficacy, safety profile, future development plans in current and anticipated indications, addressable market, regulatory success and commercial potential of our and our partners' product candidates; the efficacy of our clinical trial designs; our ability to successfully develop and achieve milestones in our azetukalner and other pipeline development programs, such as XEN1120 and XEN1701, including the anticipated filing of INDs and NDAs; the timing and results of our interactions with regulators; our ability to successfully develop and obtain regulatory approval of azetukalner and our other product candidates, including XEN1120 and XEN1701; anticipated timing of topline data readout from our clinical trials of azetukalner; and our expectation that we will have sufficient cash to fund operations into 2027.

These forward-looking statements are based on current assumptions that involve risks, uncertainties and other factors that may cause the actual results, events, or developments to be materially different from those expressed or implied by such forward-looking statements. These risks and uncertainties, many of which are beyond our control, include, but are not limited to: clinical trials may not demonstrate safety and efficacy of any of our or our collaborators' product candidates; promising results from pre-clinical development activities or early clinical trial results may not be replicated in later clinical trials; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; our ongoing discovery and pre-clinical efforts may not yield additional product candidates; any of our or our collaborators' product candidates, including azetukalner, XEN1120 and XEN1701 may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; we may not achieve additional milestones in our proprietary or partnered programs; regulatory agencies may impose additional requirements or delay the initiation or completion of clinical trials; the impact of market, industry, and regulatory conditions on clinical trial enrollment; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; the impact of new or changing laws and regulations; the impact of unstable economic conditions in the general domestic and global economic markets; adverse conditions from geopolitical events; as well as the other risks identified in our filings with the U.S. Securities and Exchange Commission and the securities commissions in British Columbia, Alberta, and Ontario. These forward-looking statements speak only as of the date hereof and we assume no obligation to update these forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.

Welcome | Today's Speakers

Ian Mortimer
President and Chief Executive Officer

Chris Kenney, MD, FAAN
Chief Medical Officer

Jim Empfield, PhD
Executive Vice President, Drug Discovery

JP Gilbert, PhD
Senior Director, Biology

Agenda

- **Introductions | Corporate Overview**
- Pain Signaling and the Role of Ion Channels
- Xenon's Early-Stage Pain Programs Targeting Kv7 & Nav1.7
- Addressing Unmet Needs | Next Steps | Conclusions
- Q & A

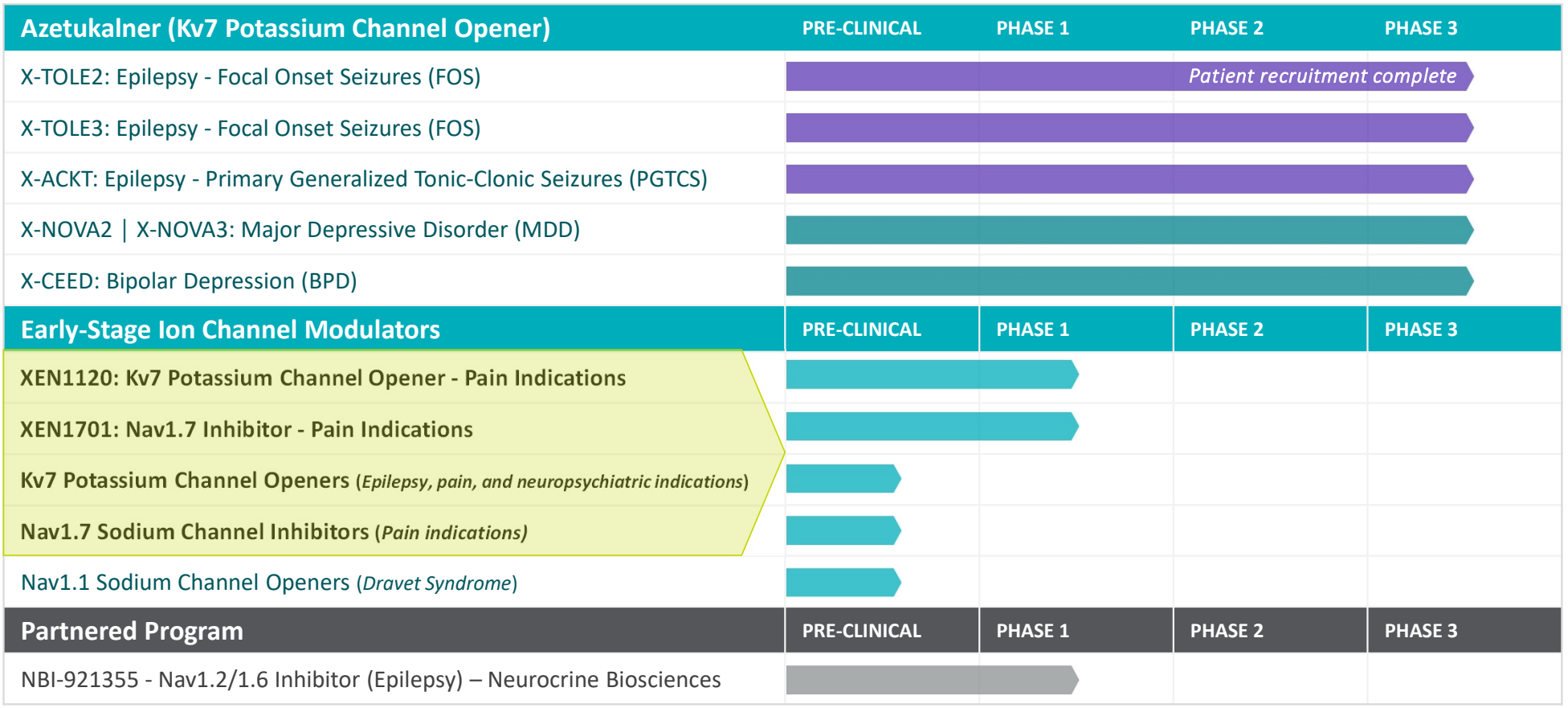
About Xenon Pharmaceuticals

- Neuroscience-focused biopharmaceutical company and leader in small molecule, highly selective ion channel drug discovery and development
- Our lead molecule, azetukalner, is a highly potent Kv7 channel opener in Phase 3 development in epilepsy and depression*
  - Represents the most advanced, clinically validated potassium channel modulator in late-stage clinical development across multiple indications and the only Kv7 program with 700+ patient-years of efficacy & safety data
- Strong financial position

We are advancing a robust early-stage pipeline of therapeutic candidates targeting selective potassium and sodium channels across various indications

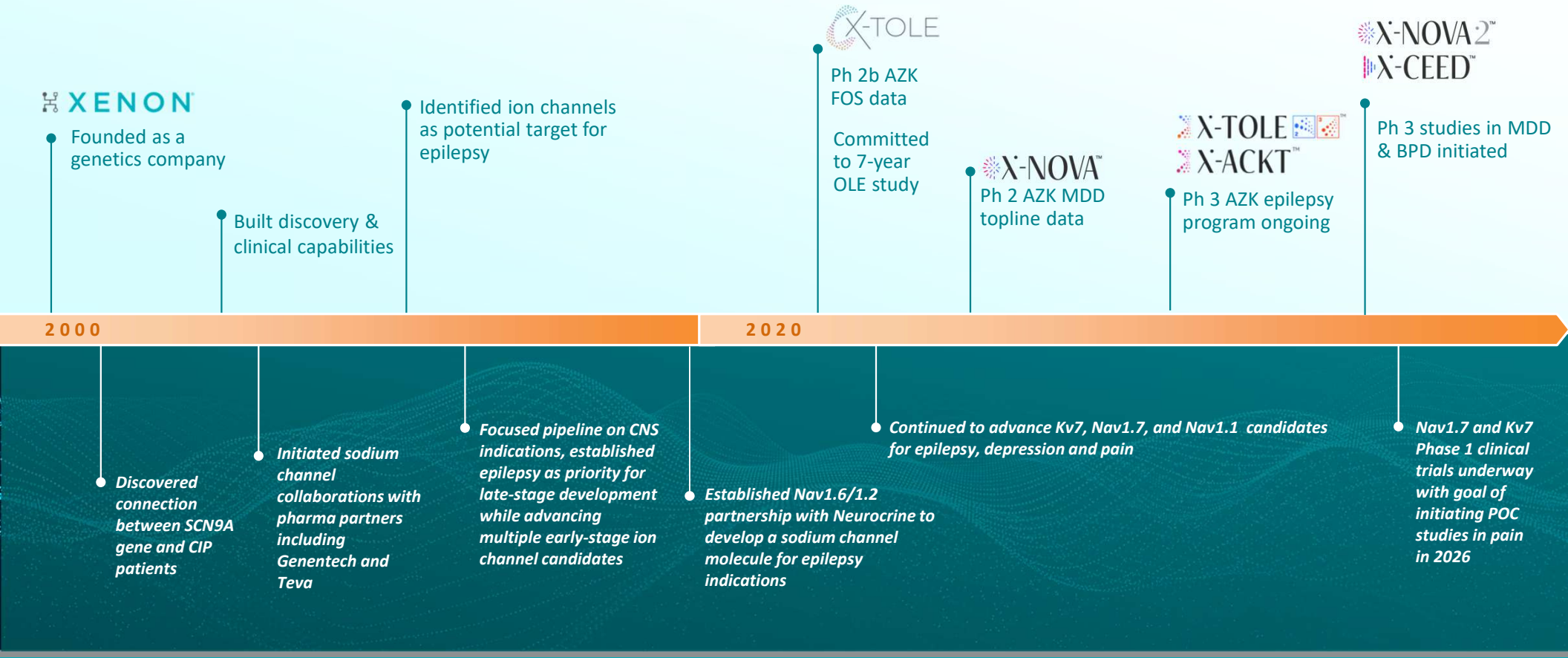
* Comprehensive intellectual property portfolio with patent coverage extending to at least 2040, absent any extensions of patent term

Xenon's Neuroscience-Focused Pipeline



This chart displays pipeline drug candidates currently undergoing clinical and pre-clinical testing in a variety of disease indications. The safety and efficacy of these investigational drug candidates have not been fully evaluated, and they have not yet been approved for use by any regulatory authorities.

