Convergence™ PHARMACEUTICALS

a Biogen company

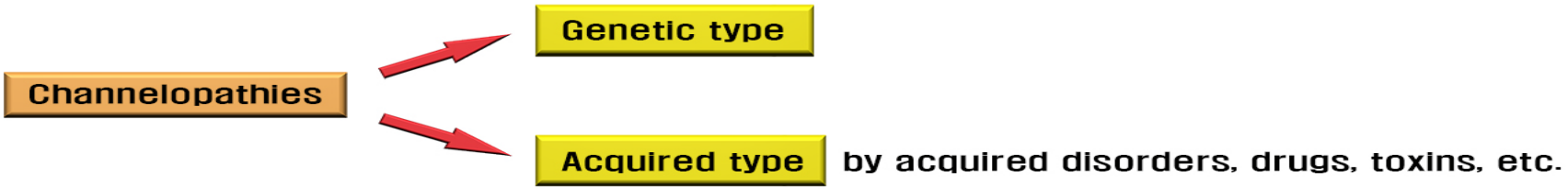
Sodium Channels as targets for precision pain medicine

IMMPACT - XIX

Simon Tate

A major insight is provided by Channelopathies

- *A disease caused by mutations of ion channels*



- *'Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease.'*
- William Harvey, 1578 - 1657

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Nervous System Channelopathies

