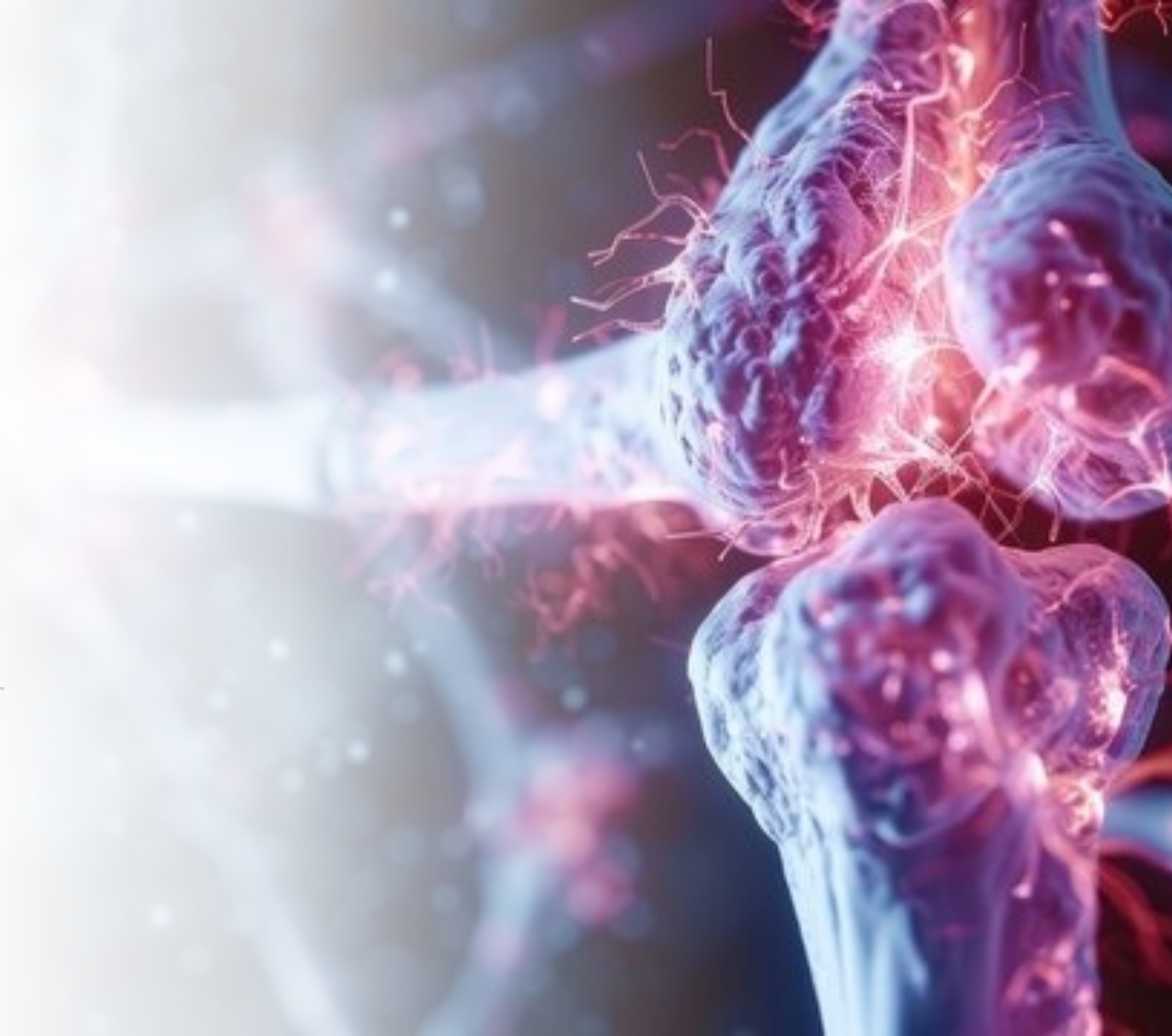
ChondroNext

Osteoarthritis (OA) Therapies with Targeted Local Delivery of Nav1.7 Inhibitors

Chuan-Ju Liu PhD & Stephen G Waxman MD, PhD



ChondroNext Team

We are an experienced team of world-class researchers with pharmaceutical development experience

Chuan-Ju Liu, PhD

Charles W. Ohse Professor of Orthopaedics

Yale School of Medicine

- Over 20 years of scientific leadership in osteo and rheumatoid arthritis
- Co-founder of Atreaon, an arthritis-focused pharmaceutical startup; helped secure $8 million in initial funding
- Over 15 years of involvement in IP and licensing, the majority of his 20 patents have been licensed

Stephen G. Waxman, MD, PhD

Bridget Marie Flaherty Professor of Neurology, Neuroscience, and Pharmacology

Yale School of Medicine

- Over 50 years of scientific leadership in ion channel structure and function
- Business experience as a founder of Neurex (acquired by Elan), and as a consultant and advisor to SiteOne, Navega Therapeutics, Sangamo Therapeutics, Third Rock, Foresite Labs, and Medtronic

Wenyu Fu, PhD

Research Scientist

Research & Development Lead

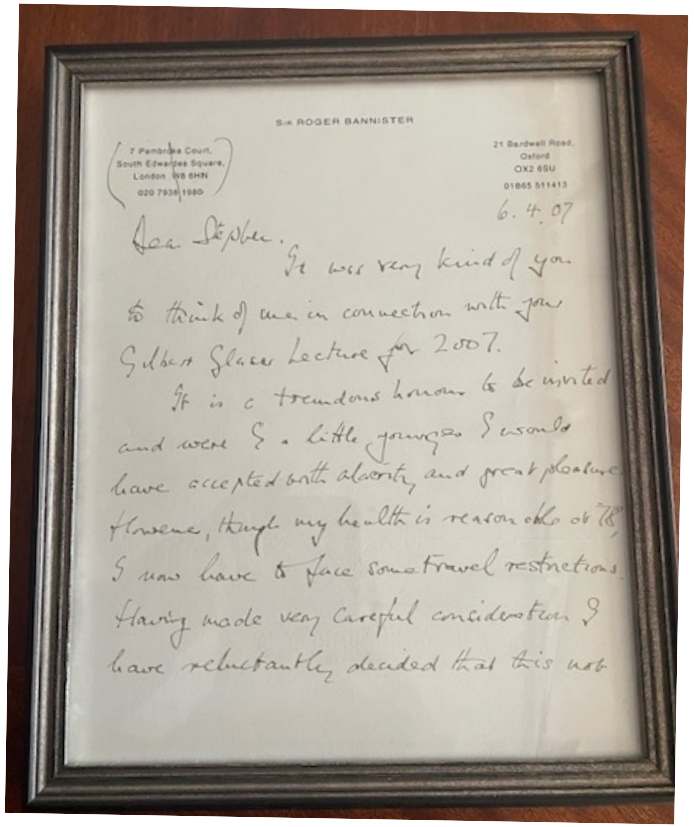
Yale School of Medicine

- ~10 years research and development experience focusing on sodium channels in osteoarthritis, and inflammatory arthritis
- Led researcher in characterizing the role of Nav1.7 channels in osteoarthritis

A major unmet medical need and an un-suspected role for Nav1.7

1954

Roger Bannister: the first 4-minute mile



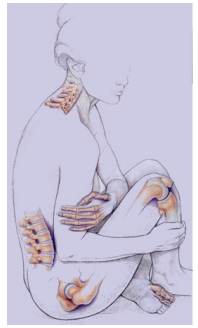
2007

He writes that he cannot travel to give a lecture at Yale due to OA

Osteoarthritis: Unmet Need

OA affects ~30M people in the US. There are no therapeutics that can prevent OA progression

Irreversible Symptoms



- Joint pain during/after movement
- Decreased range of motion
- Swelling near joints
- Bone spurs/joint deformity

Significant Disability and Comorbidity Risk

- 55% increase in all cause mortality
- 50% increased risk of heart disease
- 44% of patients have limited activity
- 41% increased risk of diabetes

Highly Prevalent

- ~750M OA patients worldwide
- ~30M OA patients in the US
- ~1M OA patients seek surgical intervention annually