Xenon's Deep History in Ion Channel Discovery & Development



Leadership in Developing Next-Gen Ion Channel Therapeutics

In Vivo
- Genetically engineered animal models (epilepsy & pain)
- EEG recordings
- Pharmacokinetics

Pre-clinical Tox

Biology
- Electrophysiology
- Screening
- Computational

Chemistry
- Medicinal
- Computational
- CMC

Compound Properties
- Bioanalytical
- In vitro properties

Xenon has extensive in-house discovery capabilities built over decades

Agenda

Introductions | Corporate Overview

Pain Signaling and the Role of Ion Channels

Xenon's Early-Stage Pain Programs Targeting Kv7 & Nav1.7

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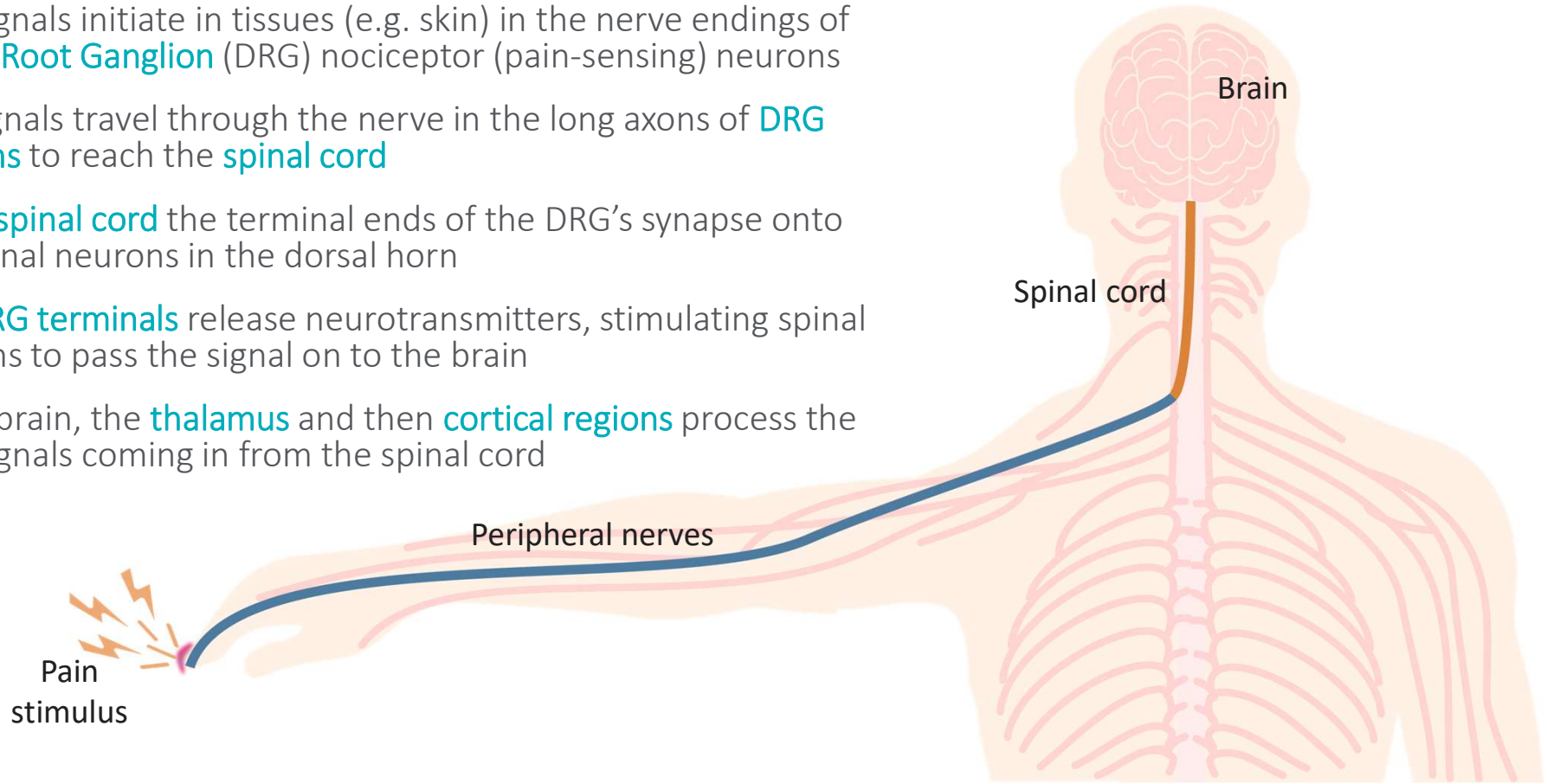
Q & A

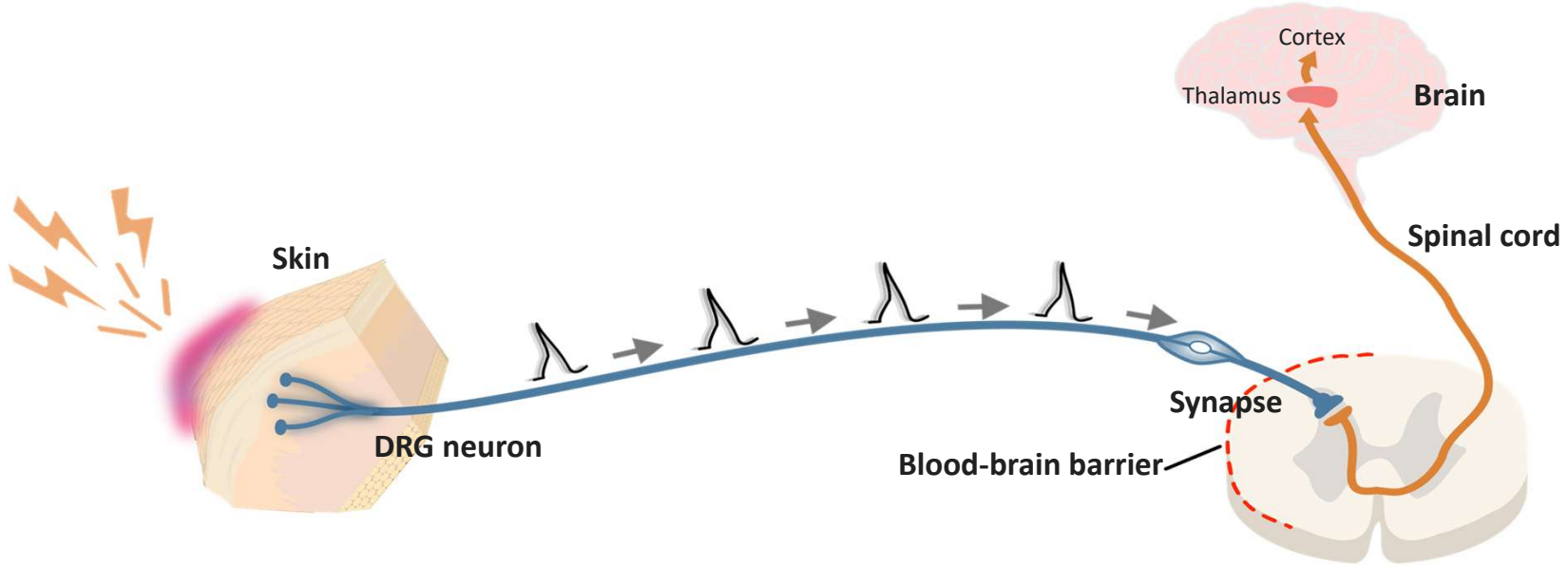
Overview of Pain Signaling Pathway

- Pain signals initiate in tissues (e.g. skin) in the nerve endings of Dorsal Root Ganglion (DRG) nociceptor (pain-sensing) neurons
- The signals travel through the nerve in the long axons of DRG neurons to reach the spinal cord
- In the spinal cord the terminal ends of the DRG's synapse onto the spinal neurons in the dorsal horn
- The DRG terminals release neurotransmitters, stimulating spinal neurons to pass the signal on to the brain
- In the brain, the thalamus and then cortical regions process the pain signals coming in from the spinal cord



Analgesics Act Along Different Points of the Pain Pathway

Transduction	Transmission	Relay / Neuro-Transmitter Release	Modulation / Central Perception
▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include: Nav1.8 inhibitors; local anesthetics; NSAIDs; antihistamines	▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include Nav1.8 inhibitors; local anesthetics; α2 agonists	▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include: gabapentinoids; NSAIDs; COX2 inhibitors	▪ Examples include: Opioids; cannabinoids; acetaminophen; NMDAR antagonists (ketamine)



Source: Adapted from Martin, E. (2018). *Pathophysiology of Pain*

Transduction: Conversion of Pain Stimuli into an Electrical Signal

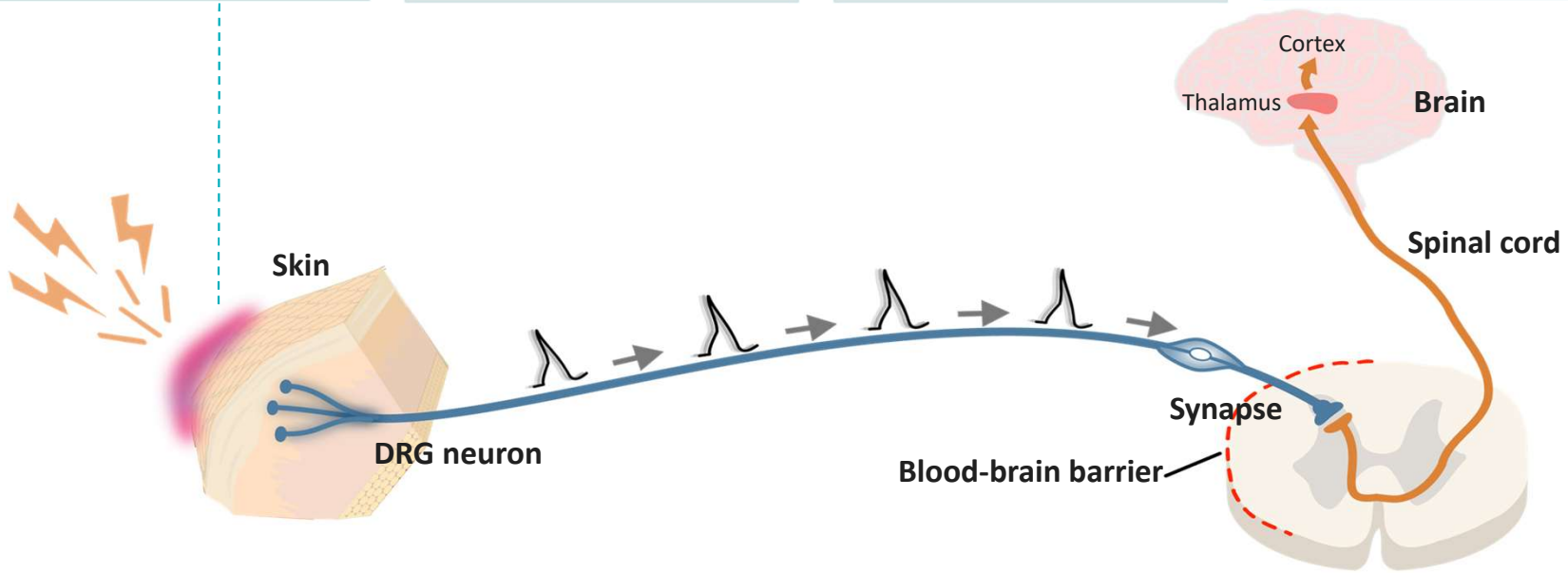
Transduction

- **Kv7 potentiator**
- **Nav1.7 inhibitor**
- Other examples include: Nav1.8 inhibitors; local anesthetics; NSAIDs; antihistamines