79 phenotypes identified to date

16 Pain and Nav channel related channelopathies

Disease	Channel protein	Gene
Achromatopsia type 2	Cyclic nucleotide-gated channel, α3 subunit	*CNGA3*
Achromatopsia type 3	Cyclic nucleotide-gated channel, β3 subunit	*CNGB3*
Aland Island eye disease	Cav1.4: calcium channel, voltage-gated, L type, α1F subunit	*CACNA1F*
Andersen-Tawil syndrome	Kir2.1: potassium channel, inwardly-rectifying, subfamily J, member 2	*KCNJ2*
Benign familial infantile epilepsy	Nav2.1: sodium channel, voltage-gated, type II, α subunit	*SCN2A*
Benign familial neonatal epilepsy	Kv7.2: potassium channel, voltage-gated, KQT-like subfamily, member 2	*KCNQ2*
	Kv7.3: potassium channel, voltage-gated, KQT-like subfamily, member 3	*KCNQ3*
Bestrophinopathy, autosomal-recessive	Bestrophin 1	*BEST1*
Central core disease	RyR1: ryanodine receptor 1	*RYR1*
Charcot-Marie-Tooth disease type 2C	Transient receptor potential cation channel, subfamily V, member 4	*TRPV4*
Childhood absence epilepsy	γ-aminobutyric acid A receptor, α1 subunit	*GABRA1*
	γ-aminobutyric acid A receptor, α6 subunit	*GABRA6*
	γ-aminobutyric acid A receptor, β3 subunit	*GABRB3*
	γ-aminobutyric acid A receptor, γ2 subunit	*GABRG2*
	Cav3.2: calcium channel, voltage-gated, T type, α1H subunit	*CACNA1H*
Cognitive impairment with or without cerebellar ataxia	Nav1.6: sodium channel, voltage-gated, type VIII, α subunit	*SCN8A*
Cone-rod dystropy, X-linked, type 3	Cav1.4: calcium channel, voltage-gated, L type, α1F subunit	*CACNA1F*
Congenital distal spinal muscular atrophy	Transient receptor potential cation channel, subfamily V, member 4	*TRPV4*
Congenital indifference to pain, autosomal-recessive	Nav1.7: Sodium channel, voltage-gated, type IX, α subunit	*SCN9A*
Congenital myasthenic syndrome	Cholinergic receptor, muscle nicotinic, α1 subunit	*CHRNA1*
	Cholinergic receptor, muscle nicotinic, β1 subunit	*CHRNB1*
	Cholinergic receptor, muscle nicotinic, δ subunit	*CHRND*
	Cholinergic receptor, muscle nicotinic, ε subunit	*CHRNE*
	Nav1.4: sodium channel, voltage-gated, type IV, α subunit	*SCN4A*
Congenital stationary night blindness type 1C	Transient receptor potential cation channel, subfamily M, member 1	*TRPM1*
Congenital stationary night blindness type 2A	Cav1.4: calcium channel, voltage-gated, L type, α1F subunit	*CACNA1F*
Deafness, autosomal-dominant, type 2A	Kv7.4: potassium channel, voltage-gated, KQT-like subfamily, member 4	*KCNQ4*
Deafness, autosomal-recessive, type 4, with enlarged vestibular aqueduct	Kir4.1: potassium channel, inwardly-rectifying, subfamily J, member 10	*KCNJ10*
Dravet syndrome	Nav1.1: sodium channel, voltage-gated, type I, α subunit	*SCN1A*
	γ-aminobutyric acid A receptor, γ2 subunit	*GABRG2*
Early infantile epileptic encephalopathy type 7	Kv7.2: potassium channel, voltage-gated, KQT-like subfamily, member 2	*KCNQ2*
Early infantile epileptic encephalopathy type 11	Nav2.1: sodium channel, voltage-gated, type II, α subunit	*SCN2A*
Early infantile epileptic encephalopathy type 13	Nav1.6: sodium channel, voltage-gated, type VIII, α subunit	*SCN8A*
Early infantile epileptic encephalopathy type 14	$K_{2P}4.1$: potassium channel, subfamily T, member 1	*KCNT1*
EAST/SeSAME syndrome	Kir4.1: potassium channel, inwardly-rectifying, subfamily J, member 10	*KCNJ10*
Episodic ataxia type 1	Kv1.1: potassium channel, voltage-gated, shaker-related subfamily, member 1	*KCNA1*
Episodic ataxia type 2	Cav2.1: calcium channel, voltage-gated, P/Q type, α1A subunit	*CACNA1A*
Episodic ataxia type 5	Cavβ4: calcium channel, voltage-gated, β4 subunit	*CACNB4*
Familial episodic pain syndrome	Transient receptor potential cation channel, subfamily A, member 1	*TRPA1*
Familial hemiplegic migraine type 1	Cav2.1: calcium channel, voltage-gated, P/Q type, α1A subunit	*CACNA1A*
Familial hemiplegic migraine type 3	Nav1.1: sodium channel, voltage-gated, type I, α subunit	*SCN1A*
Generalized epilepsy with febrile seizures plus (GEFS+)	Navβ1: sodium channel, voltage-gated, type I, β subunit	*SCN1B*
	Nav1.1: sodium channel, voltage-gated, type I, α subunit	*SCN1A*
	γ-aminobutyric acid A receptor, γ2 subunit	*GABRG2*
Generalized epilepsy with paroxysmal dyskinesia	$K_{Ca}1.1$: potassium channel, calcium-activated, large conductance, subfamily M, α1 subunit	*KCNMA1*
Hereditary hyperekplexia	Glycine receptor, α1 subunit	*GLRA1*
	Glycine receptor, β subunit	*GLRB*
Hyperkalemic periodic paralysis	Nav1.4: sodium channel, voltage-gated, type IV, α subunit	*SCN4A*
Hypokalemic periodic paralysis type 1	Cav1.1: calcium channel, voltage-gated, L type, α1S subunit	*CACNA1S*
Hypokalemic periodic paralysis type 2	Nav1.4: sodium channel, voltage-gated, type IV, α subunit	*SCN4A*
Juvenile macular degeneration	Cyclic nucleotide-gated channel, β3 subunit	*CNGB3*
Juvenile myoclonic epilepsy	γ-aminobutyric acid A receptor, α1 subunit	*GABRA1*
	Cavβ4: calcium channel, voltage-gated, β4 subunit	*CACNB4*
Malignant hyperthermia susceptibility	RyR1: ryanodine receptor 1	*RYR1*
	Cav1.1: calcium channel, voltage-gated, L type, α1S subunit	*CACNA1S*
Mucolipidosis type IV	TRPML1/mucolipin 1	*MCOLN1*
Multiple pterygium syndrome, lethal type	Cholinergic receptor, muscle nicotinic, α1 subunit	*CHRNA1*
	Cholinergic receptor, muscle nicotinic, δ subunit	*CHRND*
	Cholinergic receptor, muscle nicotinic, γ subunit	*CHRNG*
Multiple pterygium syndrome, nonlethal type (Escobar variant)	Cholinergic receptor, muscle nicotinic, γ subunit	*CHRNG*
Myotonia congenita, autosomal-dominant (Thomsen disease)	CIC-1: chloride channel 1, voltage-gated	*CLCN1*
Myotonia congenita, autosomal-recessive (Becker disease)	CIC-1: chloride channel 1, voltage-gated	*CLCN1*
Nocturnal frontal lobe epilepsy type 1	Cholinergic receptor, neuronal nicotinic, α4 subunit	*CHRNA4*
Nocturnal frontal lobe epilepsy type 3	Cholinergic receptor, neuronal nicotinic, β2 subunit	*CHRNB2*
Nocturnal frontal lobe epilepsy type 4	Cholinergic receptor, neuronal nicotinic, α2 subunit	*CHRNA2*
Nocturnal frontal lobe epilepsy type 5	$K_{2P}4.1$: potassium channel, subfamily T, member 1	*KCNT1*
Paramyotonia congenita	Nav1.4: sodium channel, voltage-gated, type IV, α subunit	*SCN4A*
Paroxysmal extreme pain disorder	Nav1.7: Sodium channel, voltage-gated, type IX, α subunit	*SCN9A*
Potassium-aggravated myotonia	Nav1.4: sodium channel, voltage-gated, type IV, α subunit	*SCN4A*
Primary erythermalgia	Nav1.7: sodium channel, voltage-gated, type IX, α subunit	*SCN9A*
Retinitis pigmentosa type 45, autosomal-recessive	Cyclic nucleotide-gated channel, β1 subunit	*CNGB1*
Retinitis pigmentosa type 49, autosomal-recessive	Cyclic nucleotide-gated channel, α1 subunit	*CNGA1*
Retinitis pigmentosa type 50, autosomal-dominant	Bestrophin 1	*BEST1*
Scapuloperoneal spinal muscular atrophy	Transient receptor potential cation channel, subfamily V, member 4	*TRPV4*
Small fiber neuropathy	Nav1.7: sodium channel, voltage-gated, type IX, α subunit	*SCN9A*
Spinocerebellar ataxia type 6	Cav2.1: calcium channel, voltage-gated, P/Q type, α1A subunit	*CACNA1A*
Spinocerebellar ataxia type 13	Kv3.3: potassium channel, voltage-gated, Shaw-related subfamily, member 3	*KCNC3*
Vitelliform macular dystrophy	Bestrophin 1	*BEST1*
Vitreoretinochoroidopathy	Bestrophin 1	*BEST1*