Insufficient Standard of Care

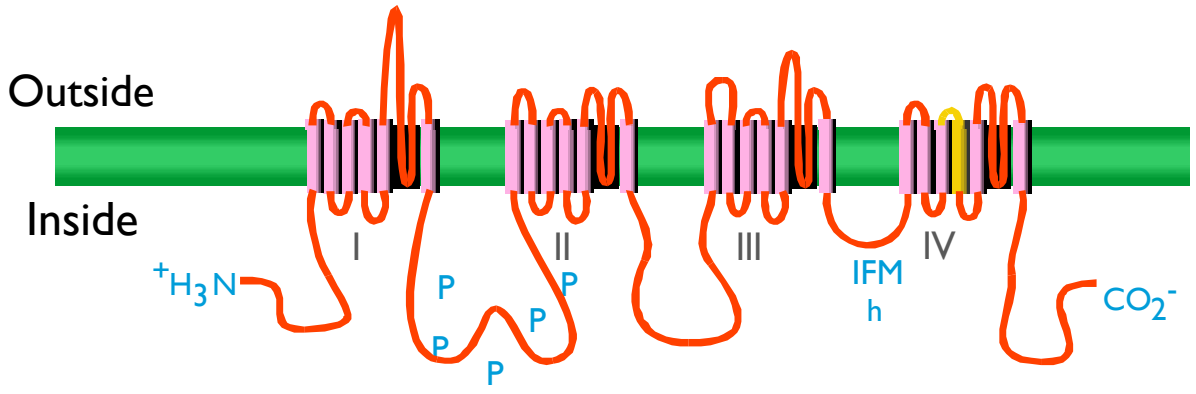
No treatment slows OA progression

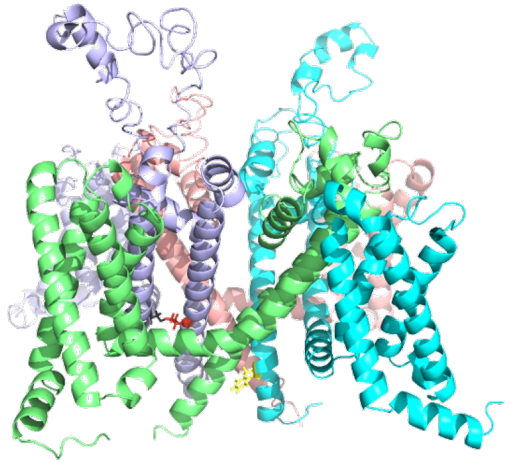
- Exercise and physical therapy
- Painkillers
- Intra-articular injection
- Surgical Joint Replacement

Overall economic burden of OA in the US : ~$136 B each year

Our team recently discovered sodium channel Nav1.7 as a disease-modifying therapeutic target for Osteoarthritis (OA)

A New Understanding of Nav1.7 channels





- Nav1.7 has traditionally been considered specific to peripheral neurons.
- **We have found that Nav1.7 channels are present and functional in chondrocytes, Nav1.7 blockade regulates chondrocyte Ca^{2+} signaling and function, and protects against OA**
- Our paper was listed as the first among the five most significant discoveries at ACR's 2024 Year in Review presentation

https://rheumnow.com/news/acr-2024-day-1-report

nature
International weekly journal of science

Article

$Na_v1.7$ as a chondrocyte regulator and therapeutic target for osteoarthritis

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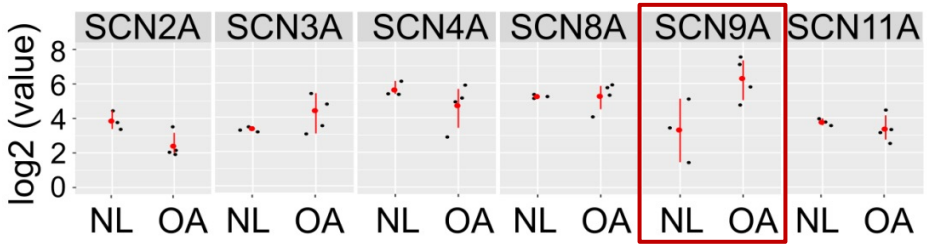
Open access

Wenyu Fu[1,2], Dmytro Vasylyev[3,4], Yufei Bi[1], Mingshuang Zhang[1], Guodong Sun[1], Asya Khleborodova[1], Guiwu Huang[1,2], Libo Zhao[1,2], Renpeng Zhou[1,2], Yonggang Li[1,2], Shujun Liu[3,4], Xianyi Cai[1], Wenjun He[1], Min Cui[1], Xiangli Zhao[1,2], Aubryanna Hettinghouse[1], Julia Good[1], Ellen Kim[1], Eric Strauss[1], Philipp Leucht[1], Ran Schwarzkopf[1], Edward X. Guo[5], Jonathan Samuels[6], Wenhuo Hu[7,8], Mukundan Attur[6], Stephen G. Waxman[3,4] ✉ & Chuan-ju Liu[1,2,9] ✉

Nav1.7: In Vitro Data

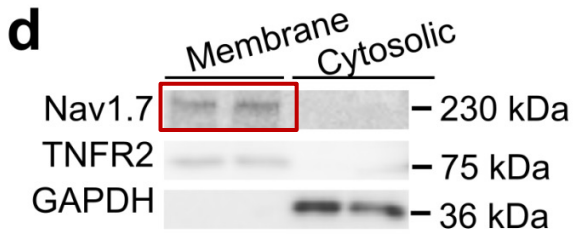
Nav1.7 is upregulated in OA cartilage, is found on the membrane of chondrocytes, and is correlated with higher severity OA

mRNA Levels of Nav Genes in Cartilage



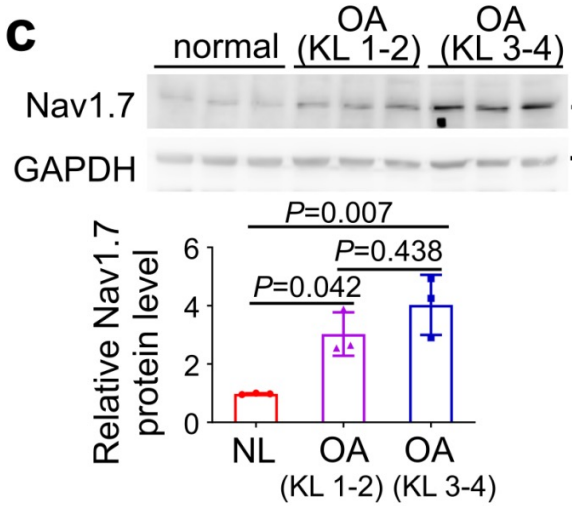
Nav1.7 is encoded by the SCN9A gene and was the only transcript to be meaningfully upregulated in OA cartilage

Location of Nav1.7 on Chondrocytes



Nav1.7 was detected in the membrane, suggesting a potential therapeutic does not need to cross the cell membrane

mRNA Levels of Nav1.7 Across Severity Levels



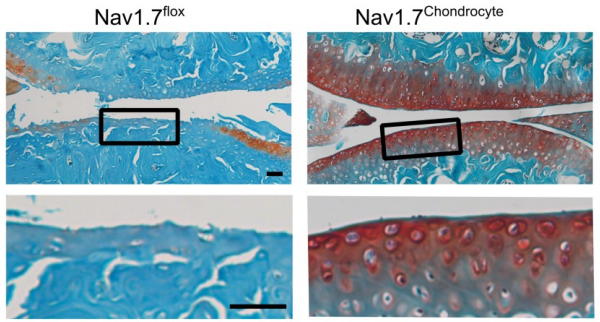
Nav1.7 was expressed at higher levels in patients with higher severity OA vs lower severity OA, suggesting that lower levels of Nav1.7 may be correlated with lower severity OA

Fu et al, Nature, 2024
OA: Osteoarthritis, NL: Non-arthritic cartilage

Nav1.7: In Vivo Data

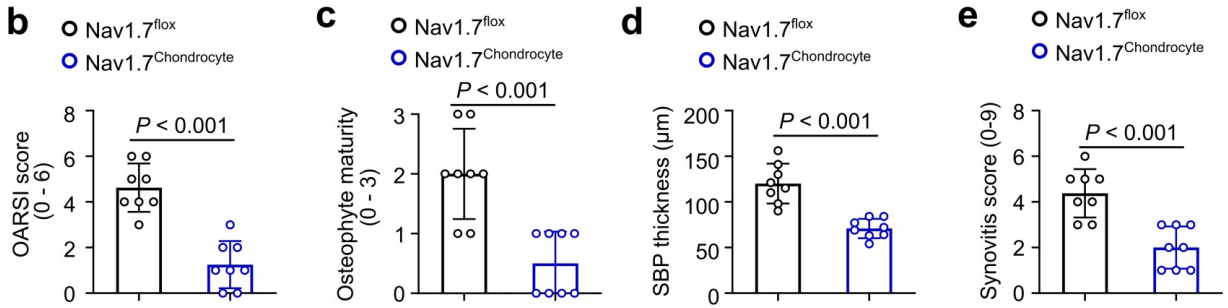
Ablation of chondrocyte-expressed Nav1.7 protects against OA and reduces cartilage loss, improves multiple OA metrics, and increases movement