Transmission

Relay / Neuro-Transmitter Release

Modulation / Central Perception



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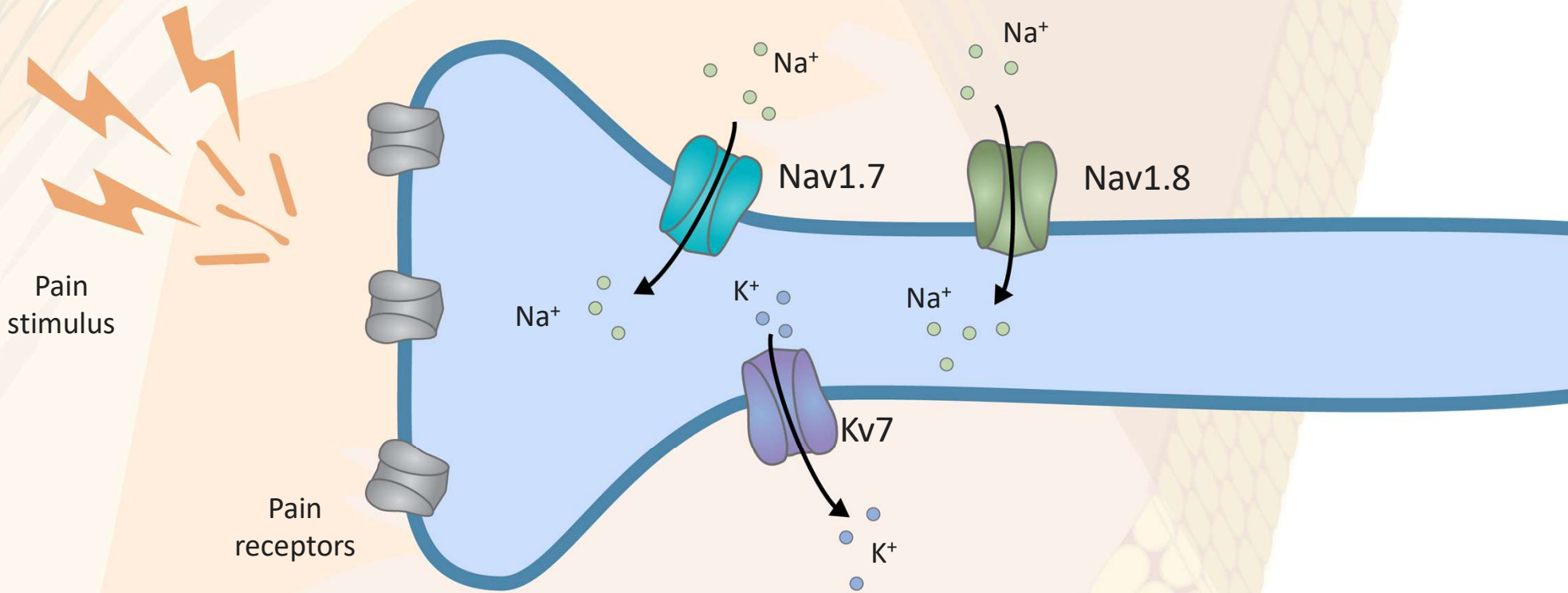
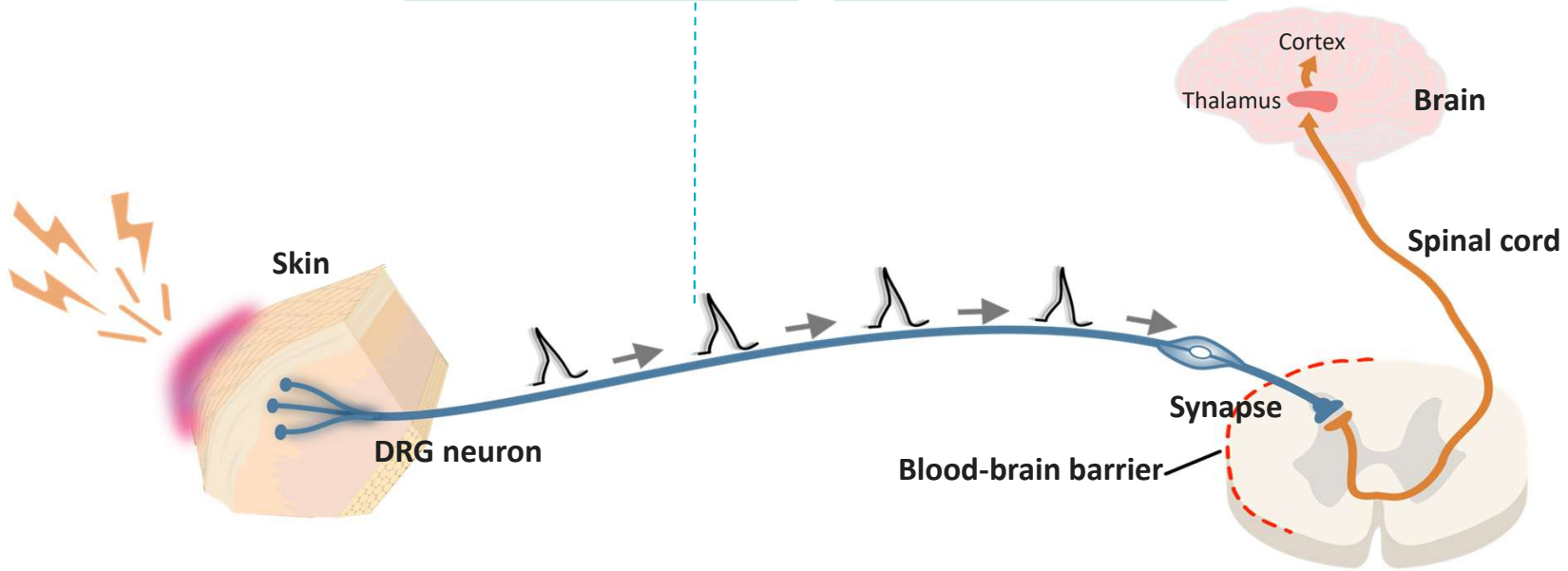
Nociceptor (terminal of sensory neuron)



Transmission: Relay of the Electrical Signal Along Pain Pathway

Transduction	**Transmission**	Relay / Neuro-Transmitter Release	Modulation / Central Perception
	▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include Nav1.8 inhibitors; local anesthetics; α2 agonists		



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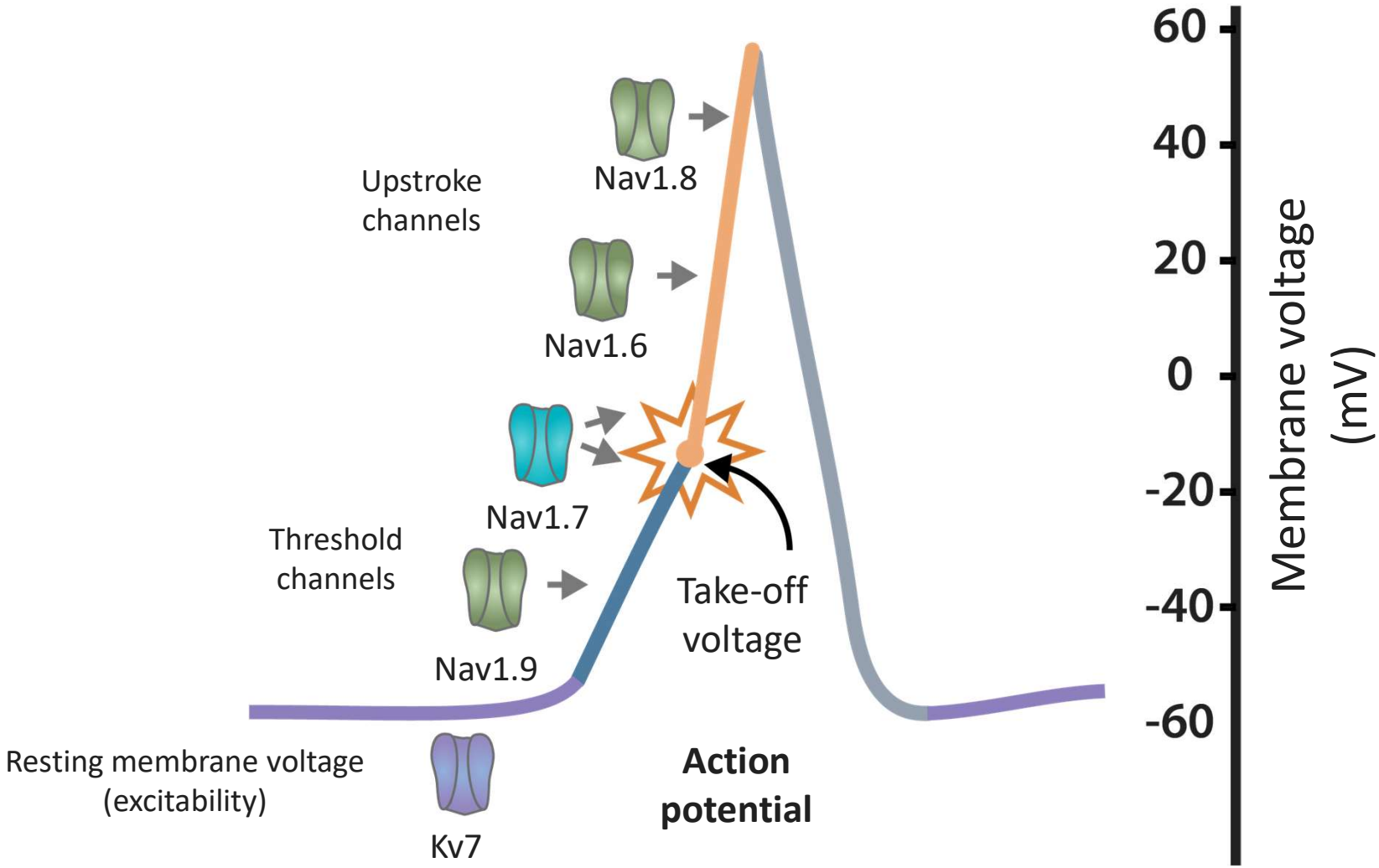
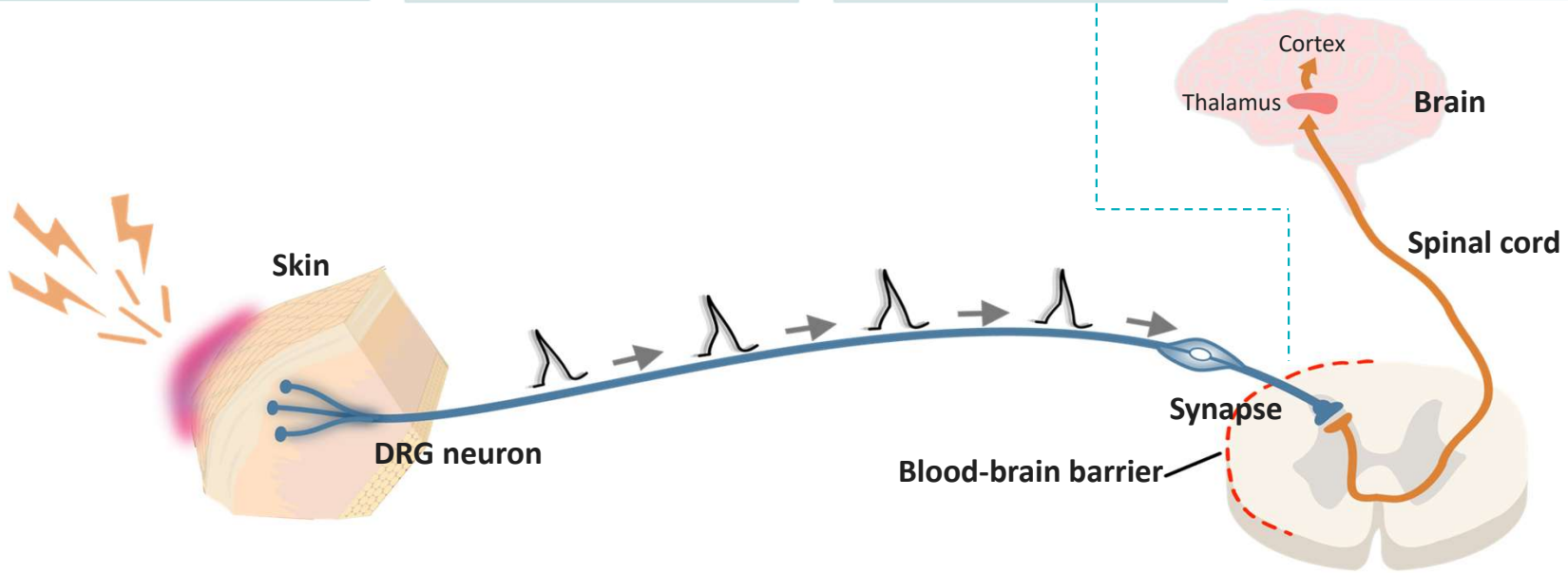