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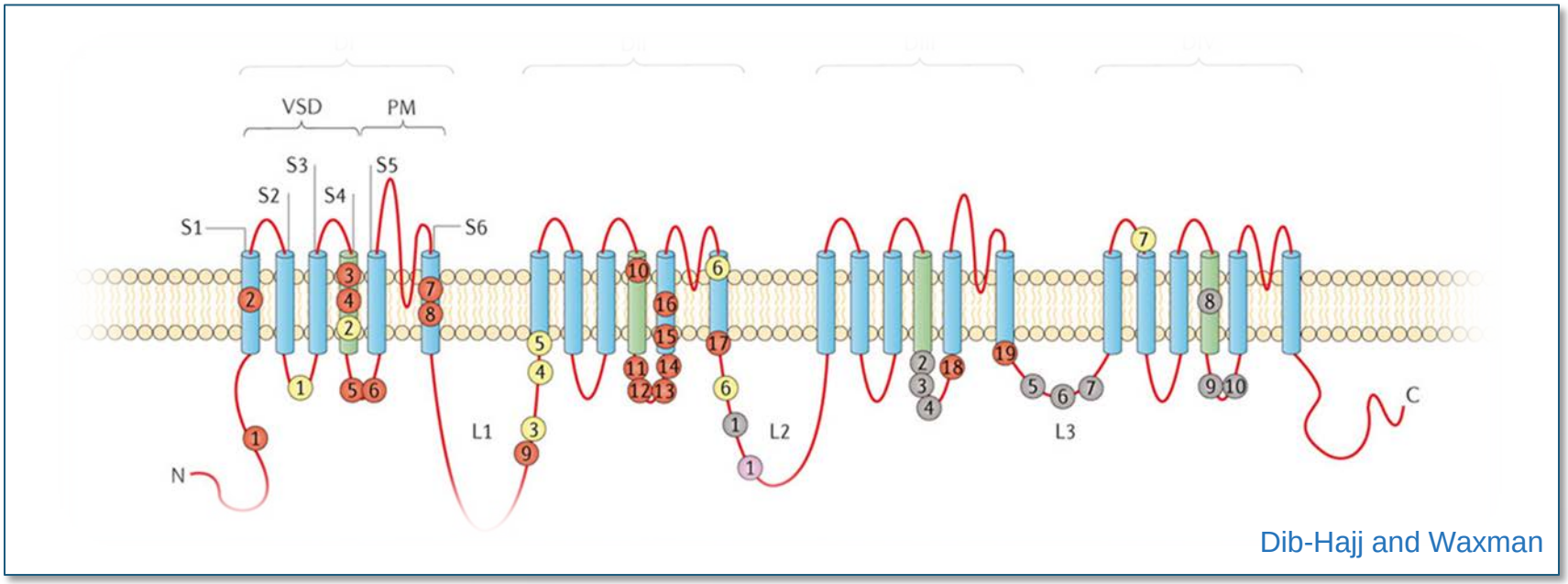
Modified from JB KIM, Korean J of pediatry, 2014

Targeting Sodium Channel (Nav) Dysfunction in Pain



Dib-Hajj and Waxman

- Voltage-gated sodium channels, play a key role in the initiation of action potentials and subsequent propagation of pain signalling
- Genetics link SCN9A ***($Na_v1.7$ channel)*** with a variety of painful clinical syndromes, such as ***Erythromelalgia*** and ***Small Fibre Neuropathy***

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Will Nav1.7 Inhibitors Work In Chronic Pain?

Molecule

Differentiate over current Nav blockers, mechanism of action, Drug like, Good TI, CNS penetrant?

Phase 1

Good PK, Orally bioavailable, Well Tolerated, Evidence of PD effect

Proof of Concept

Genetically validated population e.g. inherited erythromelalgia

Pharmacologically validated pain condition e.g. Trigeminal neuralgia

Combination of inferred pharmacology and mechanistic rationale. e.g. LSR as a compression neuropathy

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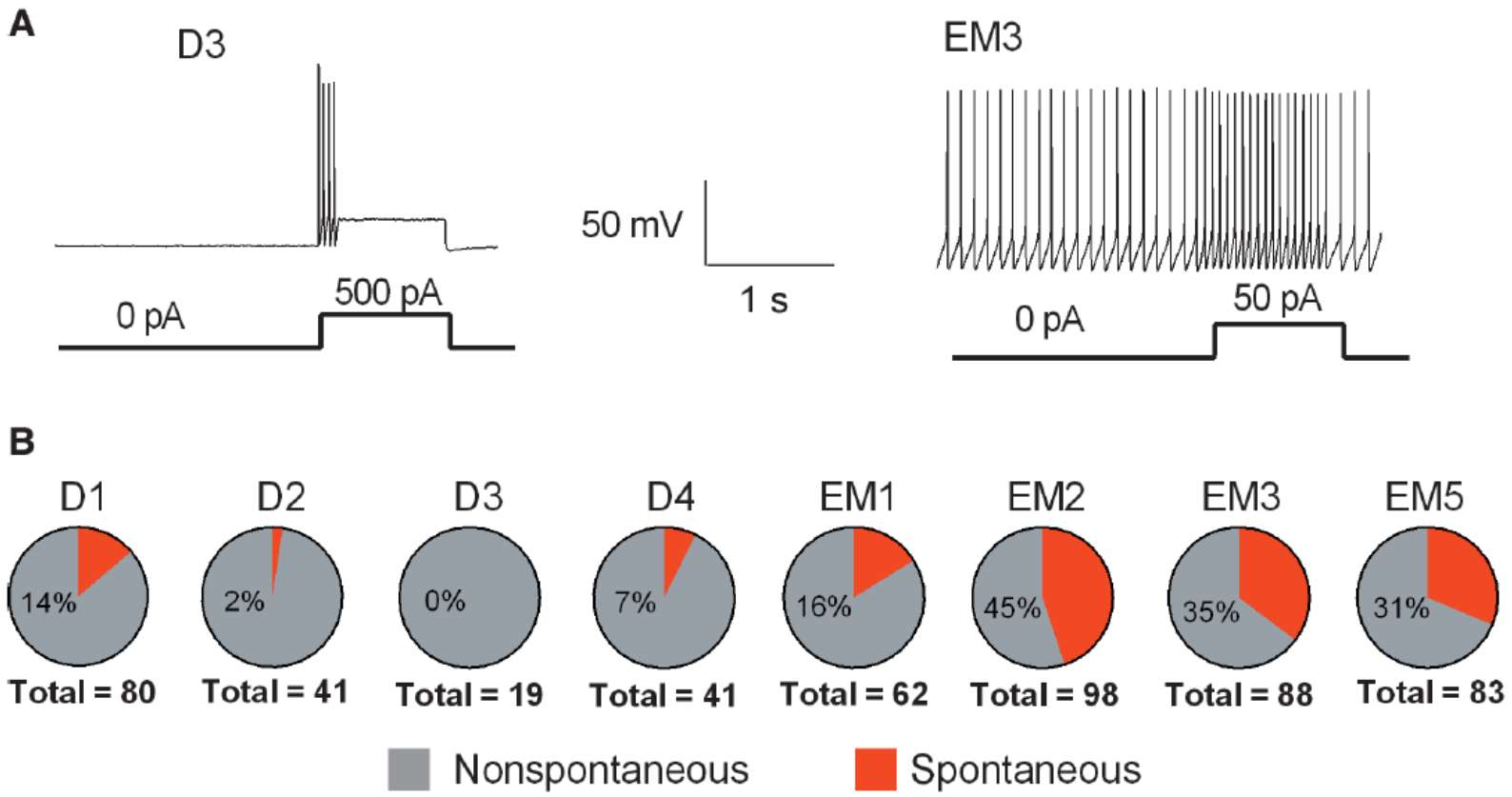
iPS derived sensory neurons from patients with inherited Erythromelalgia – spontaneous activity