Cartilage Imaging



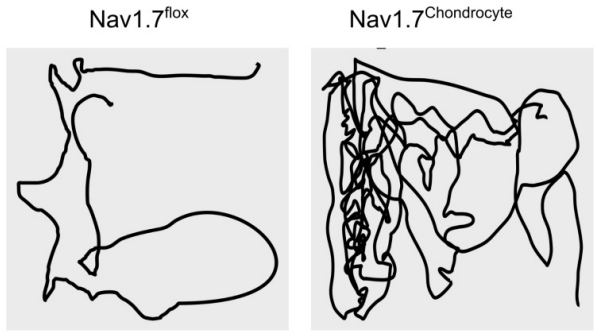
Mice with Nav1.7 knocked out in chondrocytes had noticeably less cartilage loss

Measures of OA



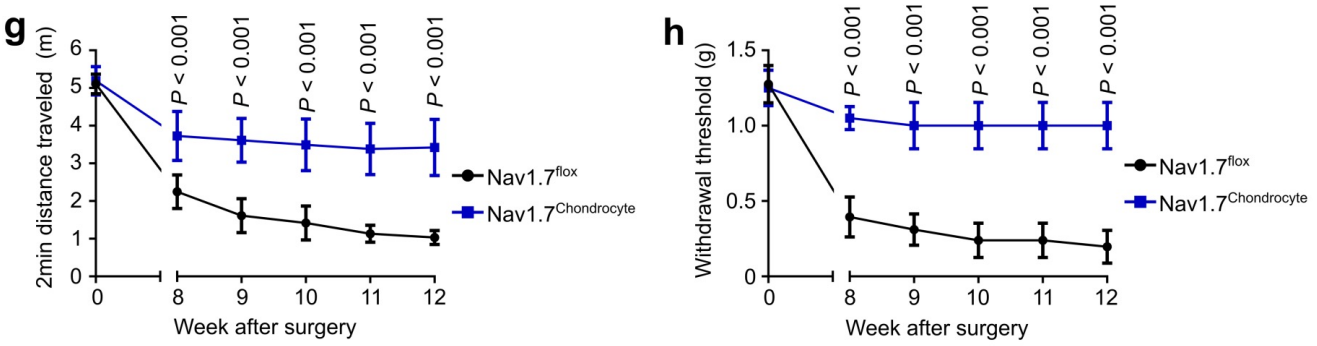
Mice with Nav1.7 knocked out showed statistically significant improvements across multiple metrics related to osteoarthritis

Movement Testing



Mice with Nav1.7 knocked out were meaningfully more mobile

OA Function Tests Over Time



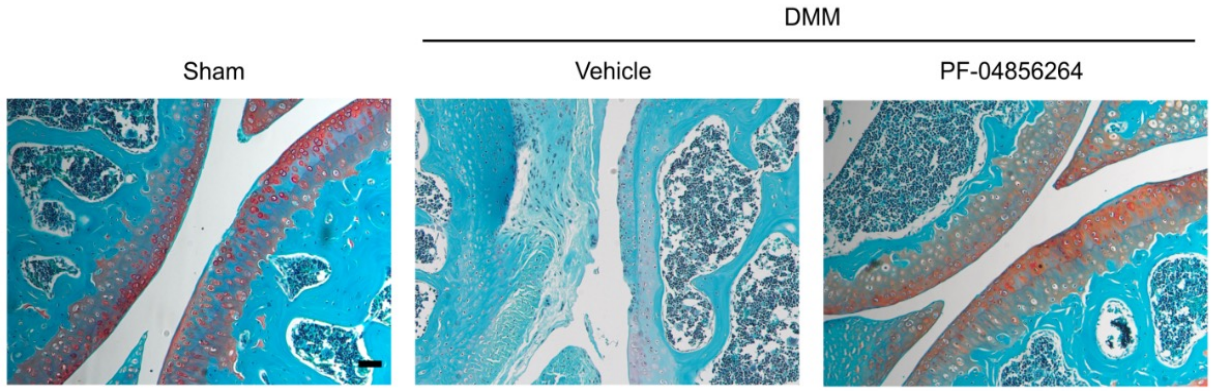
Mice with Nav1.7 knocked out demonstrated durable differences in mobility and reactions

Fu et al, Nature, 2024
Nav1.7flox: control mice with Nav1.7; Nav1.7Chondrocyte: mice with Nav1.7 knocked out in chondrocytes

Nav1.7: Inhibitor Data

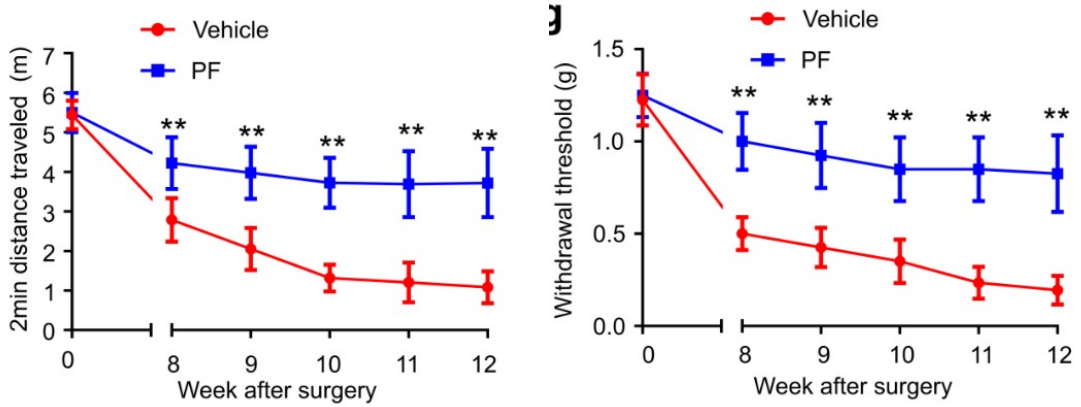
Intra-articular injection of Nav1.7 inhibitor is also therapeutic against OA and resulting pain

✓ Histological improvement with intra-articular administration of Nav1.7 inhibitor



OA model in mice demonstrated attenuation in cartilage loss with Nav1.7 inhibited