Upstroke channels
Nav1.8
Nav1.6
Nav1.7
Threshold channels
Nav1.9
Take-off voltage
Resting membrane voltage (excitability)
Kv7
Action potential
60
40
20
0
-20
-40
-60
Membrane voltage (mV)

Peripheral sensory neurons synapse onto neurons in the spinal cord to relay pain signals up to the brain

Transduction	Transmission	Relay / Neuro-Transmitter Release	Modulation / Central Perception
		▪ Kv7 potentiator ▪ Nav1.7 inhibitor ▪ Other examples include: gabapentinoids; NSAIDs; COX2 inhibitors	



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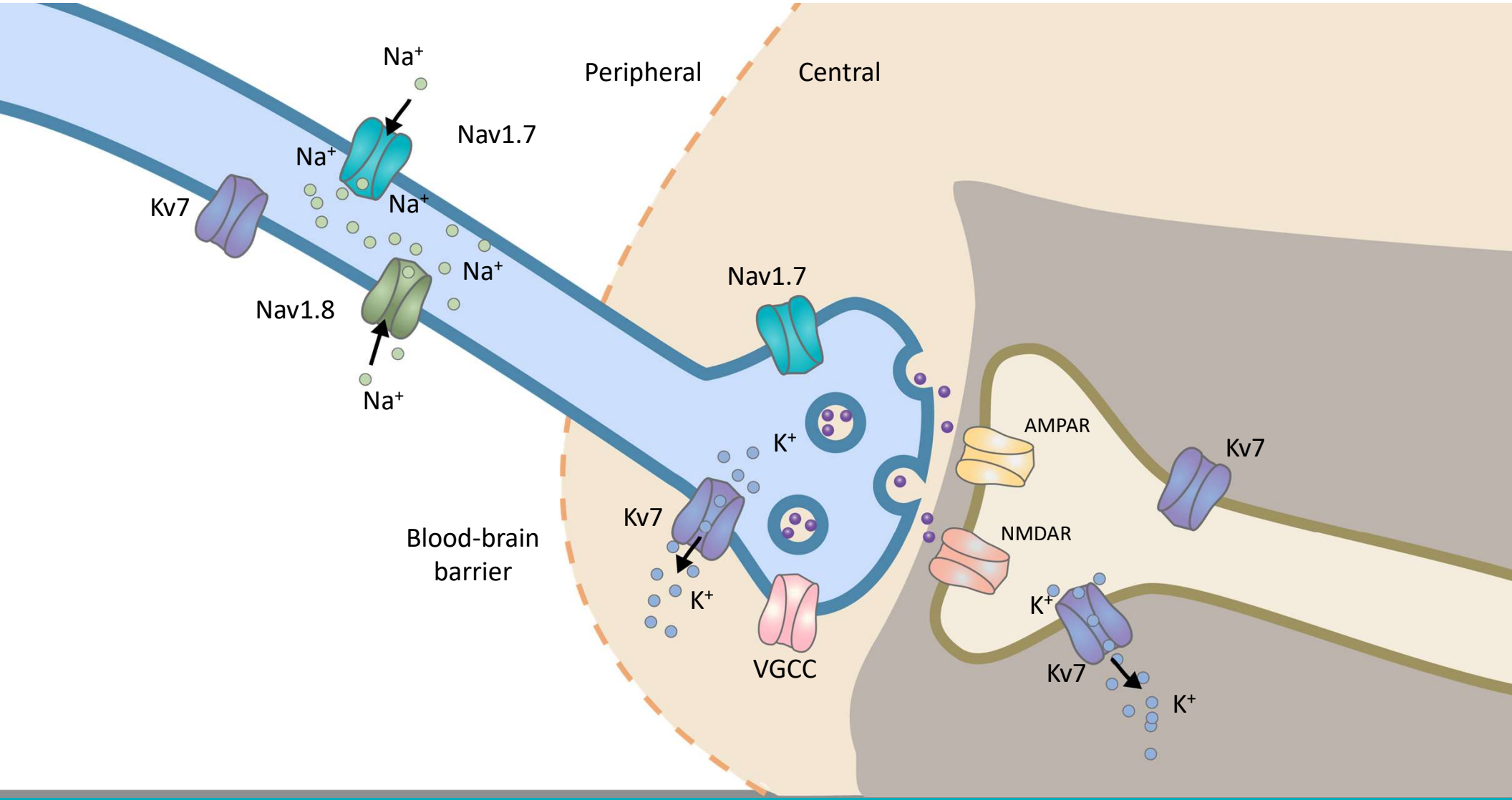
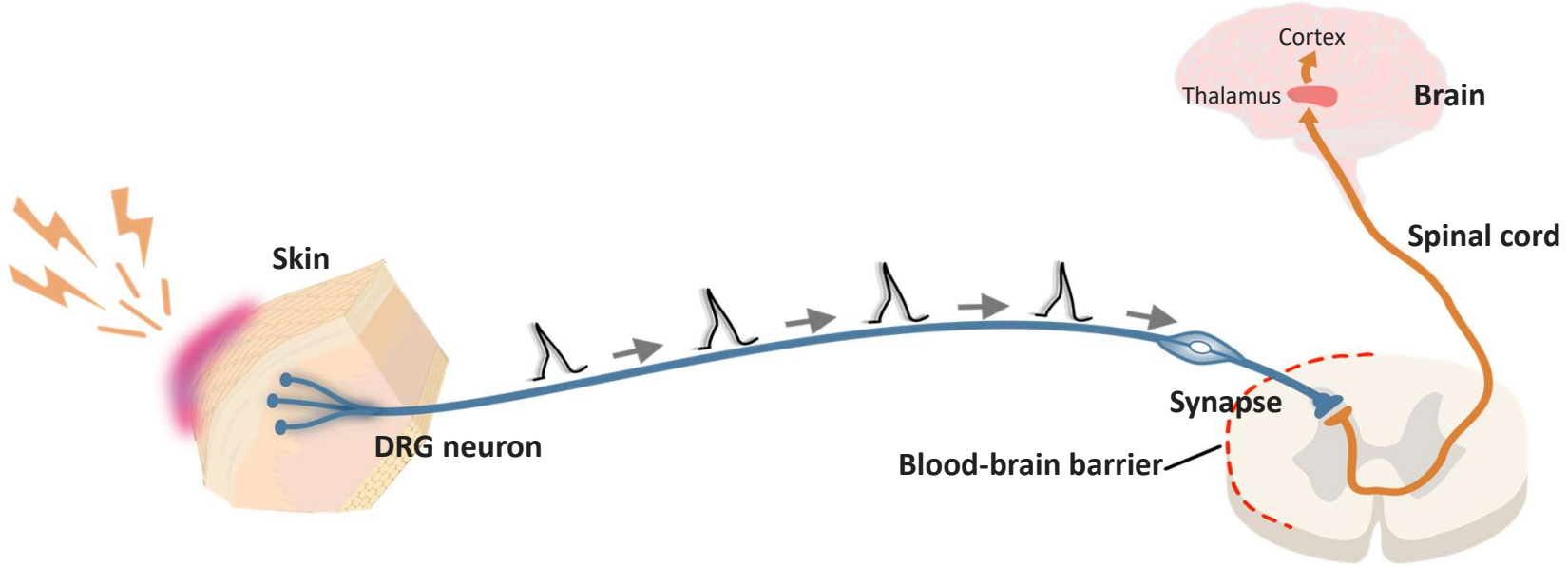

Na+
Peripheral
Central
Nav1.7
Na+
Kv7
Na+
Na+
Nav1.8
Na+
Nav1.7
K+
AMPAR
Kv7
Kv7
NMDAR
Blood-brain
barrier
K+
K+
VGCC
Kv7
K+

Importance of Nav1.7 and Kv7 in the Pain Pathway

Transduction	Transmission	Relay / Neuro-Transmitter Release	Modulation / Central Perception
▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include: Nav1.8 inhibitors; local anesthetics; NSAIDs; antihistamines	▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include Nav1.8 inhibitors; local anesthetics; α2 agonists	▪ **Kv7 potentiator** ▪ **Nav1.7 inhibitor** ▪ Other examples include: gabapentinoids; NSAIDs; COX2 inhibitors	▪ Examples include: Opioids; cannabinoids; acetaminophen; NMDAR antagonists (ketamine)



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Xenon's Early-Stage Pain Programs Targeting Kv7 & Nav1.7