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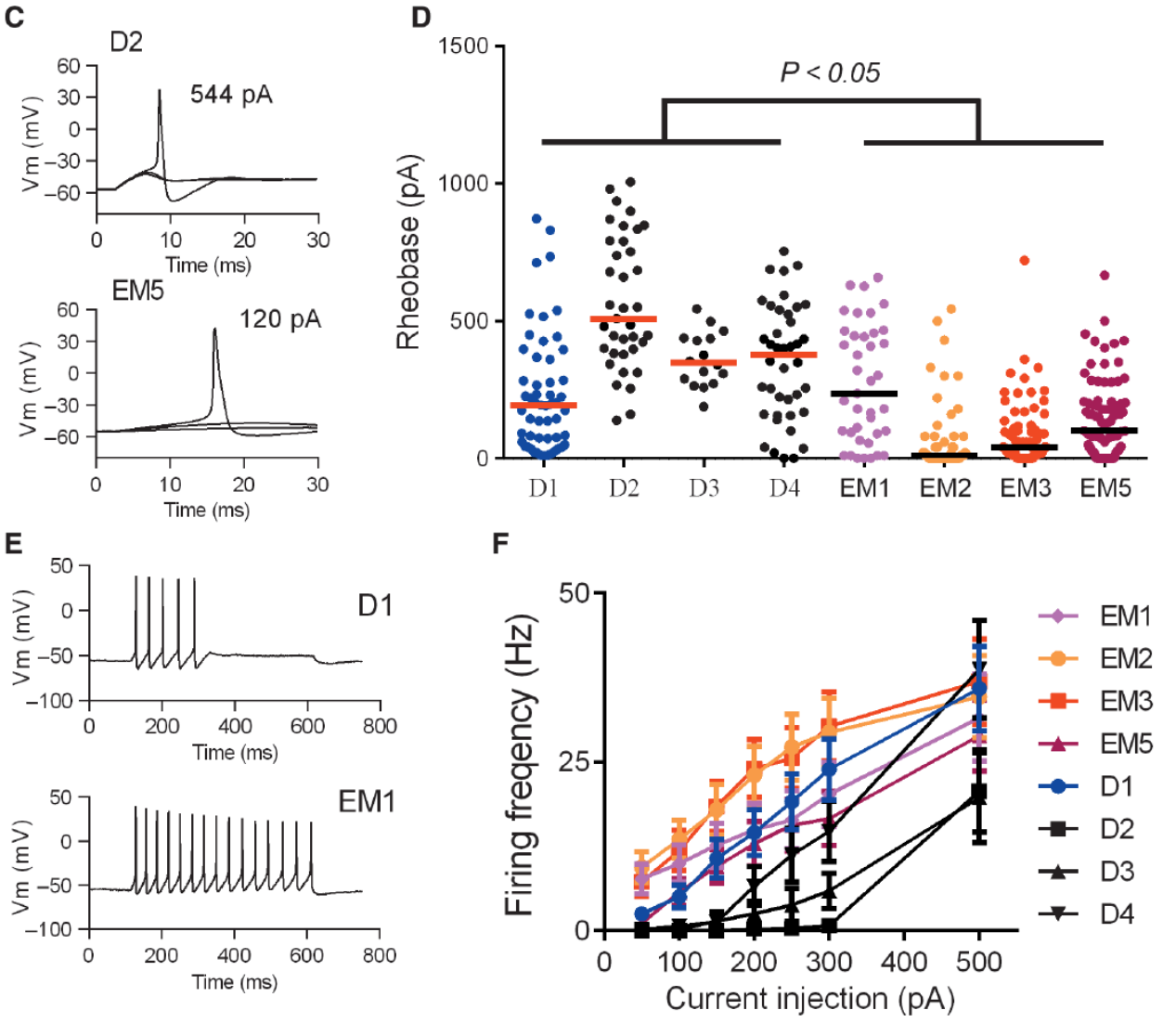
Cao et al Science Translational Medicine 2016

iPS derived sensory neurons from patients with inherited Erythromelalgia – action potentials



