Chromocell Therapeutics Development Update

September 2019

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CC8464 Executive Summary

In-vitro	• Potent (nM) inhibitor of human $Na_V1.7$ • Subtype and state selective
In-vivo	• Demonstrated *in vivo* efficacy in several rodent models of pain: Acute, chronic neuropathic, inflammatory, visceral, post-surgical and chemotherapy-induced
ADME	• 1-4hr $t_{1/2}$ in animal species • Peripherally restricted, no CNS and muscle/motor dysfunction effects
CMC	• Drug Substance scaled up to 30+ kg • Drug Product: tablet (active, 3 strengths and placebo) available for Phase 2
IP	• US species patent granted, expiration in 2034
Regulatory	• Fast track IND status for idiopathic Small Fiber Neuropathy (iSFN) indication
Clinical	**CC8464 is Phase 2 ready clinical asset**: • Phase 1 completed with good tolerability up to 1200mg x14 days, QD • Clinical data supports initiation of Phase 2a/POC studies in chemotherapy-induced peripheral neuropathy and neuropathic pain in 2019-2020

Na_V 1.7 Background

$Na_V1.7$ (SCN9A) is a Validated Target for Pain Treatment

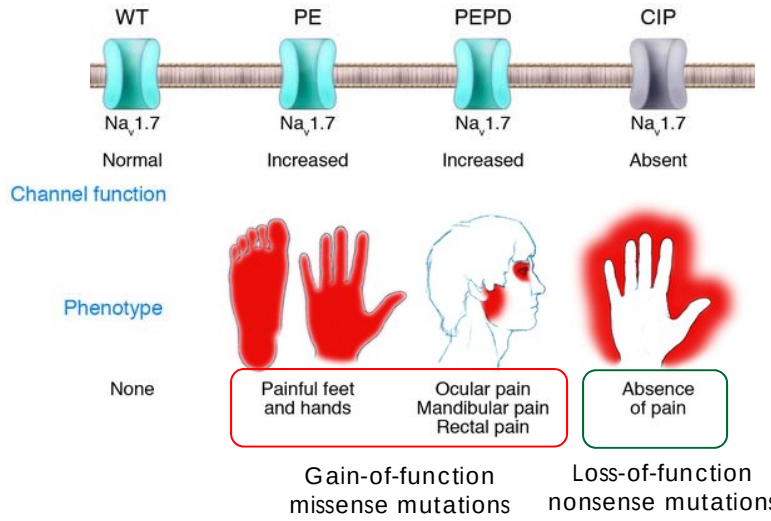
Human mutations in SCN9A have been linked to a number of inherited pain disorders

Primary Inherited Erythromelalgia, EM
- Burning pain, redness and heat in the extremities
- Mutations affecting $Na_V1.7$ activation

Paroxysmal extreme pain disorder, PEPD
- Burning pain in rectal, ocular and mandibular areas
- Mutations affecting $Na_V1.7$ fast inactivation

Idiopathic Small Fiber Neuropathy, iSFN
- Pain attacks starting in extremities
- Mutations affecting $Na_V1.7$ slow inactivation

Congenital Insensitivity to Pain, CIP
- Severe defect in pain perception, but otherwise normal phenotype
- Mutations result in truncated non-functional $Na_V1.7$ channels