Addressing Unmet Needs | Next Steps | Conclusions

Q & A

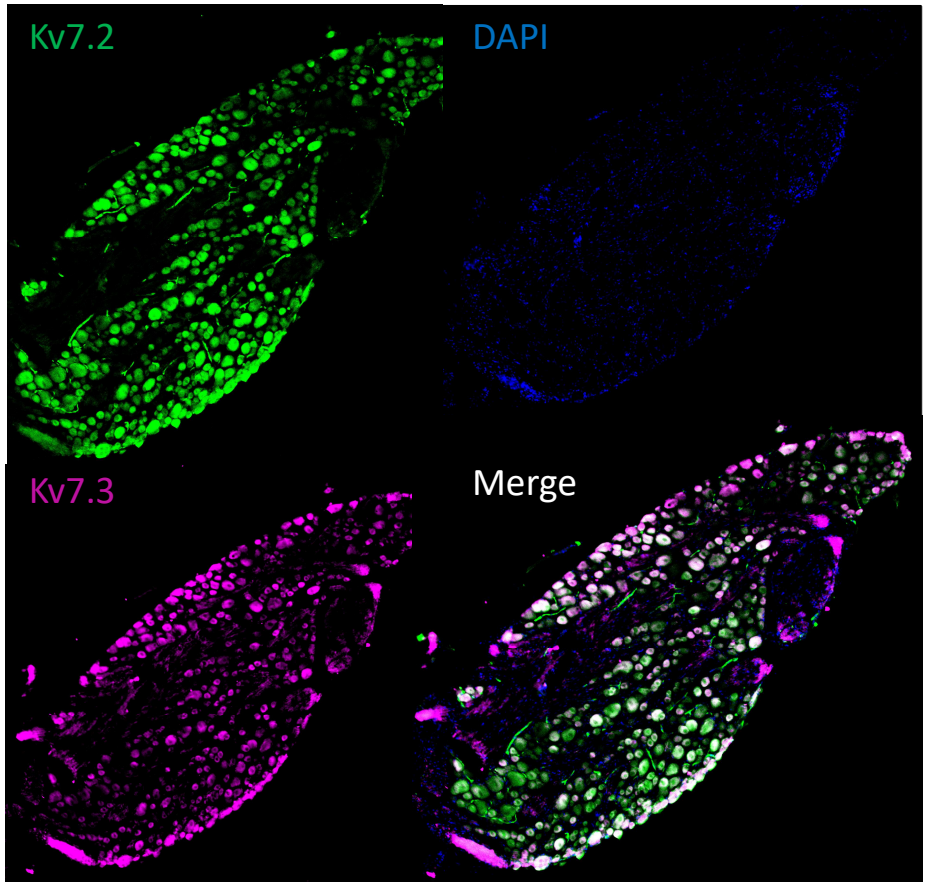
Targeting Kv7 for Pain

- Multiple lines of evidence support targeting Kv7 for pain:[1,2]
  - Kv7 channels are expressed throughout the pain pathway and can suppress repetitive firing
  - Dysfunction or downregulation of Kv7 activity has been observed in altered pain states
  - A compound previously approved for the treatment of pain with a mechanism of action that involves potassium channel opening
- Pharmacological activation of Kv7 channels offers a potential non-opioid approach to treat a range of pain conditions, including neuropathic and inflammatory pain

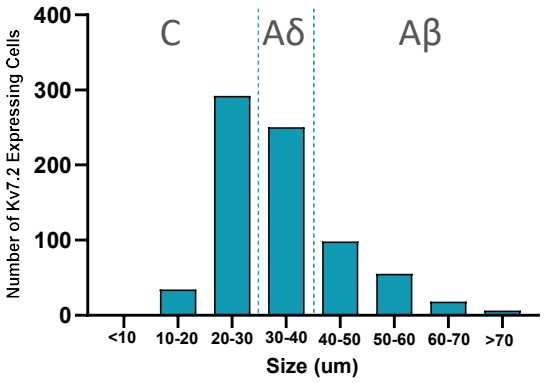
Kv7 is a compelling pain target to modulate neuronal hyperexcitability

Source: [1] Kim et al, *Mol Brain Res,* 2002; [2] Yuan et al, *Brain Commun*, 2021

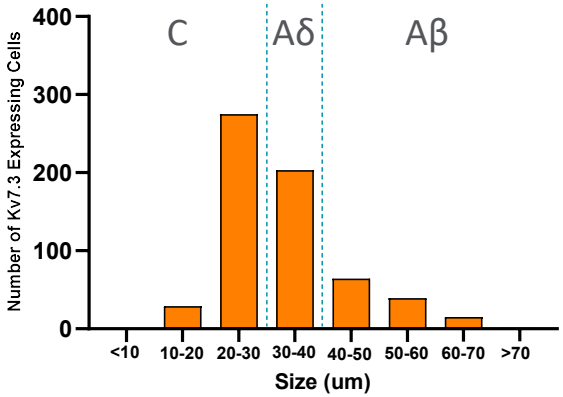
Kv7 Protein is Widely Expressed In DRG Neurons



Diameter of Kv7.2 cells



Diameter of Kv7.3 cells

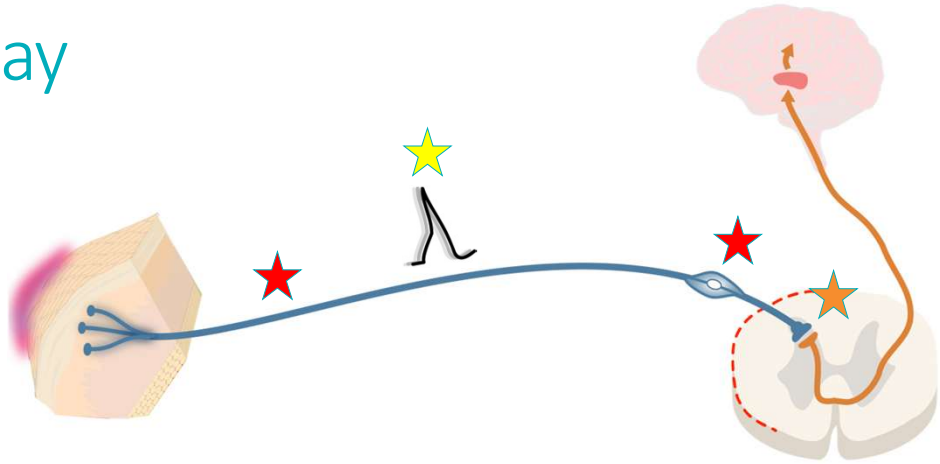


Subtype	Appearance	Size
C-Fiber	Small	**< 30 µm**
Aδ	Medium	**30-40 µm**
Aβ	Large	**> 40 µm**

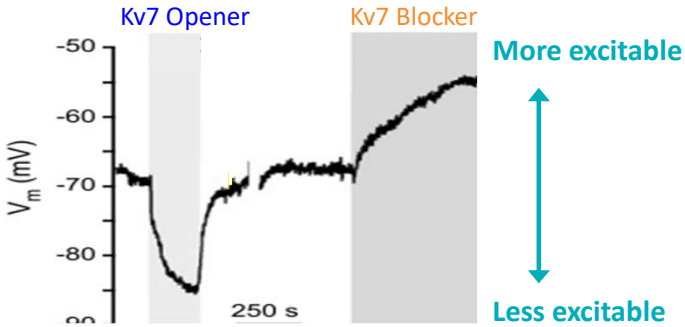
Xenon in house rat DRG data 2025

Kv7's Role Across the Pain Pathway

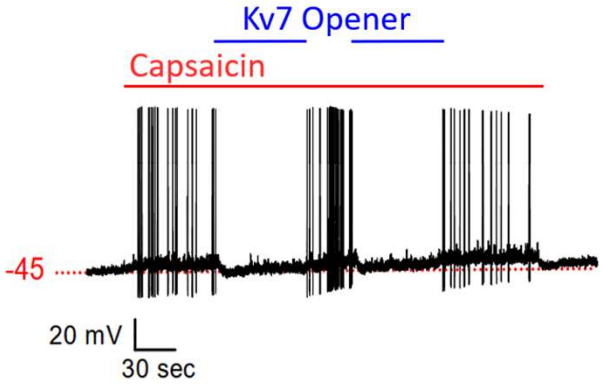
- Kv7 channel openers decrease excitability throughout the pain pathway including DRG axons and cell body; and spinal cord dorsal horn



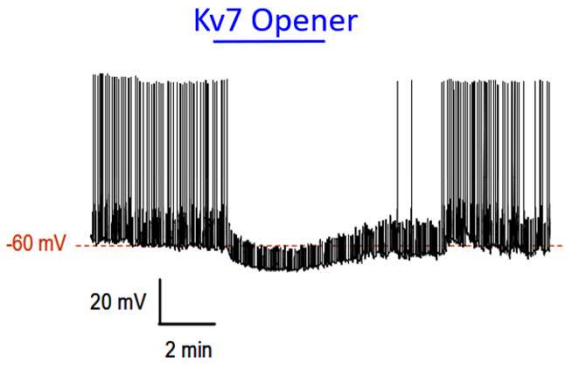
DRG Resting Voltage[1]



DRG (L4) firing[2]



Spinal Cord DH firing[2]



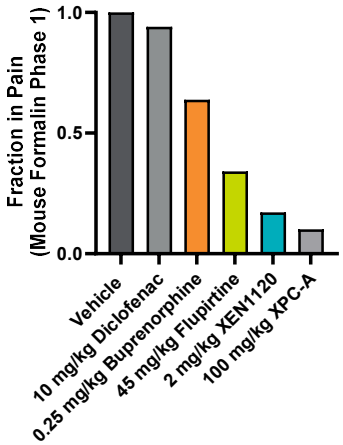
Kv7 channel openers can block signaling across the pain pathway

Source: [1] Adapted from Du Gamper 2018 BPJ 175_2158; [2] Adapted from Martin, E. (2018). *Pathophysiology of Pain*

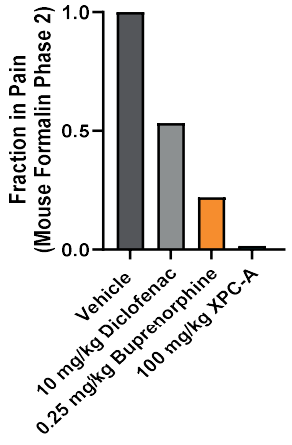
Formalin Acute Sensory Pain Model

- Formalin injected into paw of animal
- Phase 1 (0-5 min) direct effect on nociceptors; phase 2 (30-45 min) an inflammatory response
- Most analgesics only work in phase 2, except opioids that work in phase 1

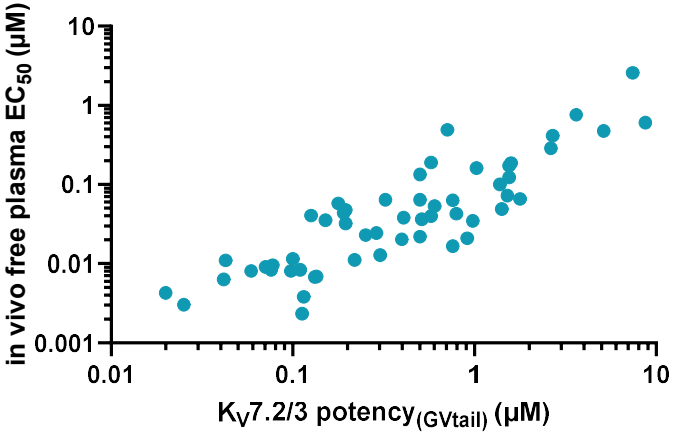
Formalin Phase 1
(0-5 Min)



Formalin Phase 2
(30-45 min)