✓ Significant functional improvement

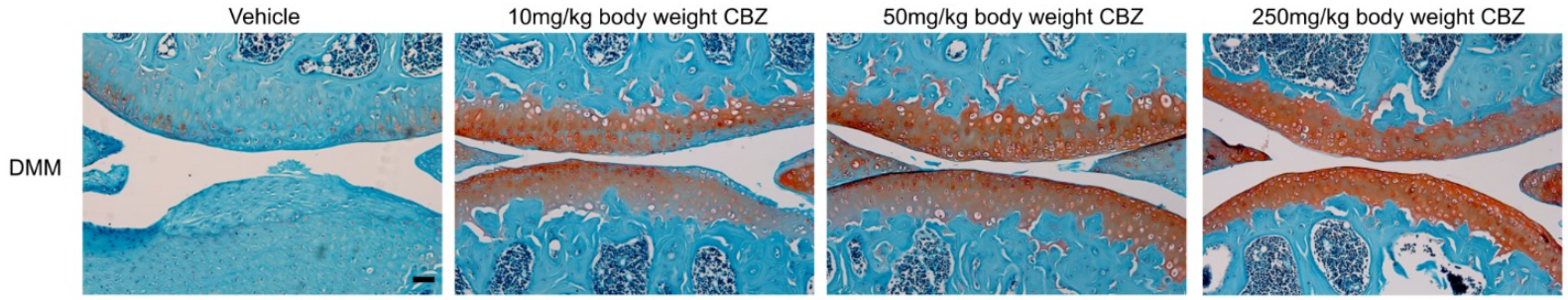


Treatment improves movement and pain response

Fu et al, Nature, 2024

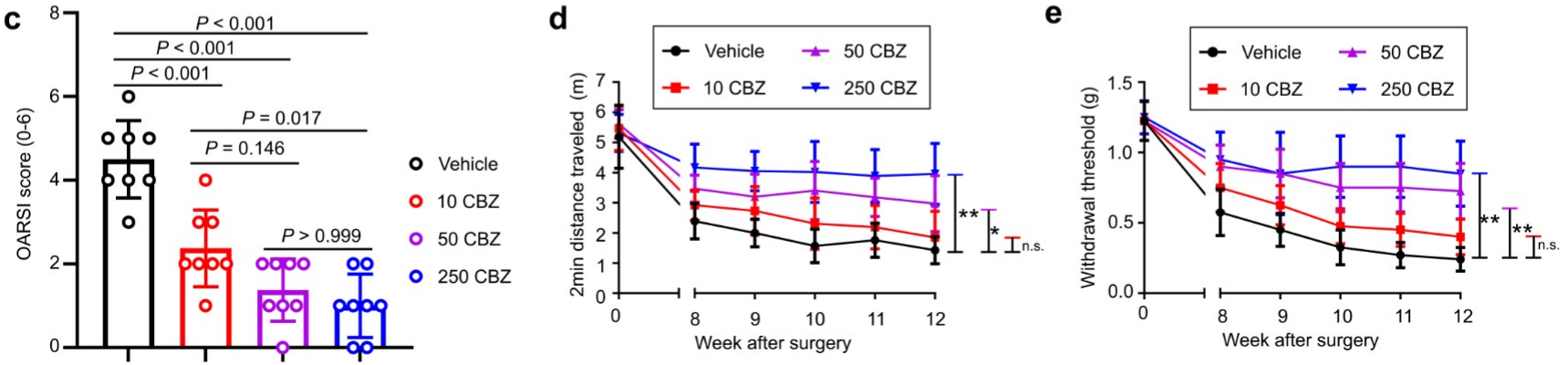
Carbamazepine (CBZ), a clinically used sodium chancel pan-inhibitor, attenuates OA progression and pain

Cartilage Imaging



OA model mice demonstrated dose-dependent attenuation in cartilage loss when treated with CBZ

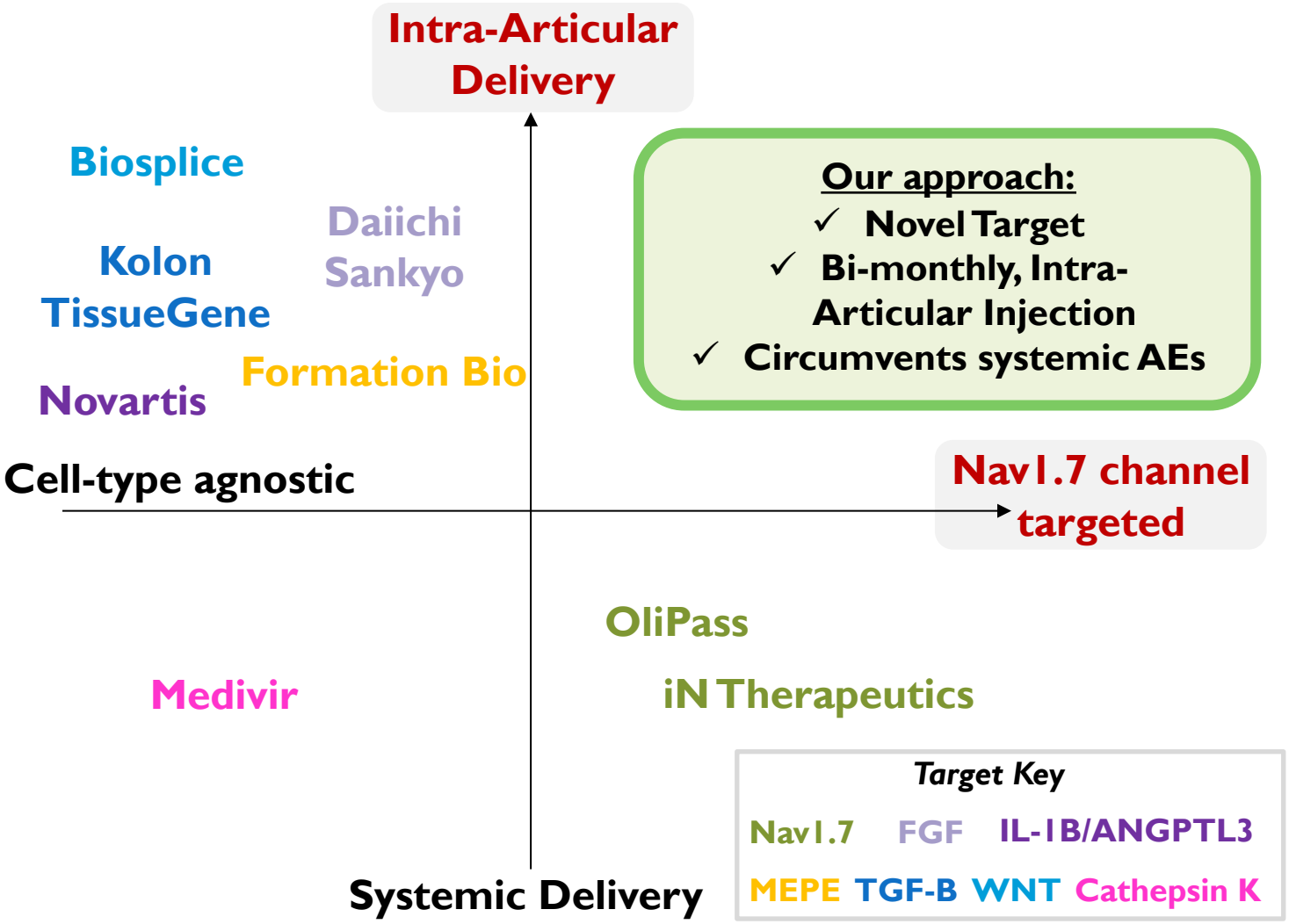
OA Function Tests



OA model mice demonstrated dose-dependent improvements across OARSI score, movement, and reaction when treated with CBZ

Fu et al, Nature, 2024

Local targeting of chondrocyte Nav1.7 has strong mechanistic preclinical validation



US. Osteoarthritis Market:

- 2023: **$4.1B**
- 2030: **$4.75B**
- CAGR: **5.5%**

Our approach will differentiate from the pipeline

- Targets studied as OA DMTs target catabolic mediators with questionable significance
- Approaches using Nav1.7 inhibitors for OA pain will not reach the chondrocyte for disease modifying benefit

We propose a targeted, locally delivered approach

Development of Bi-Monthly, Intra-articular Nav Blocking Drug that Inhibits Nav1.7

Our plan is to reformulate an FDA-approved drug for slow release in the joint space

TOTAL COST
$300,000

MILESTONE 1

Development of Extended Release Formulation of Nav Inhibitor

$100,000

✓Preliminary Formulation Tested *in vitro*
- Optimize Extended-Release Formulation
- Selectivity, Potency, Release Rate

May 2025

MILESTONE 2

In Vivo Efficacy Studies in Rabbits

$200,000

- Document protection from joint degeneration
- Measure pain and animal activity
- Verify safety and lack of systemic effects

June 2026

Intellectual Property
- ✓ PCT Patent Filed for Methods of Use for Nav channel 1.7 inhibitors in OA
- ❑ Prior to publication of PCT, IP will be filed to protect novel formulation

Path to Clinic
- ✓ OA is a large population for trial recruitment
- ✓ Precedent for study design using intraarticular injection

Alternative Approach
- ✓ In collaboration with YCMD, design of a novel, patentable Nav1.7 inhibitor with desired PK is an alternative option

Appendix

The Development of Bi-Monthly Intra-articular Nav 1.7 Inhibitor

Option A:
Development of Novel Molecule

TOTAL COST of Each Option: $300,000

Option B:
Reformulation of Drug (FDA-approved) for Intraarticular Injection

MILESTONE 1

Novel Small Molecule Screen

$100,000

- Collaboration with YCMD
- Develop Assay Na Channel 1.7 Screen
- Design and Synthesize novel Na Channel 1.7 inhibitor

June 2025

MILESTONE 2

Lead Optimization for Potency

$120,000

- Reiterative med chem to increase potency
- Run Selectivity Assays

January 2026

MILESTONE 3

In vitro Efficacy Studies

$50,000

- Evaluate compound in chondrocytes

September 2026

MILESTONE 4

In vivo Efficacy Studies

$130,000

- Measure OA in mice models
- Assess joint degeneration
- Movement Tests , Pain

January 2027

MILESTONE 1

Development of Extended Release Formulation of Carbamazepine

$100,000

- Selectivity, Potency, Release Rate
- Achieve Extended Release Formulation

August 2025

MILESTONE 2

In Vivo Efficacy Studies in Rabbits

$200,000

- Document protection from joint degeneration, Measure pain, activity,

June 2026

Provisional Patent Filed for Methods of Use for Nav channel 1.7 inhibitors in OA

Osteoarthritis: Competitive Landscape

No other compounds being studied in OA directly target chondrocyte Nav1.7 sodium channels