From Drenth JP, Waxman SG., J Clin Invest. 2007 Dec;117(12):3603-9

> Alterations in $Na_V1.7$ properties can profoundly impact pain sensitivity

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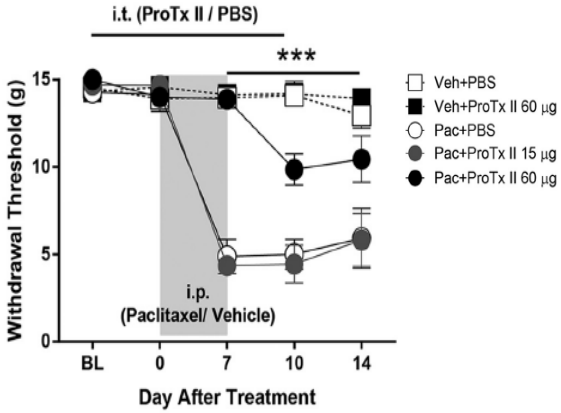
Na_V 1.7: Increasing Evidence of Target Relevance for Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- Chemotherapy-induced neurotoxicity presents as a predominantly sensory peripheral neuropathy associated with spontaneous activity/hyperexcitability of the dorsal root ganglion (DRG) due to neuronal cell damage
- Application of oxaliplatin to rat DRG neurons increases Na(+) current & alters Na_V channel kinetics
- Na_V1.7 protein expression and current density increases in DRGs from rats with paclitaxel-induced peripheral neuropathy
- Na_V1.7 protein expression and current density are increased in human DRGs with spontaneous ectopic activity from patients who have undergone chemotherapy
- A selective Na_V1.7 blocker, ProTx II, prevents the development of, and alleviates established, mechanical hypersensitivity in paclitaxel CIPN rat model



Park et al. Curr Med Chem. 2008;15(29):3081-94
Adelsberger et al. European Journal of Pharmacology 2000;406(1):25-32
Li Y et al. J Neurosci. 2018;38 (5) 1124-1136
Egashira et al. J Pharmacol Sci. 2010;112, 473 – 476

> Accumulating evidence suggests that Na_V1.7 modulation has the potential to prevent and treat chemotherapy-induced peripheral neuropathy

Na_V 1.7 Inhibition – a Non-Opioid Alternative for Pain Management

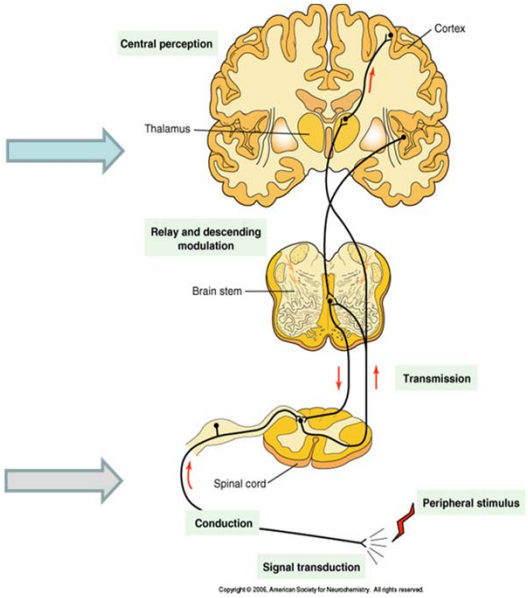
Challenges of the Opioid Epidemic:

Francis Collins, M.D., Ph.D.
Director, NIH September 18, 2017

- *25.5 million adults have pain every day*
- *Opioids are overprescribed, but often not effective for chronic pain*
- *More than 2 million Americans are addicted to opioids, most started with prescription medicines*
- *Huge increase in opioid-induced overdose death rates over recent years*
- *New, non-addictive pain medicines are urgently needed*

Opioids work predominantly via central nervous system (CNS)
- In the CNS opioids have direct effects on brain reward systems (abuse liability)

Selective Na_V 1.7 blockers (CC8464) attenuate pain signal conduction peripherally
- CC8464 does not penetrate CNS
- No rewarding effects (no abuse liability)



Human genetics and nonclinical research data support that Na_V 1.7 inhibitors have potential to provide treatment options for pain without opioid induced side-effects

$Na_V1.7$ Competitive Landscape

$Na_V1.7$ Competitive Intelligence Overview

Pfizer PF-05089771

- Most similar profile to CC8464 (peripherally restricted, high potency and subtype selectivity)
- Positive efficacy and trends in Phase 2
- Dose limited due to side effect of increased LDL-cholesterol: Discontinued

Xenon

- Teva TV-45070 (XEN402)
  - Limited to topical administration due to CNS adverse effects of oral
  - Phase 2 (topical) in osteoarthritis (OA) and post-herpetic neuralgia (PHN) negative
  - XEN402 licensed by Flexion for the treatment of post-operative pain via peripheral nerve block in Sept. 2019
- Genentech GDC-0310 Phase 1: Delayed by toxicology and program discontinued