Mouse Phase 1 Formalin



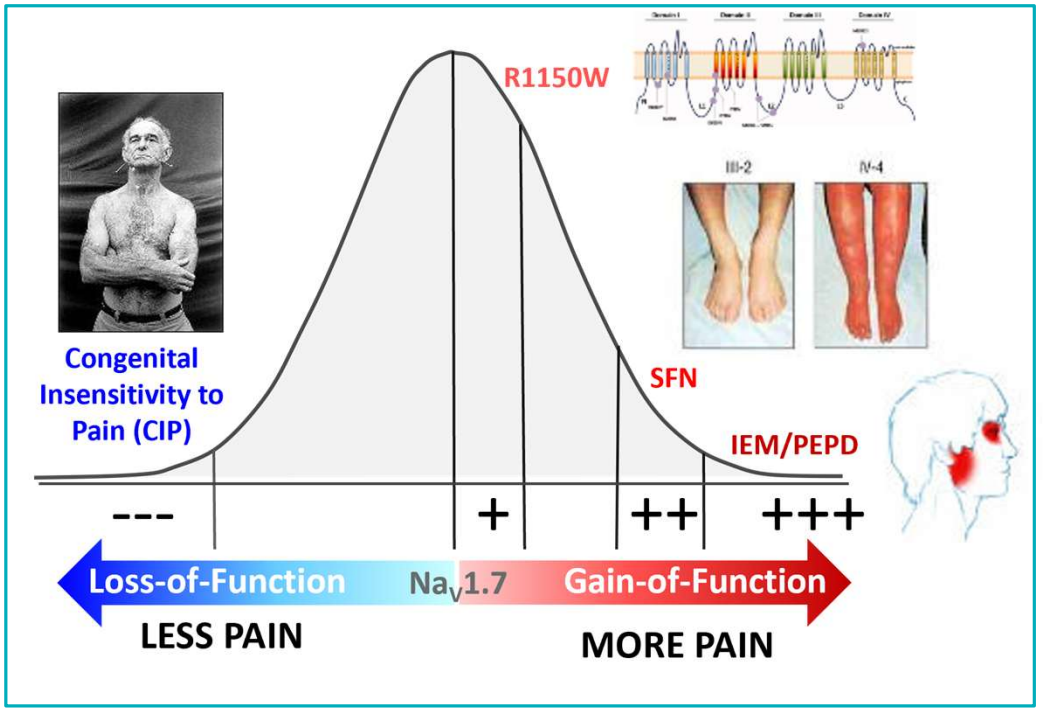
Exemplary Xenon Kv7 compounds show efficacy in Formalin Phase 1, where most nonopioid drugs are ineffective

Summary of Kv7 Pain Program

- ✓Kv7 is a compelling pain target to modulate neuronal hyperexcitability at multiple points along the pain pathway
  - Kv7 channels play important roles in the initial transduction of pain stimuli, transmission along the pain pathway, as well as in the spinal cord
  - Kv7 potentiators can decrease neuronal hyperexcitability for the potential treatment of a range of pain conditions
- ✓A clinical compound previously approved for the treatment of pain has a mechanism of action that involves potassium channel opening
- ✓Lead Kv7 compound, XEN1120, now in Phase 1 clinical study
- ✓Growing early-stage pipeline of numerous other compounds and distinct chemistries advancing into IND-enabling studies

The Human Genetics of Nav1.7 and Pain

- Loss-of-function mutations in SCN9A (the gene encoding Nav1.7) can cause congenital indifference to pain (CIP) - individuals that are otherwise healthy but cannot feel pain
- Gain-of-function mutations in SCN9A can lead to extreme pain disorders, such as inherited erythromelalgia (IEM) or paroxysmal extreme pain disorder (PEPD), demonstrating that excessive Nav1.7 activity can drive pain



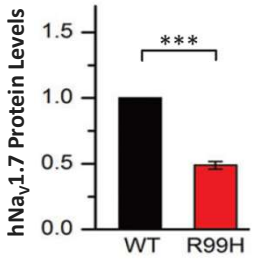
There is strong human genetic evidence to support Nav1.7 as a compelling, superior target for pain drug development

Recent Research Has Informed Latest Development Efforts

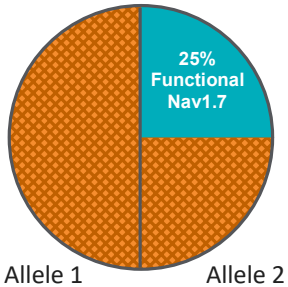
- Incomplete loss of Nav1.7 identified in 2 families with lack of pain according to two independent research groups
- The subjects in these families have Nav1.7 mutations in both alleles
  - One mutation in each family is a null variant → No functional channels
  - One mutation in each family is a hypomorph → Reduced current

Family 1 (R99H mutation)

~50% Reduction of $Na_V1.7$ Protein



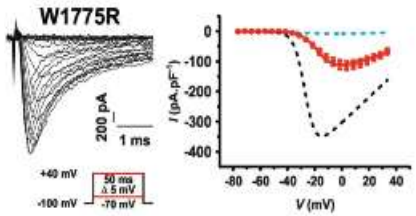
75% $Na_V1.7$ Reduction



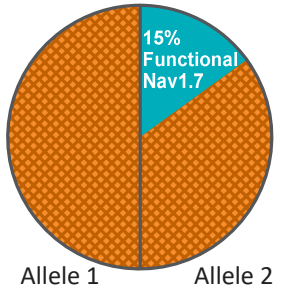
Allele 1 (null) | Allele 2 (50% Loss)

Family 2 (W1775R mutation)

~65% Reduction in $Na_V1.7$ Current



85% $Na_V1.7$ Reduction



Allele 1 (null) | Allele 2 (65% Loss)

Recent research suggests ~75-85% loss of Nav1.7 sufficient for CIP phenotype

Source: Adapted from Sun, et al., 2020; adapted from Emery, et al., 2015

Xenon's Lead Nav1.7 Compounds Demonstrate a Differentiated Profile in the Preclinical Setting

Target Compound Profile

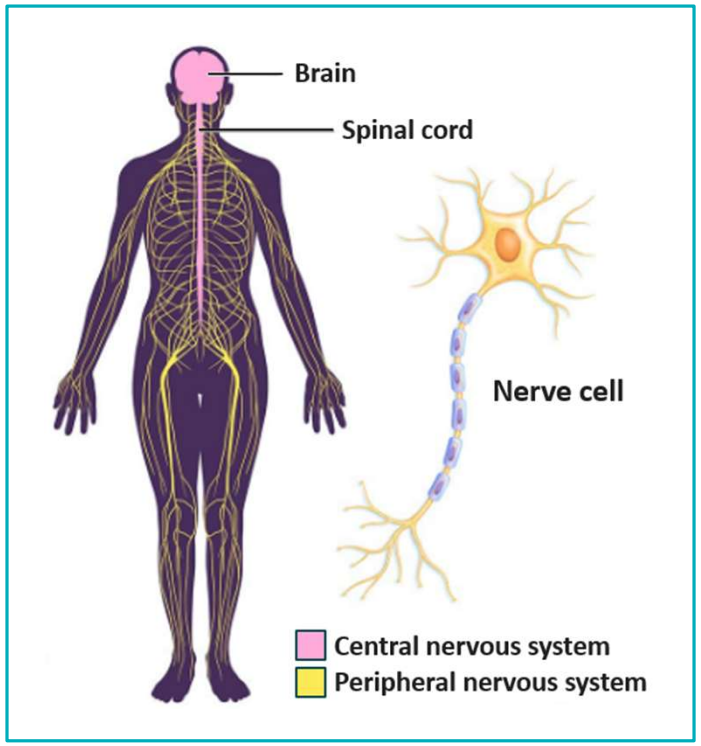
- CNS exposure: engagement of Nav1.7 in the spinal cord: best mimics the genetics
- Improved free fraction and tissue distribution
- Comprehensive selectivity over Nav subtypes

Lead Xenon Compounds Meet These Criteria

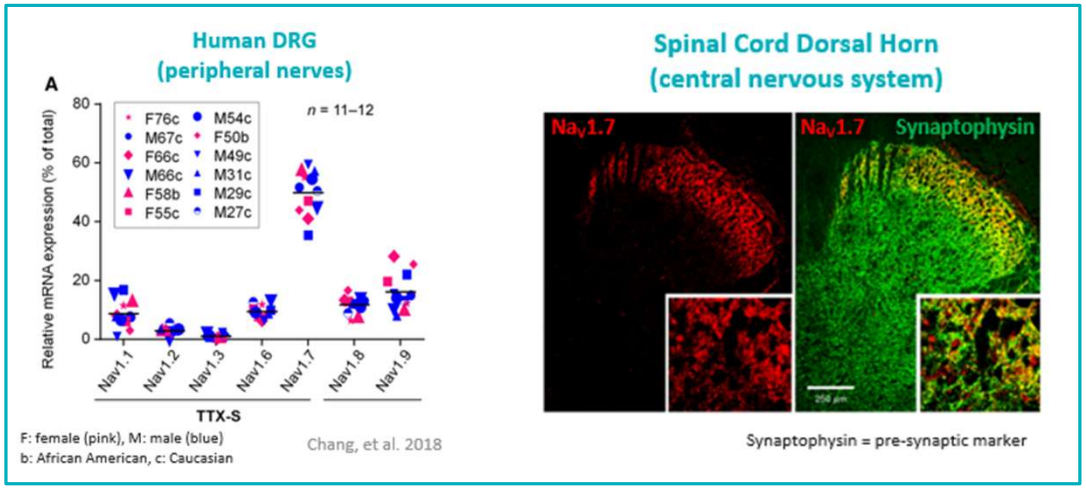
Compound	CNS Exposure	Free Fraction	Selectivity
First-Gen (e.g., vixotrigine)			
Second-Gen (e.g., PF-771, GD-0276)			
Xenon Lead Compounds			

A Nav1.7 inhibitor with this target profile has never been tested in the clinic

Nav1.7 is Expressed in the Periphery and CNS



- Nav1.7 is highly expressed in nociceptive neurons along the pain pathway
  - Initiates pain signals in the periphery
  - Facilities neurotransmitter release in spinal cord
- Inhibition in both compartments may better mimic the human genetics



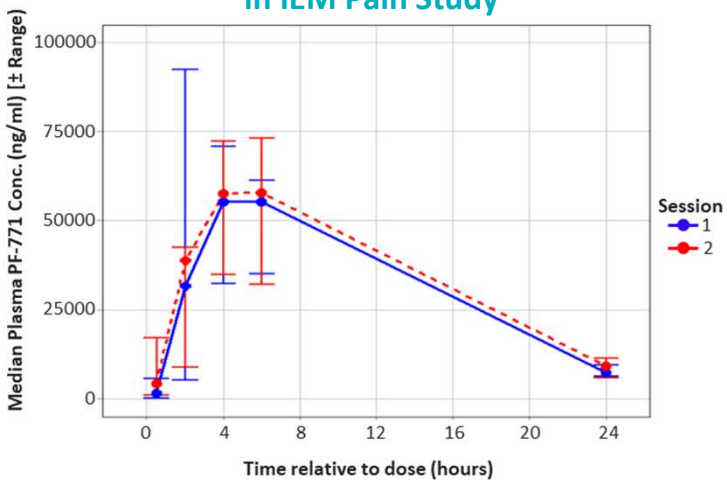
Inhibiting Nav1.7 in both the CNS and PNS may better mimic the human genetics

Source: Chang, et al., 2018

Free Fraction in Nav1.7 Inhibition

- Low free faction = trapped drug. High binding to plasma proteins or lipids keeps drug away from Nav1.7
- Past attempts like PF-771 had very low free fraction, limiting Nav1.7 target engagement and likely contributing to poor efficacy
- In IEM and dental pain - PF-771 showed some efficacy when dosed up to 1600mg, but due to low free fraction, likely didn't achieve high enough Nav1.7 receptor occupancy
- In peripheral diabetic painful neuropathy - PF-771 dosed at 150mg and failed to demonstrate efficacy likely due to insufficient Nav1.7 inhibition