Asset *Company*	Phase of Development	Indication	ROA	MOA	Class
Lorecivivint *Biosplice*	Phase III *completed*	OA (DMT)	IAI	Wnt inhibitor	Small molecule
TG-C *Kolon TissueGene*	Phase III	OA (DMT)	IAI	TGF-B expression	Cell therapy
MIV-711 *Medivir*	Phase II *completed*	OA (DMT)	Oral	Cathepsin K inhibitor	Small molecule
TPX-100 *Daiichi Sankyo*	Phase II *completed*	OA (DMT)	IAI	MEPE	Peptide
Canakinumab & LNA043 *Novartis*	Phase II	OA (DMT)	IAI	IL-1B inhibition & ANGPTL3	Biologic
Sprifermin *Formation Bio*	Phase II	OA (DMT)	IAI	FGF	Biologic
OLP-1002 *OliPass*	Phase II	OA pain	SC	Nav1.7 Inhibitor (Systemic)	Antisense RNA
iN1011-N17 *iN Therapeutics*	Phase I	OA pain	Oral	Nav1.7 Inhibitor (Systemic)	Small molecule

Other Nav1.7 inhibitors have raised questions of autonomic AEs due to Nav1.7 presence in sympathetic ganglia, which we plan to mitigate with IAI ROA

ROA: Route of Administration; MOA: Mechanism of Action; DMT: Disease modifying therapy; IAI: intra-articular injection

ChondroNEXT: A Novel Strategy for Targeting the Cause of OA

Our team is uniquely positioned to address OA because we:

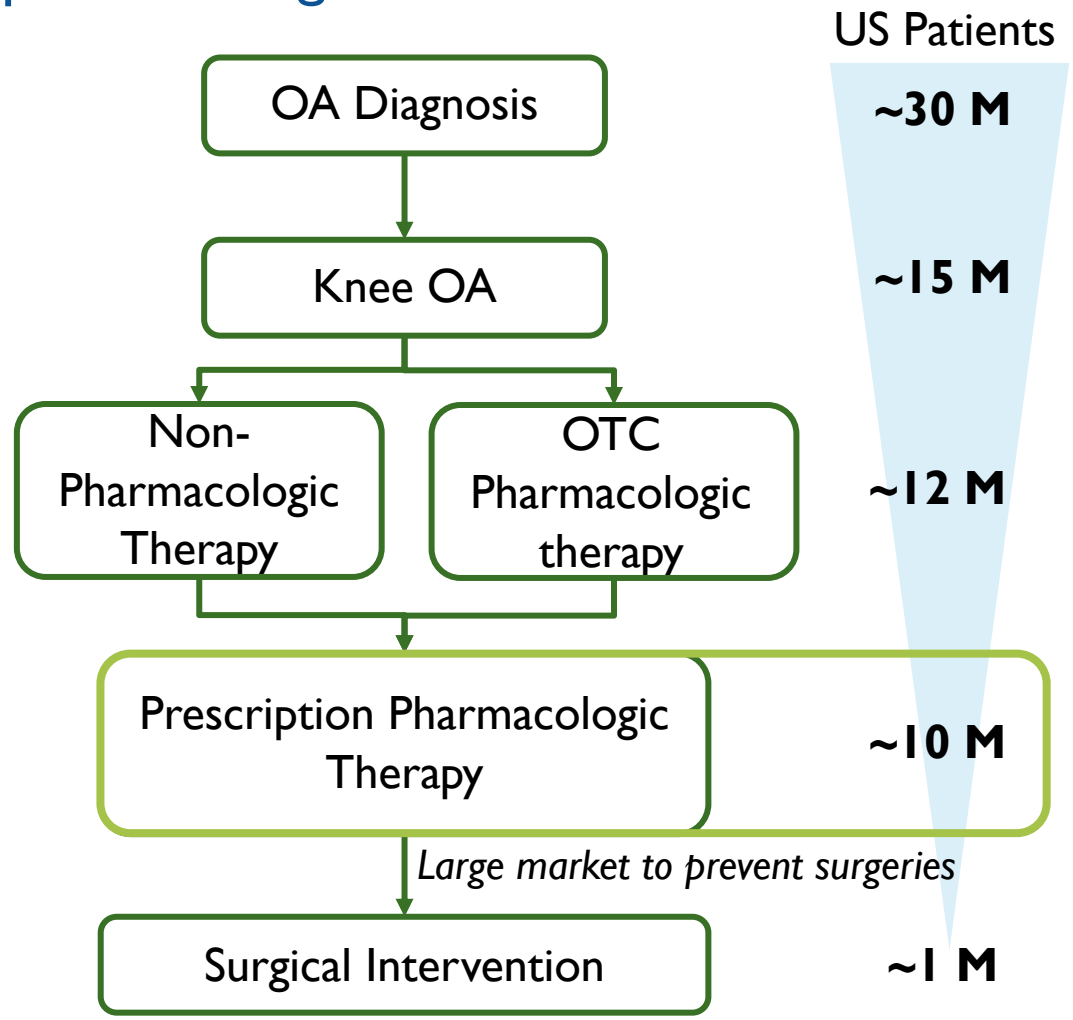
- Demonstrated that **chondrocytes express Nav1.7**, which is associated with both the **progression of joint damage and pain in OA**
- Elucidated **the mechanisms by which Nav1.7 regulate** intracellular signaling and the chondrocyte secretome, which affect OA progression
- Have demonstrated that the **pharmacological inhibition of Nav1.7 ameliorates** the progression of joint damage and pain behavior

Our ChondroNEXT approach and IP are differentiated because we:

- Will **administer Nav1.7 inhibitors via intra-articular injection** into joints, which will **avoid autonomic side effects** and **eliminate the risk of systemic side effects**
- Will combine injectable biomaterials with Nav1.7 inhibitors for sustained release to **generate a novel formulation** that will **significantly reduce the frequency of injections**
- Are **uniquely targeting the root cause of OA**, by protecting joints from degeneration – this will **maintain joint integrity**, and secondarily, **preempt pain**

Osteoarthritis: Treatment Landscape

~1M knee replacements are performed in the US annually – there is a large market to prevent surgical interventions



Knee OA
- The most common form of OA
- Validated preclinical models

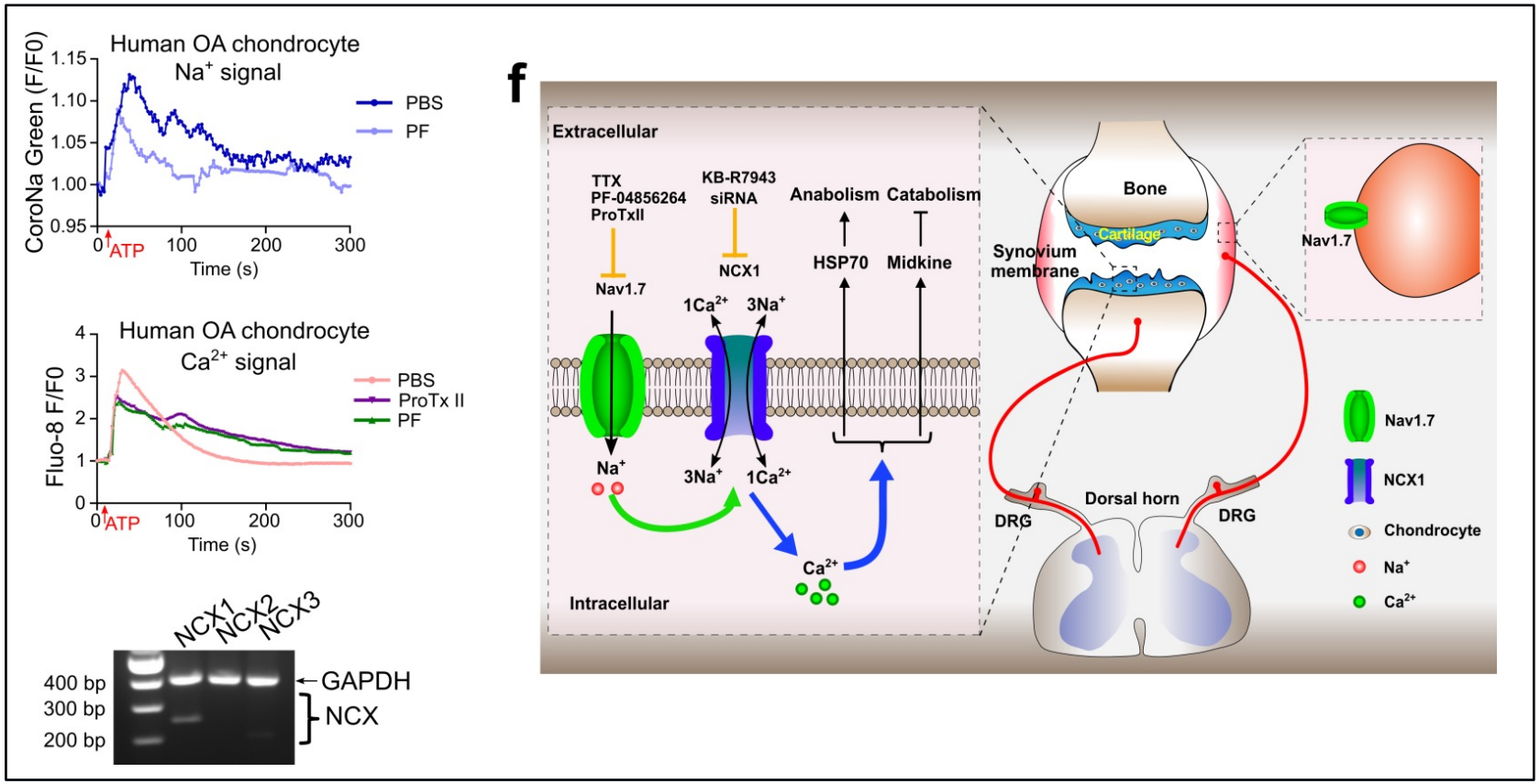
Non-Pharmacologic Therapy
- Can alleviate pain
- Low adherence rates can lead to low efficacy