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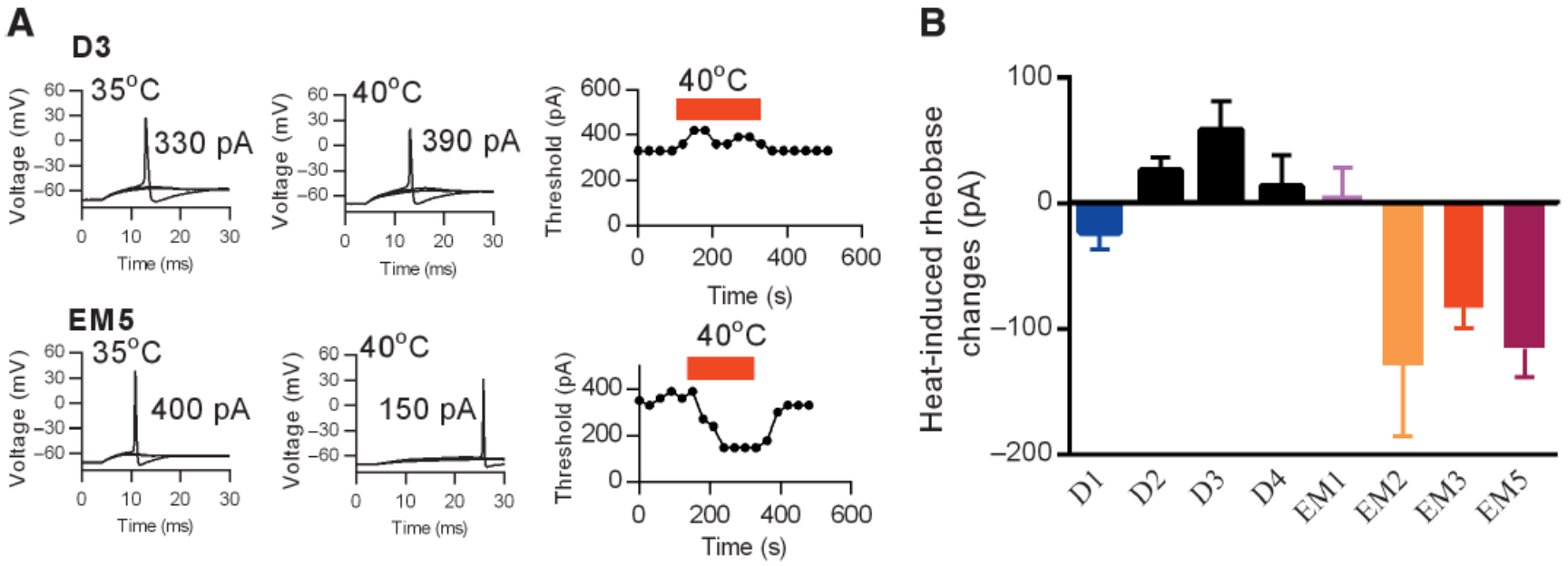
Cao et al Science Translational Medicine 2016

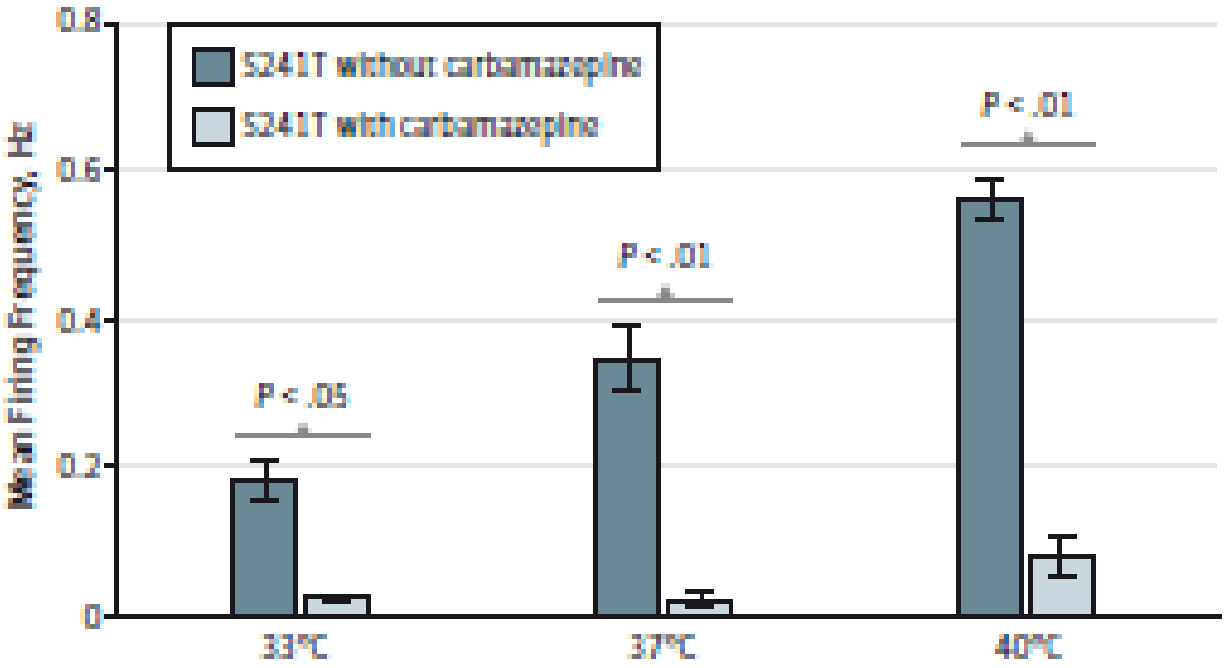
iPS derived sensory neurons from patients with inherited Erythromelalgia – heat sensitivity