Single 1600 mg dose of PF-771 in IEM Pain Study



PF-771

C_{max} = 57,000 ng/ml (114 µM)
T_{max} = 4-6 hr
$Na_V1.7$ EP IC_{50} = 4.1 nM*
Plasma protein binding = ~99.9%*

Improving a compound's free fraction could increase target engagement

*Xenon assay; Source: Cao et al, *Pain*, 2016

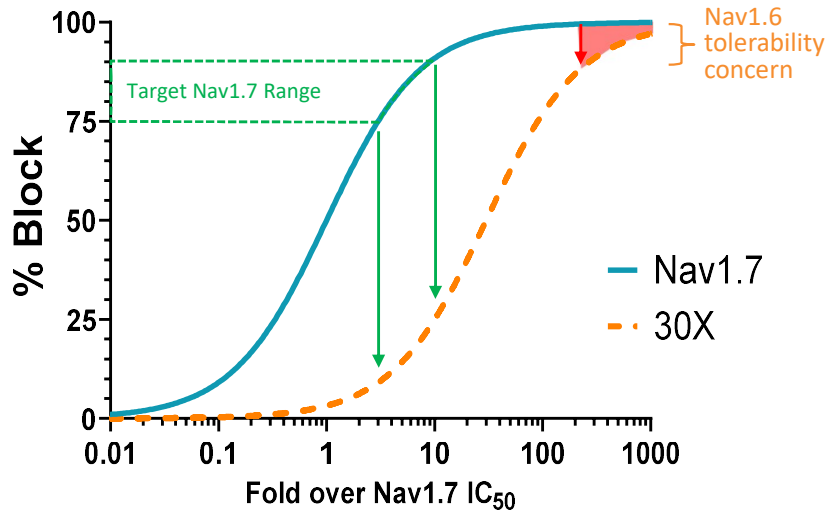
Strong Selectivity Supports High Levels of Nav1.7 Inhibition

- Greater selectivity over other Nav subtypes could provide a **wider therapeutic window**, which could allow for efficacious dosing with a reduced risk of dose-limiting toxicities

Protein (Gene)	Expression Sites	Related Diseases
$Na_V1.1$ (*SCN1A*)	CNS, PNS	Epilepsy, autism, intellectual disability
$Na_V1.2$ (*SCN2A*)	CNS, PNS	Epilepsy, autism, intellectual disability
$Na_V1.3$ (*SCN3A*)	CNS, PNS	Epilepsy (?)
$Na_V1.4$ (*SCN4A*)	Skeletal muscle	Myotonia, paralysis
Nav1.5 (*SCN5A*)	Heart muscle	Heart block, long-QT syndrome
$Na_V1.6$ (*SCN8A*)	CNS, PNS	Intellectual disability, ataxia, epilepsy
$Na_V1.7$ (*SCN9A*)	**CNS, PNS**	**Pain**
$Na_V1.8$ (*SCN10A*)	PNS	Pain
$Na_V1.9$ (*SCN11A*)	PNS	Sensory loss, pain

With 30X selectivity:

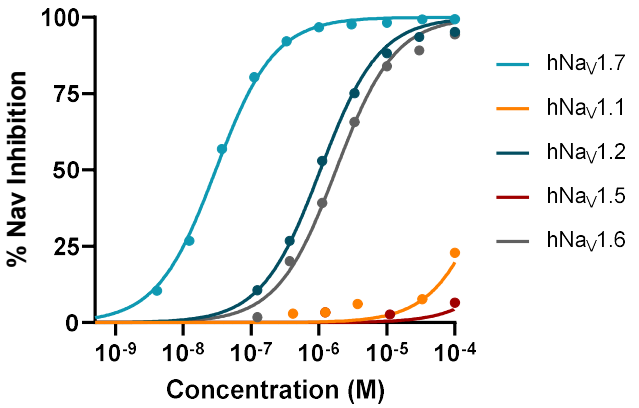
- 75% block of Nav1.7 = 10% block of off-target Navs
- 90% block of Nav1.7 = 25% block of off-target Navs



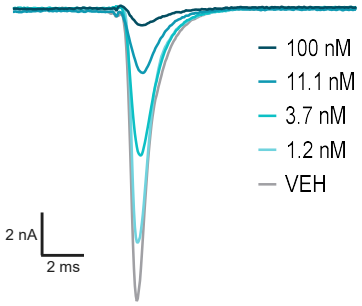
Initial drug development focused on achieving selectivity over the cardiac channel Nav1.5

Nav1.7 Inhibition Can Block Action Potential Firing in DRG Neurons

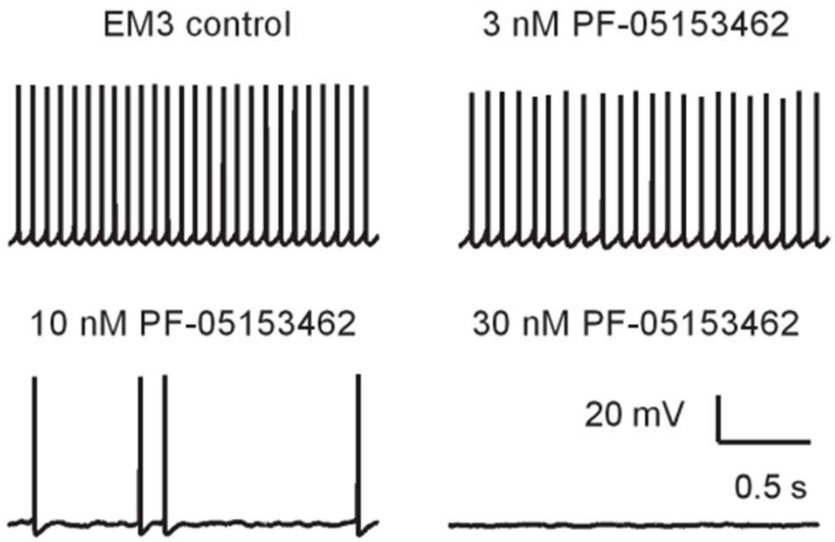
XEN1701 Potency and Selectivity



XEN1701 hNav1.7



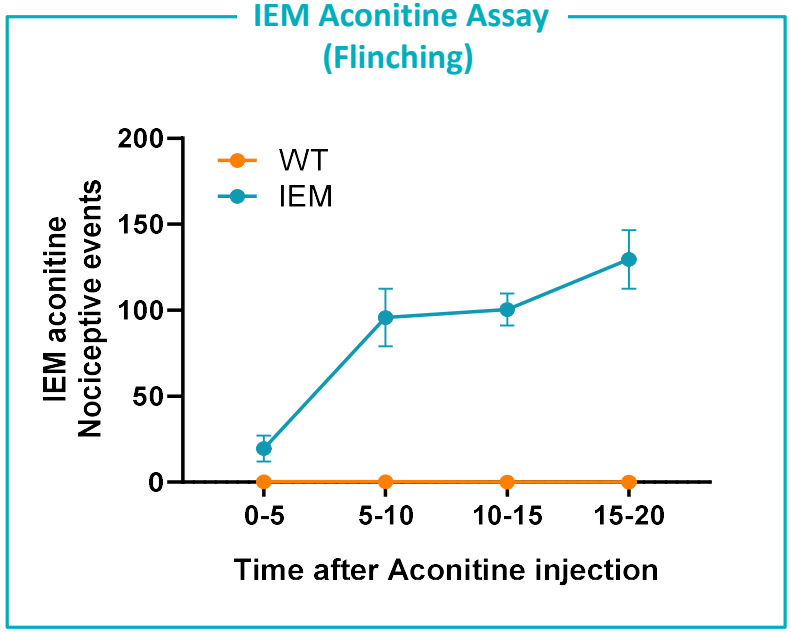
- Increasing Nav1.7 inhibition can block action potential firing in iPSC sensory neurons from IEM patients[1]



[1] Adapted from Cao et al, *Pain*, 2016

Interrogating Nav1.7 Target Engagement With an IEM Model

- Inherited erythromelalgia (IEM) is a severe pain syndrome caused by GOF mutations in Nav1.7
- Transgenic mice express a copy of human Nav1.7 with a mutation (I848T) observed in IEM patients[1]
- Paw injection of a sodium channel activator, aconitine, produces flinching (pain) in IEM mice, but not wild-type mice
- In-house developed machine learning-based automated tracking scores paw flinches as a readout of pain

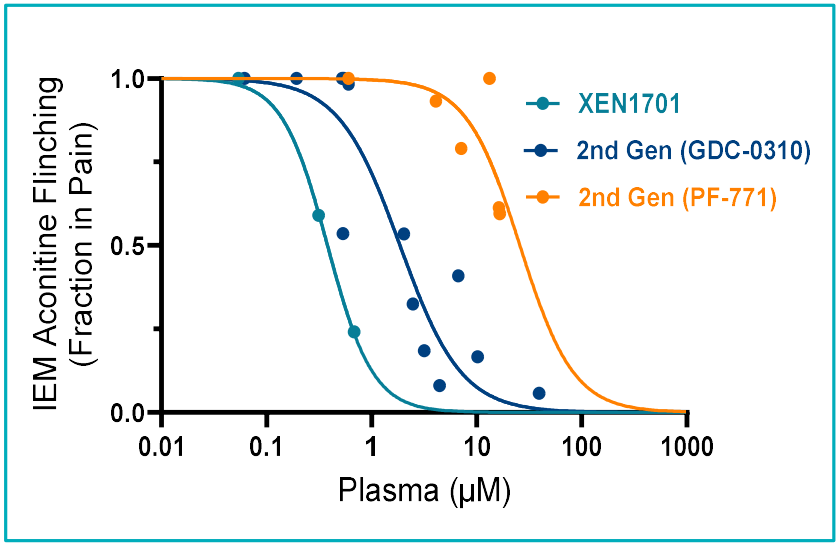


Target engagement in the IEM model is dependent on human Nav1.7

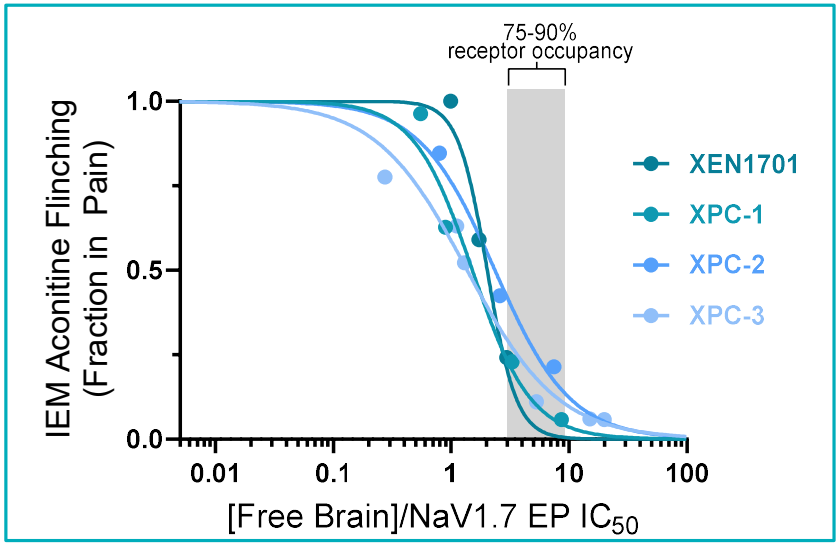
Source: [1] Bankar, et al., *Cell Rep*, 2018