OTC Pharmacologic Therapies
- Start with topical NSAIDs for favorable safety profile

Prescription Pharmacologic Therapies
- Prescription, oral NSAIDs, SSNRIs, opioids
  - Unfavorable long-term safety
- Intra-articular corticosteroids or hyaluronic acid
  - High cost and questionable efficacy

OTC: Over-the-counter

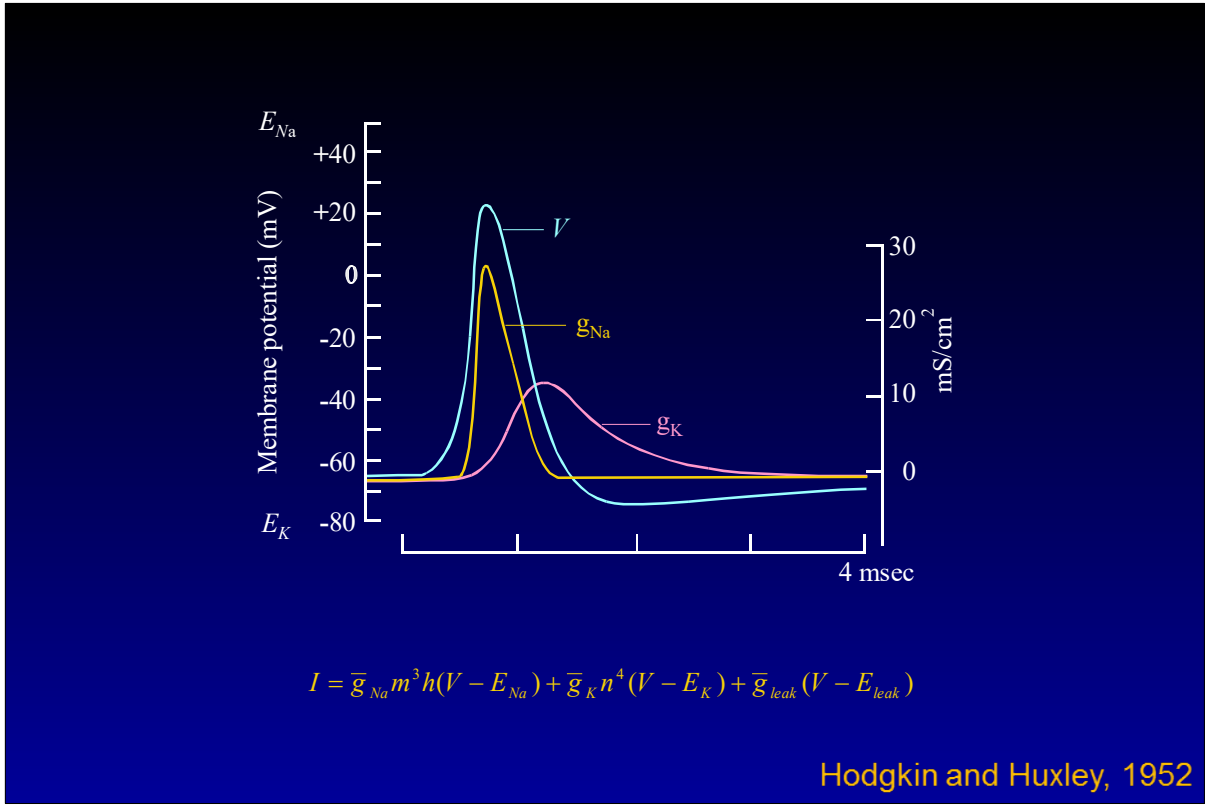
Chondrocyte-specific Nav1.7 biases intracellular Ca^{2+} via an action on NCX1, with a resultant change in midkine and HSP70 secretion



Fu, Vasylyev… Waxman, Liu, *Nature*, 2023

Nav1.7: Background

The discovery of voltage-gated channels was a profound discovery, and there is still a wealth of untapped therapeutic potential in understanding them better



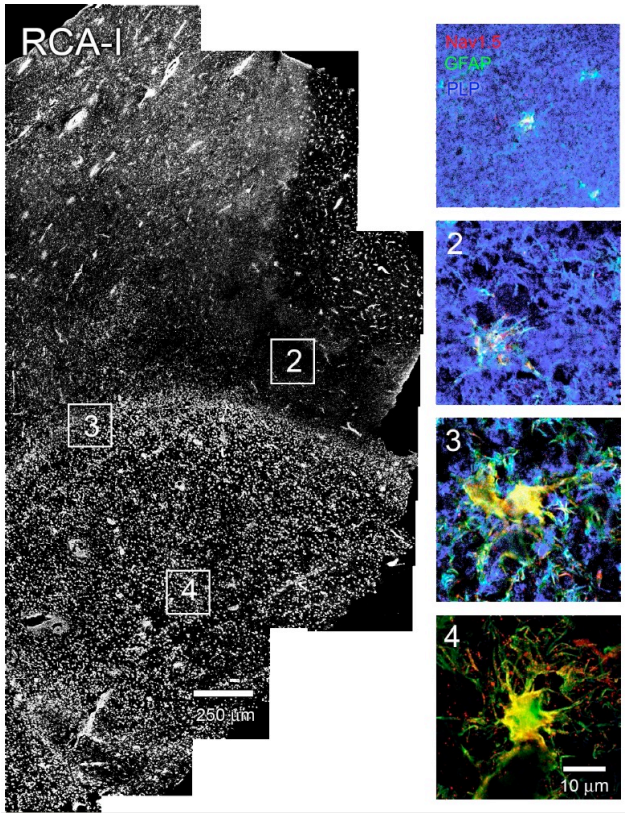
"When Hodgkin and I finished the 1952 papers, we moved to other lines of work … Any idea of analyzing the channels by molecular genetics or patch clamp would have seemed to be … science fiction"

Andrew Huxley, in *The Axon*, 1995

Nav1.7: Background

"Below the Surface": Nav channels are present in low densities within some "non-excitable" cells

Nav1.5 Expression in Astrocytes within MS Tissue



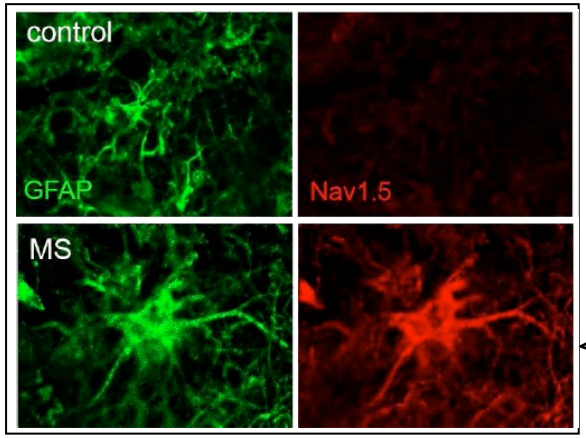
Astrocyte in normal-appearing white matter
Exhibits strong PLP but minimal Nav1.5 labelling
(Not pictured)