Cao et al Science Translational Medicine 2016

CBZ effect on firing frequency in EM patients with S241T mutation

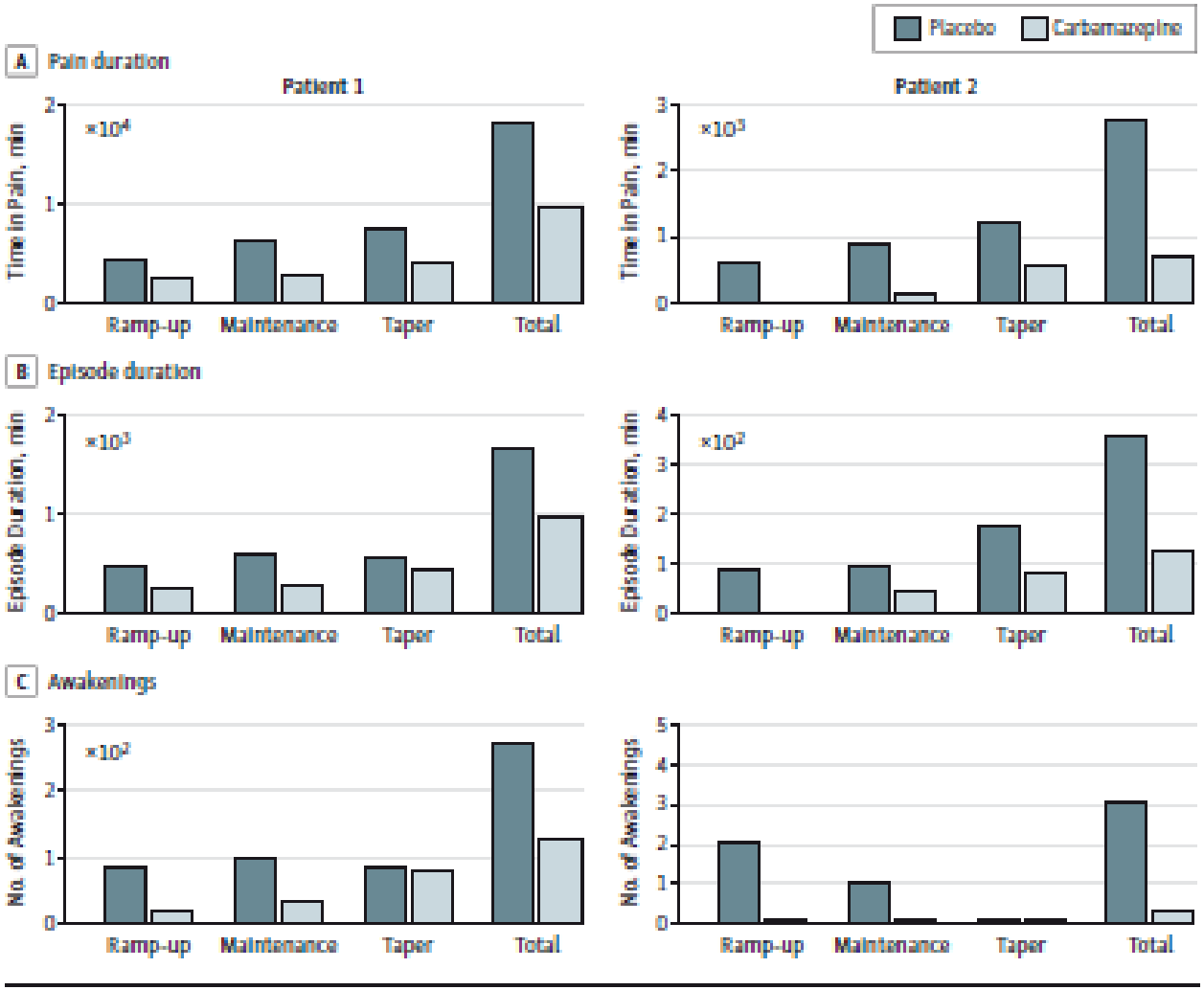
Figure 7. Firing Frequency



Mean firing frequency of neurons (n = 98) expressing $Na_v1.7$ S241T before and after carbamazepine treatment at all 3 temperatures.

Geha et al JAMA Neurol 2016

CBZ treatment in EM patients with S241T mutation



Pain characteristics and effects of carbamazepine treatment vs placebo for patients 1 and 2. A, Time in pain as reported in patients' diaries during the 3 phases of treatment ramp-up, maintenance, and taper. Histograms represent means. B, Same as in panel A for the reported duration of inherited erythromelalgia episodes. C, Number of awakenings due to pain during 3 phases of ramp-up, maintenance, and taper.

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Geha et al JAMA Neurol 2016

Tremendous Unmet Need in Trigeminal Neuralgia

- Attacks of facial pain (paroxysms) - usually associated with entrapment of the trigeminal nerve with a blood vessel
  - "..sudden, severe, brief, stabbing pain occurring in attacks lasting at the most a few seconds usually only on one side of the face and provoked by light touch"
  - "an electric shock"
  - "stabbing, shooting, burning, excruciating.."
  - "unlike any other pain previously experienced"

  (quotes above taken from Trigeminal Neuralgia Association - 'Facing Pain Together')
- Paroxysm frequency depends on severity of disease
  - Range: a few times a month to several times each day
- Treatment options are limited: anticonvulsants or surgery