Biogen

- BIIB074: Non-selective, low potency, CNS active
  - Positive Phase 2a in trigeminal neuralgia (TGN)
  - Positive Phase 2a in painful lumbosacral radiculopathy (PLSR) not replicated in large Phase 2
  - Ongoing Phase 2 in small fiber neuropathy (SFN)
  - Delayed start of Phase 3 in trigeminal neuralgia (TGN)
- BIIB095: Phase 1, may be incremental improvement on BIIB074

SiteOne/Amgen

- State-independent $Na_V1.7$ blocker inhibits protective pain perception: Pre-clinical

Comparison with Clinical Competitor Compounds

	IC_{50}, nM						
Compound	**$hNa_V1.1$**	**$hNa_V1.2$**	**hNav1.3**	**$hNa_V1.4$**	**$hNa_V1.5$**	**$hNa_V1.6$**	**$hNa_V1.7$**
CC8464	7300	90	> 3,000	5300	> 100,000	130	12
PF 050897771 [1)]	700	120	11,000	10,000	25,000	170	11 (40)
Biogen BIIB074 [2)]	2000	2500	1500	800	6000	7900	1000-2600 (>3000)
Xenon/Teva TV-45070 [3)]	Not reported						80 (500)
Xenon/Genentech [4)]	100-150	400-700		40-70	> 2000	> 2000	4-7

Internal data generated at the $V_{1/2}$ - the half-maximal voltage of inactivation/holding potential. Values in parenthesis are measured in-house using the same electrophysiology assay as for CC8464. 1) US 2010-0197655, selectivity data from poster at IASP, 2012; 2) Poster at IASP, 2012; and Keppel Hesselink 2017; 3)Goldberg et al. Pain 2012; TV-45070 reported as "inhibitor of $Na_V1.7$ and other sodium channels"; 4) Poster at IASP, 2014 presented as Compound A.

- CC8464 is 4x more potent $hNa_V1.7$ than PF 05089771 measured in the same assay/cell line
- BIIB074 appears to be a non-selective blocker of sodium channels
- Xenon/TEVA TV-45070 inhibits additional sodium channels [3)], topical formulation only
- Xenon/Genentech GDC-0310 structure is not disclosed; reported Compound A has low fold selectivity on $Na_V1.4$

CC8464 target potency and selectivity profile is superior to Biogen and Teva; and similar to Genentech and Pfizer

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Pfizer PF-05089771

- Selective, high potency, peripherally restricted $Na_V1.7$ sodium channel inhibitor
- Phase 1 SAD/MAD/rBA/DDI/PainCart studies:
  - Overall well tolerated up to 2.4 g in SAD / up to 600 mg BID MAD
  - *Maculopapular rash/pruritus* observed in MAD studies with increasing doses from 450 mg – 600 mg BID
    - Rash and skin AEs were mostly mild to moderate
    - Pruritus/rash avoided by titration* (150: 300: 450 mg BID 1wk: 1wk: 2wk)
  - *Increase in LDL-cholesterol* observed at 450 mg BID; dose limiting factor for DPN Ph 2
- Phase 2 studies:
  - Dental Post-Operative Pain: Parallel group, vs. PBO & ibuprofen, single dose 150 mg, 450 mg, 1600 mg, n=235*; efficacy over PBO demonstrated for all doses*
  - Erythromelalgia: Crossover, vs. PBO, single dose 1600 mg, n=5; *demonstrated analgesic efficacy*
  - Diabetic Peripheral Neuropathy: Parallel group, vs. PBO & pregabalin, 4-wk treatment, 150 mg BID, n=135
    - *Trends for improvement* in primary and secondary endpoints some of which were significantly improved vs. PBO (PF-05089771 difference vs PBO -0.51 [-1.07, 0.05[#], 0-10 Pain NRS])
    - *No cardiovascular or CNS-related adverse events*, which limited the utility of non-selective channel blockers in the treatment of pain

Summary:

- PF-05089771 demonstrated efficacy across multiple pain indications supporting development of high potency, peripherally restricted and subtype selective $Na_V1.7$ channel blockers. Commercial considerations limited the dose of based on LDL findings resulting in suboptimal efficacy; program discontinued
- **CC8464: No LDL signal identified; opportunity to dose higher with an increase in efficacy**

*Results presented at 16th Annual Pain Therapeutics Conference, London, May 2016
[#]90% confidence interval

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Xenon/Teva TV-45070

- TV-45070 (also XPF-001, XEN401, XEN402, Funapide,) is a chiral small molecule "inhibitor of $Na_V1.7$ and other sodium channels" (Xenon releases)
- Xenon reported low nanomolar potency in the guanidine influx assay (US 2011/0087027A1); Chromocell synthesized and tested both S-and R- enantiomer in the electrophysiology assay: IC50 ~0.5 μM (inactivated state protocol)

Phase 2 studies by Xenon:

- Dental Post-Operative pain: vs. PBO, oral 500mg QD, n=61; *strong positive trends, CNS related AEs*
- PHN: Cross-over, vs. placebo, 8% topical ointment BID, 21 days of treatment, n=56.
  - *Significantly improved responder rates over placebo, no CNS-related AEs*
  - Two exploratory studies in erythromelalgia, oral and topical, n=12: *Both show positive efficacy trends*

Phase 2 studies by Teva:

- OA: Parallel group, 4% or 8% vs. placebo, BID, 4 weeks, n=389: *Negative*
- PNH: Parallel group, 4% or 8% vs. placebo, BID, 4 weeks, n=300*: Negative*

Summary:

- TV-45070 oral efficacious doses were not well tolerated/consistent with other non-selective CNS-penetrating sodium channel blockers
- Topical formulation was developed to reduce CNS-related AEs by decreasing systemic exposure
- Topical/local effect did not provide adequate pain relief; program discontinued

Xenon/Genentech GDC-0310

Q3 11-05-2017 Xenon Pharmaceuticals Earnings Summary:

- Xenon's collaborator, Genentech, has completed a Phase 1 clinical trial for GDC-0310, which is an oral, selective Nav1.7 small-molecule inhibitor
- *Based on new data from ongoing pre-clinical toxicology studies, Genentech has indicated that GDC-0310 will not enter a Phase 2 clinical trial* in the first quarter of 2018, as previously guided
- Guidance around the future clinical development of GDC-0310 will be updated once these pre-clinical studies are completed and the final results are analyzed

October 17, 2018 Roche/Genentech discontinued GDC-0310 (RG6029) and Xenon collaboration

Presumed that program discontinued due to non-clinical toxicology findings

Biogen BIIB074 (Vixotrigine, CNV1014802)

- Non-selective sodium channel inhibitor with low ~1-5μM potency on Nav1.7 IC50
- Originally developed by GSK as a central NaV1.3 blocker (GSK1014802) for epilepsy, bipolar disorder, pain
- Convergence was GSK spinoff company to develop CNV1014802 for pain indications

Studies by Convergence

- Phase 1: *Dose-related CNS adverse* events *appeared to require limiting the maximum dose and dividing daily dose to lower* C_{max}
- Phase 2a PLSR: PBO vs active, cross-over, 3 weeks treatment, 350mg BID, n=82, *positive*
- Phase 2a TGN: enriched randomized withdrawal, 3 wks run-in/4 wks DB, 150mg TID, n=30, *efficacy trend*

Biogen

- Phase 2
  - PLSR: Parallel, vs. PBO, 14 wks, high & low dose BID, n=502; *negative/PLSR discontinued*
  - SFN: Enriched randomized withdrawal, run-in period/12 weeks DB, 350mg & 200mg BID, n=186, *estimated completion 2020*
- Planned Phase 3: Two randomized withdrawal studies in TGN

Summary:

- In contrast to CC8464, BIIB074's pharmacological and clinical profile is consistent with the low potency, non-selective sodium channel blocking antiepileptic class of drugs
  - e.g. lamotrigine: negative in Phase 3 neuropathic pain indication
- Patients unlikely to tolerate maximally efficacious dose levels of BIIB074
  - Low potency requiring high doses
  - Non-selectivity and CNS penetration resulting in dose limiting AEs