Astrocyte between two areas of macrophage infiltration
Hypertrophic and shows upregulation of Nav1.5, with disrupted PLP labelling

Astrocyte at the border of macrophage infiltration
Displays intense Nav1.5 labelling

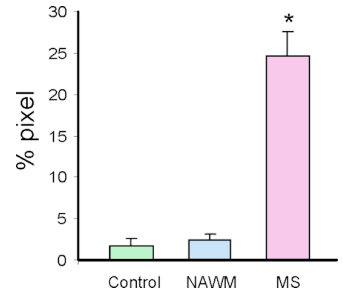
Astrocyte within macrophage infiltration
Displays intense Nav1.5 labelling

Nav1.5 GFAP PLP



Astrocytes with active MS display NAV1.5 labelling

Reactive astrocytes in active MS lesions showed ~10-fold increase in Nav1.5 signaling



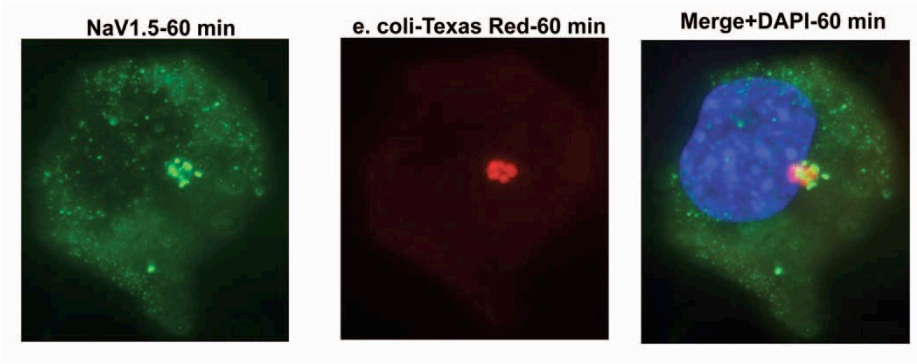
Expression is dynamic: Astrocytes within multiple sclerosis (MS) lesions up-regulate Nav1.5

Black et al, 2010
GFAP: glial fibrillary acidic protein; PLP: proteolipid protein

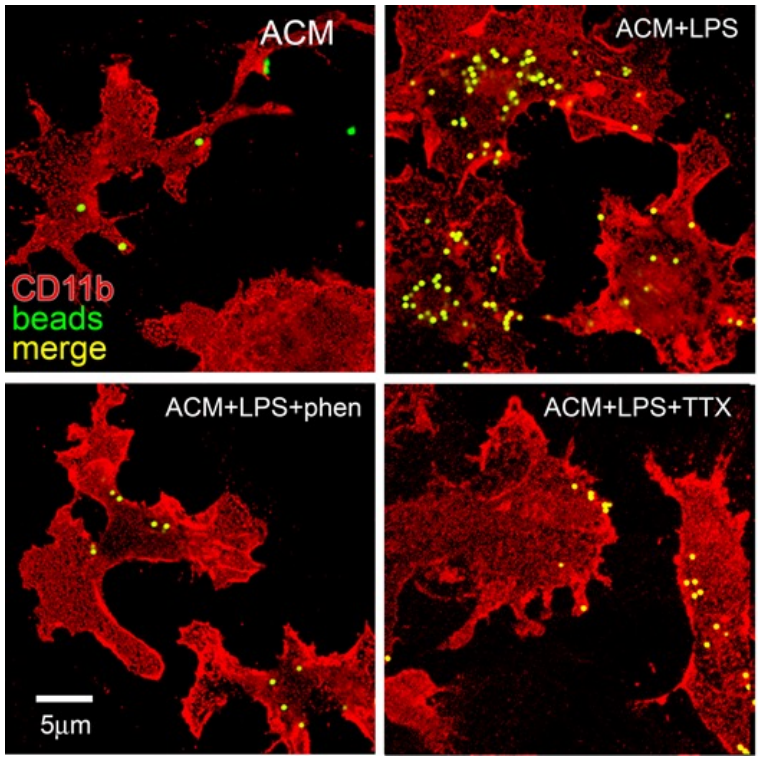
Nav1.7: Background

The presence and role of Nav channels in non-excitable cells have been established for 15+ years

Nav channels are present in macrophages and microglia, and Nav channel blockers were shown to attenuate effector functions (2007)

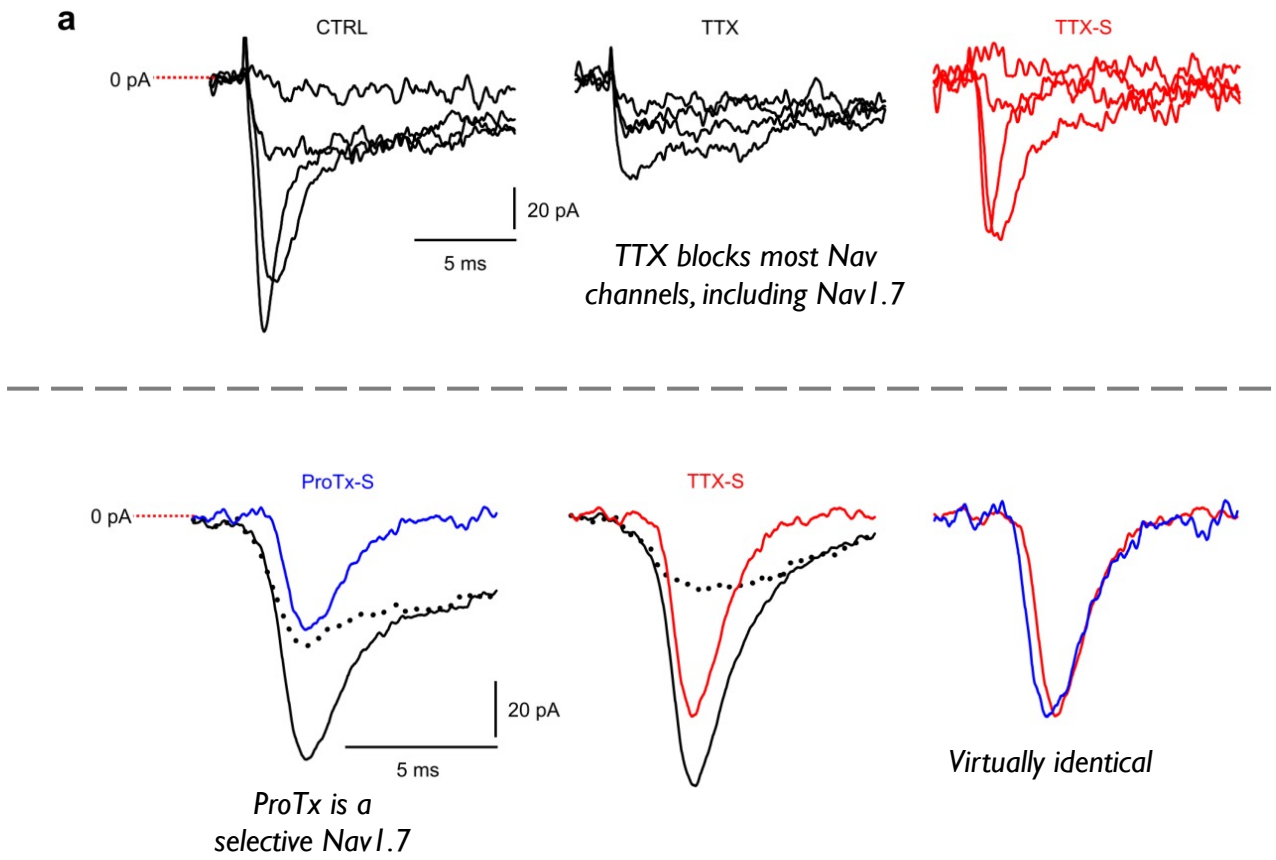


Phenytoin and TTX are shown to inhibit phagocytosis by microglia by blocking Nav channels (2009)