Only one drug licensed for this condition (Carbamazepine)
UK 1965, USA 1974

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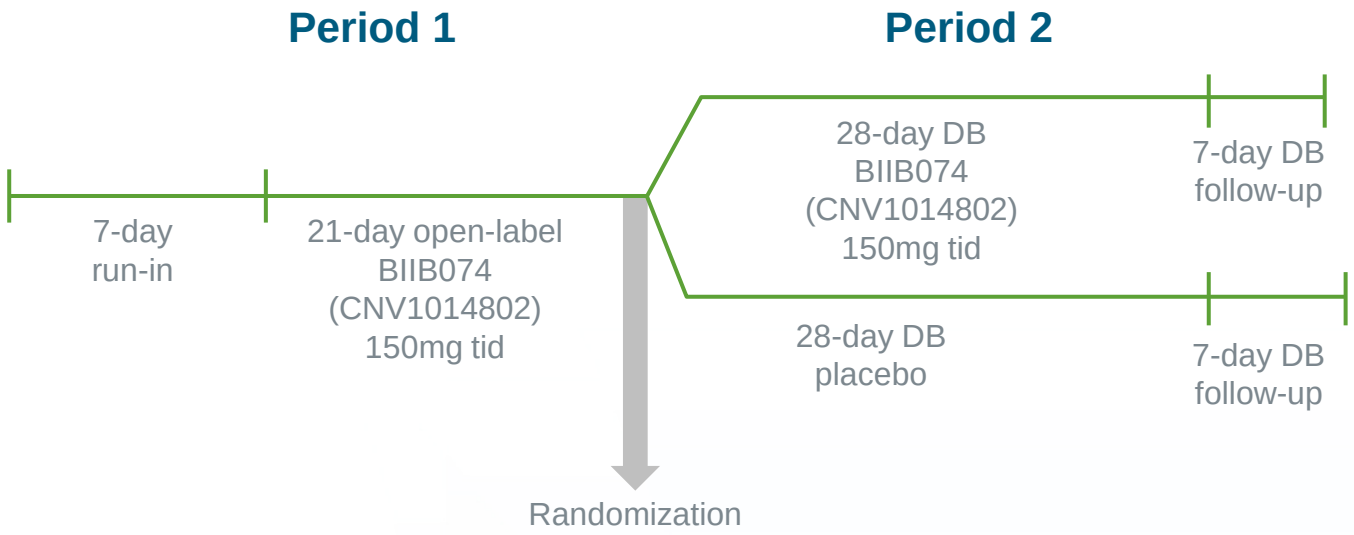
Phase 2 Clinical Protocol in Trigeminal Neuralgia*



ITT population, n=29

70.5% (31/44 pts) completing open-label treatment had a significant response

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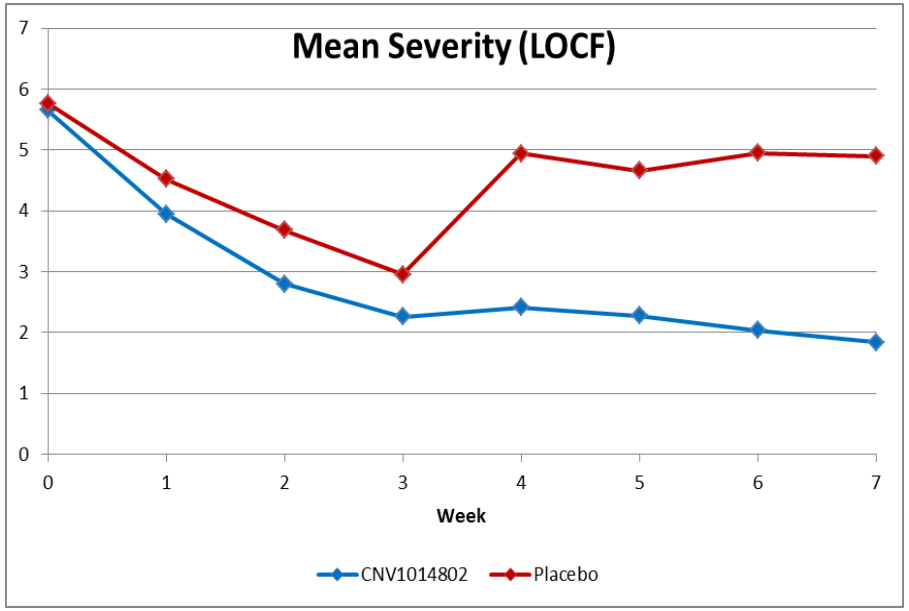
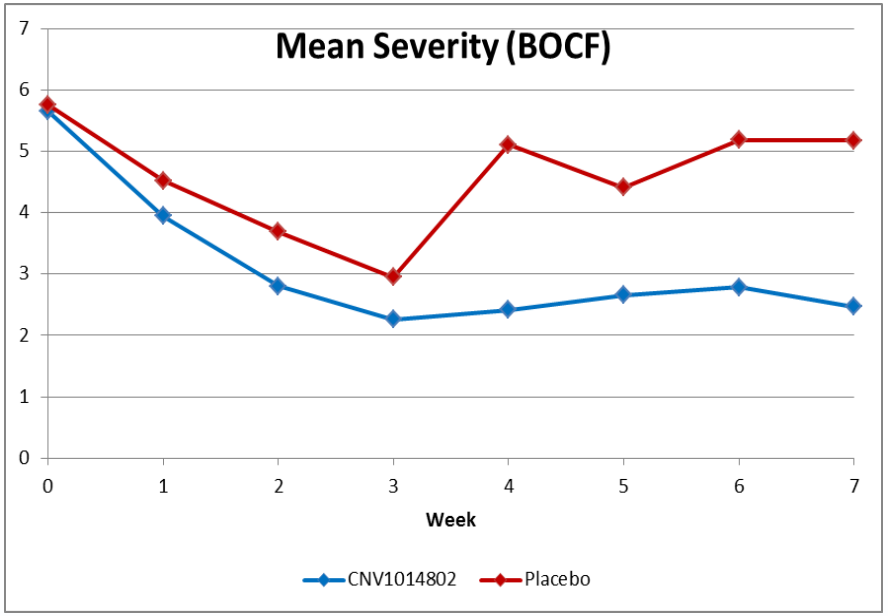
* Presented at World Pain Congress 2014 and American Pain Society 2015.