XEN1701 Performance in IEM Mouse Model

XEN1701 demonstrates target engagement at low total plasma concentrations



In vivo activity correlates to free brain concentrations across Xenon's lead compounds

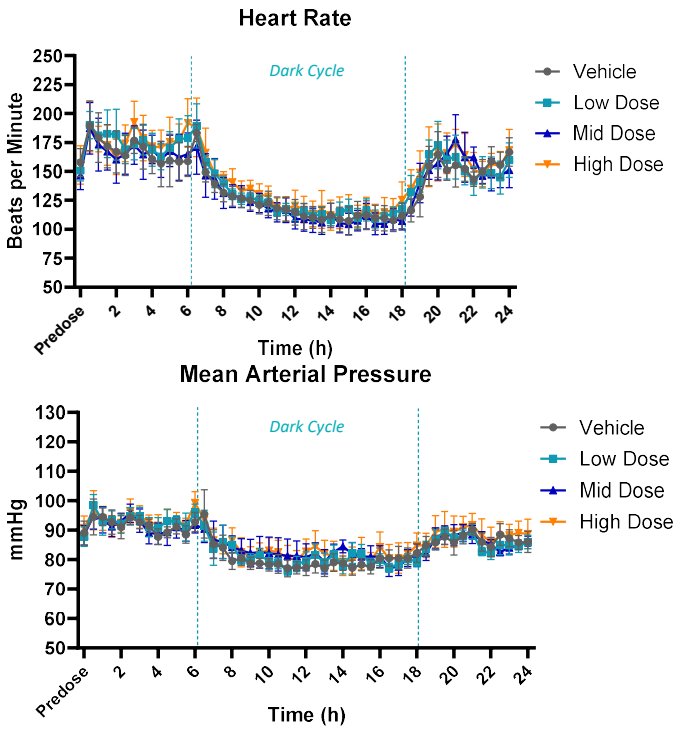


CNS penetrance, improved free fraction and good potency and selectivity demonstrate target engagement at low plasma exposures

Nav1.7 and Cardiovascular Observations

- Nav1.7 is expressed in pain sensory neurons as well as autonomic neurons
  - Autonomic abnormalities reported in patients with Nav1.7 GOF mutations (SFN, PEPD, IEM)[1-3]
  - Patients with Nav1.7 LOF mutations (CIP) have normal autonomic function
  - Main concerns would be syncope (loss of consciousness) or orthostatic hypotension (dizziness upon standing from sitting or supine position)
- To potentially mitigate autonomic findings:
  - Avoid too rapid of an onset of Nav1.7 inhibition[5]
  - Avoid peripheral receptor occupancies at or greater than 99%[4]
- XEN1701 has not shown CV effects at exposures greater than predicted therapeutic levels based on preclinical studies conducted to date
  - Cardiovascular effects are easily monitorable in the clinic

XEN1701 Heart Rate and Blood Pressure in Cynomolgus Monkey



Xenon's target profile differentiates from other published compounds that demonstrated autonomic effects[5-6]

Source: [1] Faber, et al., 2012; [2] Hisama, et al., 2020; [3] Kurban, et al., 2010; [4] Regan et al., *Circulation Res. Lett.,* 2024; [5] Rothenberg, et al., 2019; [6] Mulcahy et al., British Pharm. Society, 2023

Summary of Nav1.7 Pain Program

- ✓Nav1.7 is compelling, genetically validated pain target
- ✓Xenon has long history with Nav1.7 science and deep ion channel drug discovery expertise and is applying this knowledge to generate pipeline of lead Nav1.7 molecules with differentiated profiles:
  - CNS penetrant to globally inhibit Nav1.7, better mimicking patient genetics
  - Demonstrates good free fraction and tissue distribution, achieving high levels of target engagement
  - Excellent potency and selectivity to safely achieve target therapeutic levels of Nav1.7 inhibition
- ✓Lead Nav1.7 compound, XEN1701, in Phase 1 clinical study with profile that has never been tested in clinic
- ✓Growing early-stage pipeline of numerous other compounds and distinct chemistries advancing into IND-enabling studies

Agenda

Introductions | Corporate Overview

Pain Signaling and the Role of Ion Channels

Xenon's Early-Stage Pain Programs Targeting Kv7 & Nav1.7

Addressing Unmet Needs | Next Steps | Conclusions

Q & A

Pain Landscape Segmented By Type and Duration

Type / origin

Nociceptive		Neuropathic	Mixed	Nociplastic
Tissue injury	Tissue injury	Nervous system dysfunction	Contribution from injury & nervous system dysfunction	Genetic, environmental and psychosocial factors

Duration*

Acute	Chronic
< 3 months	Persists for 3+ months

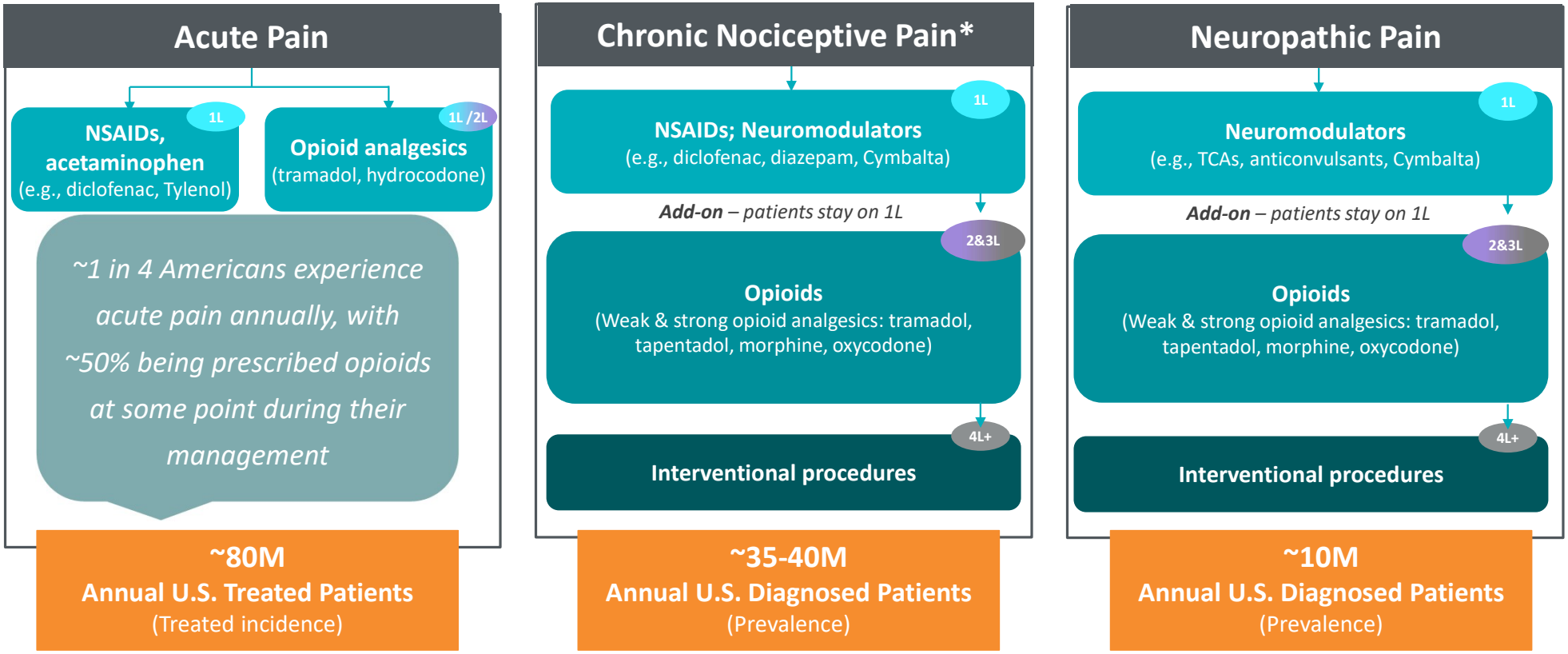
Example indications

• Peri-operative • Post discharge (procedure) • Acute musculoskeletal • Trauma (e.g., fractures) • Other (e.g., visceral)	• Chronic lower back pain • Osteoarthritis • Other arthritis (e.g., RA) • Other (e.g., idiopathic)	• Diabetic neuropathic pain • Lumbosacral radiculopathy • Post-herpetic neuralgia • Trigeminal neuralgia • Idiopathic / hereditary neuropathy	• Cancer pain	• Fibromyalgia

Note: * The CDC defines chronic pain in their clinical practice guidelines as pain > 3 months

Source: IQVIA; Pharmaprojects; SymphonyRx; TD Cowen Pain Management Report; Precedence Research; Allied Market Research; BCC Research; CDC

Prevalence and Treatment Paradigms Across Pain Types



Current pain treatments rely on NSAIDs, neuromodulators and opioids, which pose risks of addiction and poor tolerability

Note: * Patients cycle through opioid treatment in chronic pain; patients often cycle between medications and therapeutic lines in all three pain categories and occasionally use medicines together
Source: External expert interviews; Mayo Clinic; Johns Hopkins; Cleveland Clinic

Xenon's Early-Stage Clinical Development Plans

Kv7 Program

- Designated lead molecule, XEN1120
- Phase 1 study underway
- Goal to initiate Phase 2 POC study in 2026
- Robust pipeline of additional Kv7-targeted compounds being advanced through IND-enabling studies
  - Distinct molecules targeting unique:
    - Binding sites/mechanisms
    - Tissue distribution profiles

Nav1.7 Program

- Designated lead molecule, XEN1701
- Phase 1 study underway
- Goal to initiate Phase 2 POC study in 2026
- Robust pipeline of additional Nav1.7-targeted compounds being advanced through IND-enabling studies
  - Differentiated compound profile
    - CNS exposure
    - Free fraction and tissue distribution
    - Selectivity

Conclusions

- Current pain treatments rely on NSAIDs, neuromodulators, and opioids, which pose risks of addiction and poor tolerability
- There is significant unmet need for non-opioids that provide effective analgesia and minimize safety and tolerability issues
- As a leader in developing ion channel modulators, Xenon is advancing modulators of Kv7 and Nav1.7 - with both targets believed to have significant impact in the transduction, transmission and relay of pain signals
- Xenon's pain programs aim to address liabilities of earlier compounds by leveraging our extensive ion channel expertise

Q&A

PLEASE SUBMIT YOUR QUESTIONS VIA THE CHAT FUNCTION

Thank you for attending!

PLEASE SUBMIT FOLLOW-UP QUESTIONS VIA EMAIL TO:

INVESTORS@XENON-PHARMA.COM