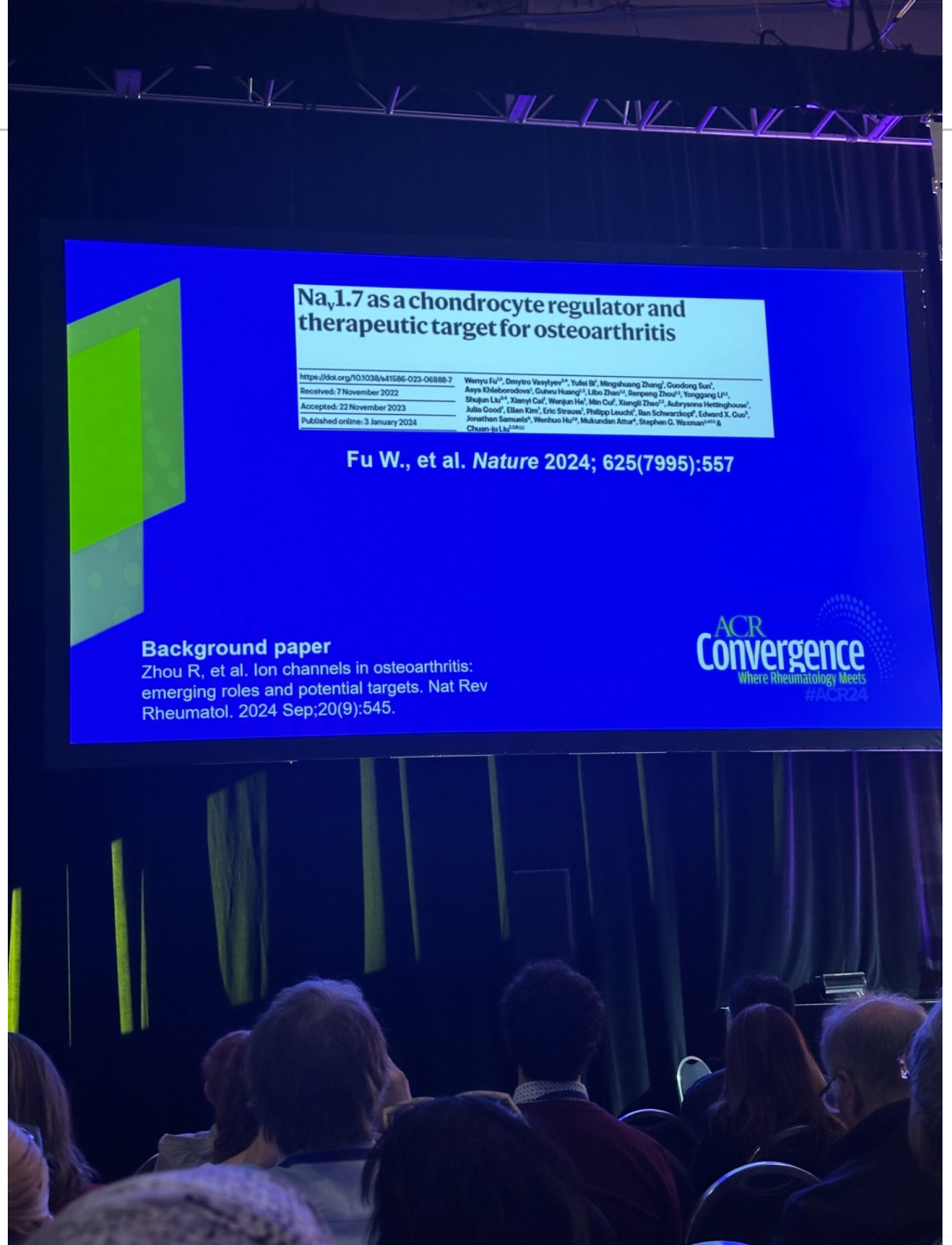


Black et al, 2009; Carrithers et al, 2007
ACM: astrocyte-conditioned medium, LPS: lipopolysaccharide, TTX: tetrodotoxin

Nav1.7 channels are present in the membrane and are functional in OA chondrocyte



Fu et al, Nature, 2024
TTX-S: TTX-sensitive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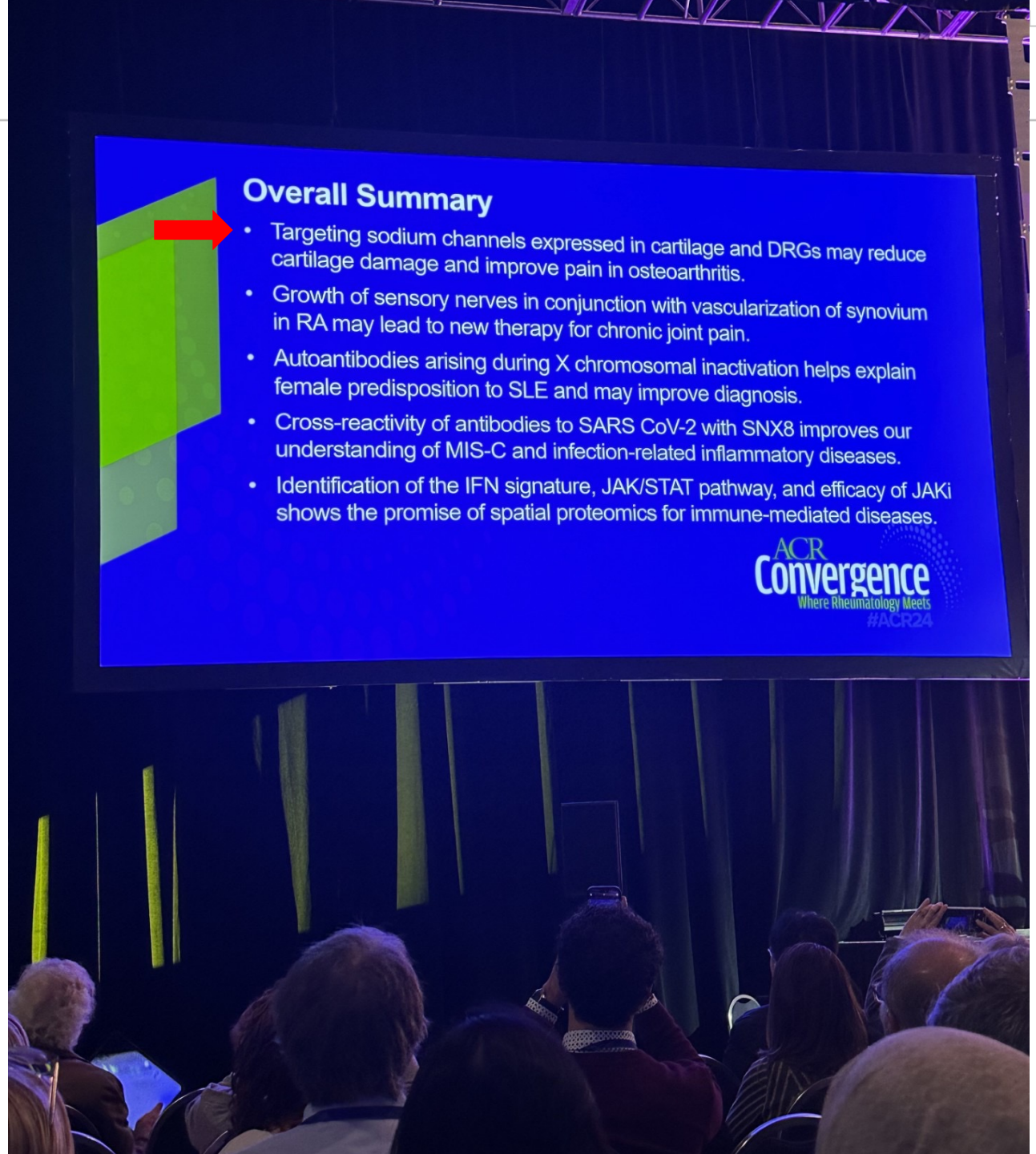
Fu W., et al. Nature 2024; 625(7995):557
Background paper
Zhou R, et al. Ion channels in osteoarthritis: emerging roles and potential targets. Nat Rev Rheumatol. 2024 Sep;20(9):545.
ACR Convergence
Where Rheumatology Meets
#ACR24


Overall Summary
Targeting sodium channels expressed in cartilage and DRGs may reduce cartilage damage and improve pain in osteoarthritis.
Growth of sensory nerves in conjunction with vascularization of synovium in RA may lead to new therapy for chronic joint pain.
Autoantibodies arising during X chromosomal inactivation helps explain female predisposition to SLE and may improve diagnosis.
Cross-reactivity of antibodies to SARS CoV-2 with SNX8 improves our understanding of MIS-C and infection-related inflammatory diseases.
Identification of the IFN signature, JAK/STAT pathway, and efficacy of JAKi shows the promise of spatial proteomics for immune-mediated diseases.
ACR Convergence
Where Rheumatology Meets
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