$Na_V1.7$ Competitive Intelligence Summary

- $Na_V1.7$ continues to be a promising drug target for a novel non-opioid pain medication
- Encouraging efficacy demonstrated across a number of pain indications / sponsors
- Development programs have been challenged due to toxicology/tolerability
  - Failure to achieve efficacy is likely due to a non-selective profile, and/or CNS or other adverse events
- CC8464 can address these issues due to it's unique pharmacological and clinical profile
  - Potent, highly selective, state-dependent and peripherally restricted, $Na_V1.7$ blocker
  - No significant toxicology findings
  - Well tolerated Phase 1/2 compound
    - No clinical evidence of CNS adverse events
    - No clinical evidence of LDL-increase

CC8464 Development Overview

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Intellectual Property Status

Patent Family 1

- PCT/US14/25809 (Mar. 13, 2014)
- Pub. No. WO/2014/151472 (Sept. 25, 2014)
- Priority U.S. 61/787,618 (Mar. 15, 2013)
- National Stage 14/776,016 (Sept.14, 2015)

Granted in EP and China. Expect grant in US.

Pending in: AU, BR, CA, HK, IN, ID, IL,EP, CN, JP, KR, MY, MX, NZ, PH, RU, UA, US

Patent Family 2

US 9,458,118 Expected Base Expiration Date is September 9, 2034. Issued Claims to:

- Composition of matter directed to Compound CC8464
- Pharmaceutical composition comprising CC8464
- Method of treating pain by administering CC8464
- Method of treating prediabetes or diabetes by administering CC8464

Additional grants in EP, & SG

Pending in: AU, BR, CA, CN, HK, IN, ID, IL, JP, KR, MY, MX, NZ, PH, RU, ZA, TH, UA, US, VT

Patent Family 3 and 4

U.S. 62/657,097 (April 13, 2018)	Directed to compounds and methods for prevention or treatment of peripheral nerve damage
U.S. 62/670,072 (May 11, 2018)	Directed to compounds and methods for prevention or treatment of inflammatory conditions