Analysis Reveals Clinically Significant Benefit in Average Daily Pain Score





Analysis	Least Square Means		Comparison (BIIB074 (CNV1014802) – Placebo) (95% CI)	p-value
	Placebo (N=14)	BIIB074 (CNV1014802) (N=15)		
BOCF*	-0.74	-3.05	-2.31 (-3.78, -0.83)	0.0035
LOCF**	-1.10	-3.59	-2.50 (-4.16, -0.84)	0.0048

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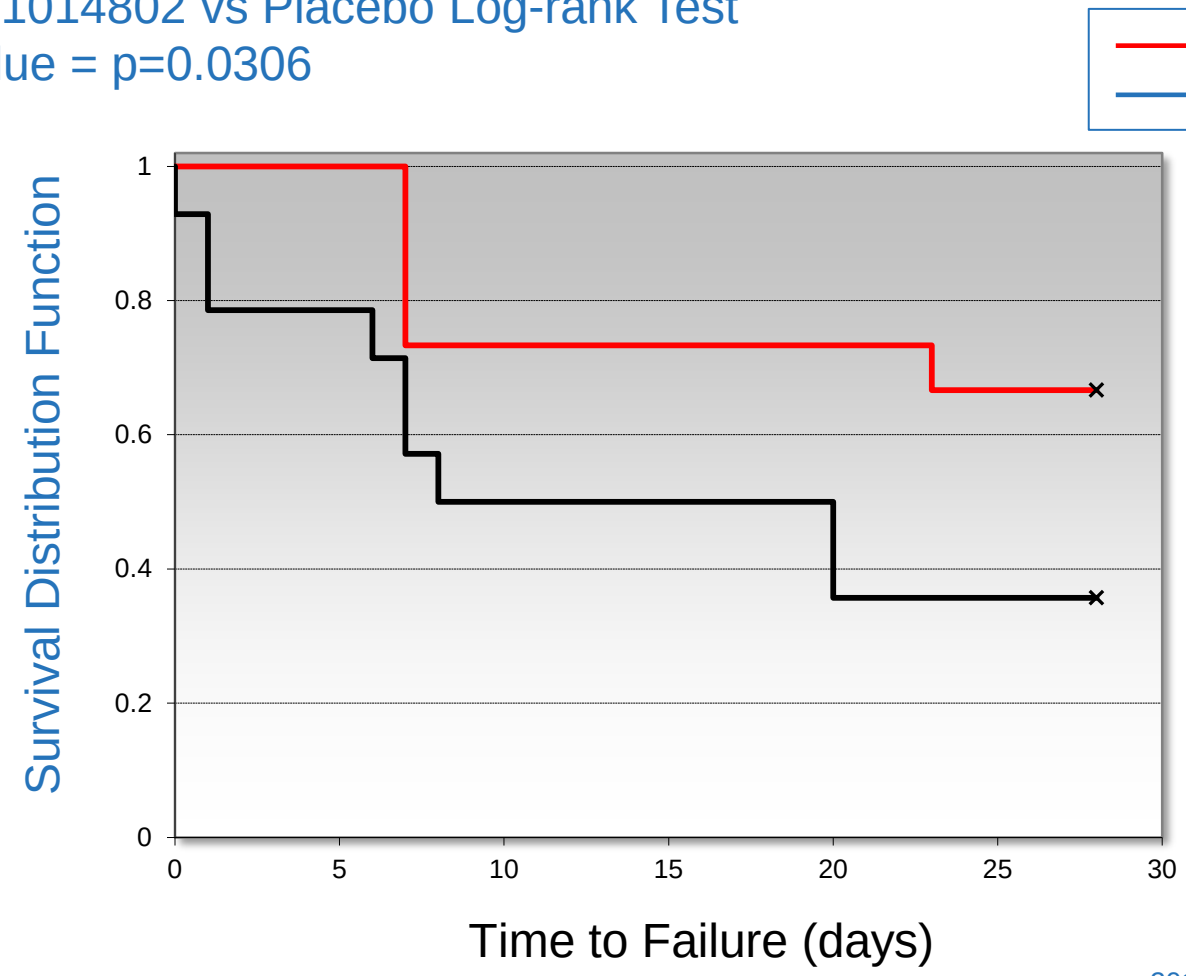
** BOCF = Baseline observation carried forward*
*** LOCF = Last observation carried forward*

2014. **S. Tate**, et al.
15th World Congress on Pain, Buenos Aires.

Kaplan-Meier Analysis of Time to Failure During the Randomised Double Blind Phase

CNV1014802 vs Placebo Log-rank Test
p-value = p=0.0306



- 2 out of 10 CNV1014802 completers were taking GBP
- 3 out 5 placebo completers were taking GBP or PGB

2014. **S. Tate**, et al.
15th World Congress on Pain, Buenos Aires.

Favourable Efficacy Outcomes on All Endpoints

- Fewer patients experienced treatment failure (33.3%) versus placebo (64.3%) (p=0.0974)
- Longer time to treatment failure versus placebo (p=0.0306; KM analysis)
- After 4 weeks, pain intensity NRS values were 50% lower versus placebo (p=0.0009)
- Clinicians and patients reported greater improvement rates versus placebo
  - CGIC: improvement rate for BIIB074 (CNV1014802) was 80% vs 35% for placebo (p=0.0051)
  - PGIC: improvement rate for BIIB074 (CNV1014802) was 73% vs 50% for placebo (p=0.0265)

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Safety and Toleration Profile

- In the open label phase, CNV1014802 was well tolerated with small numbers of patients experiencing one or two episodes of mild dizziness or headache
- In the double blind phase, the overall profile of CNV1014802 was similar to placebo with remarkably few AEs
- Three patients discontinued with adverse events in the open-label period (dry skin/increased turgor, dyspnoea, hypertension)
- Three SAEs were reported; none related to study medication
- Data from laboratory safety tests, blood pressure measurements, heart rate and ECG indicate no clinically significant change

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