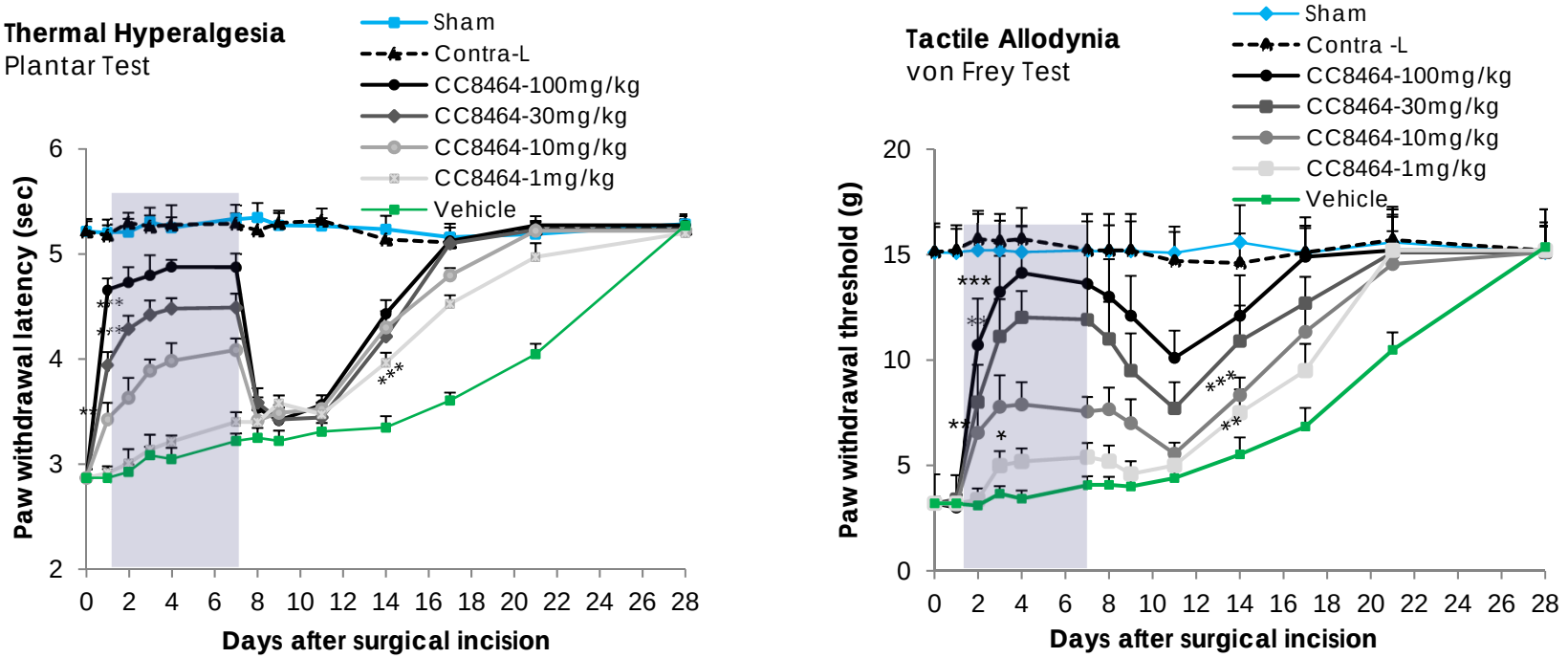
CC8464 Nonclinical Pharmacology Summary

- CC8464 is **potent** (nM) and state-dependent inhibitor of the human $Na_V1.7$ with **high target selectivity** and a favorable in vitro/in vivo safety profile
- CC8464 may preferentially affect injured or inflamed tissues while having minimal effect on the $hNa_V1.7$ channels in uninjured/healthy tissues
- **Orally bioavailable** with half-life supporting once or twice a day dosing
- **Peripherally restricted**, no distribution to CNS (rat ^{14}C-ADME)
- No measured or observed CNS and muscle/motor dysfunction effects
- No effect on **normal pain sensitivity**
- Statistically significant **efficacy in reversing pain** and/or **preventing** the emergence of neuropathic pain in rat models of the partial sciatic nerve ligation (PSNL), streptozotocin-induced diabetic neuropathy (STZ-DN) and oxaliplatin-induced chemotherapy neuropathy (CIPN)
- CC8464 has shown dose-dependent **efficacy** in reversing pain in models of **inflammatory** (CFA-induced/rat), **acute** (formalin and acetic acid writhing/mouse) and acute **post-operative** (surgical incision/rat) models

> Nonclinical *in vivo* studies predict a broad potential of CC8464 to treat acute and neuropathic pain. CC8464 is an ideal candidate compound for non-opioid pain management

CC8464 Efficacy in Postoperative Pain

Surgical Incision Model (rat)



CC8464 was administered by ip at 1, 10, 30 or 100 mg/kg in CD male rats once a day. Sham animals received no surgery as normal control. n=10 per group. Behavioral tests done at 30-40 mins post-dose. Treatment period is shown in grey color, Day 1 through Day 7. Behavioral tests were done during a washout/recovery period. *p<0.05,**p<0.01, ***p<0.001, compared to vehicle group. Positive controls: morphine and ibuprofen – data not shown.

> CC8464 inhibits thermal hyperalgesia and tactile allodynia pain in rat surgical incision model

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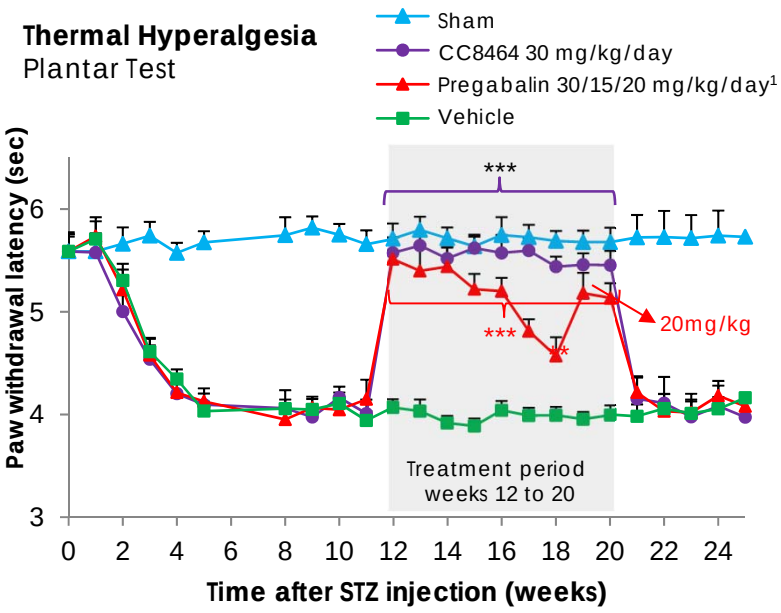
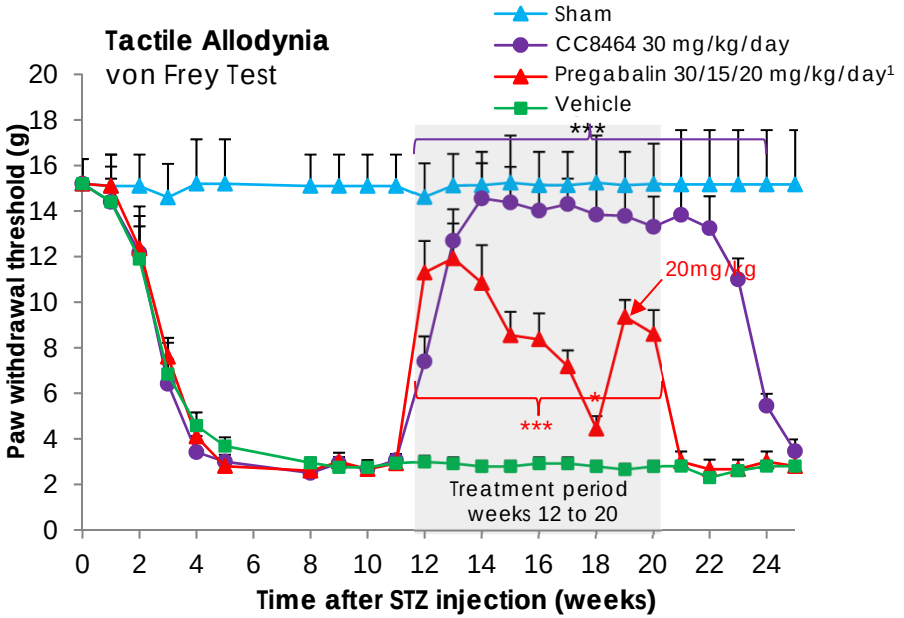
CC8464 Efficacy in Diabetic Neuropathy Pain

Streptozotocin (STZ)-Induced Type I Diabetes Model (rat)





1) Initial dose of Pregabalin, 30 mg/kg/day, in rats' drinking water caused immobility and extreme lethargy and was subsequently reduced to 15 mg/kg/day through week 18. The dose of Pregabalin was then increased to 20 mg/kg/day for the last two weeks of the study due to an observed drop in efficacy beginning 3 weeks after the start of treatment.

CC8464 and positive control Pregabalin were self-administered in drinking water. Drug treatment started after the full development of neuropathic pain (week 12 after STZ injection). The neuropathic pain was assessed weekly. 1st behavioral test done 24hr after the start of dosing and then weekly including a washout/recovery period from week 21). Data are presented as mean +/- SEM; n = 10-16, t-test, *p < 0.05, **p < 0.01, ***p < 0.001 (relative to vehicle). There was no evidence of motor/balance impairments on observational measurements in the foot-fault test, or of any adverse effects in cage side observations of CC8464 treated animals.

> CC8464 reverses thermal hyperalgesia and tactile allodynia pain with no tachyphylaxis

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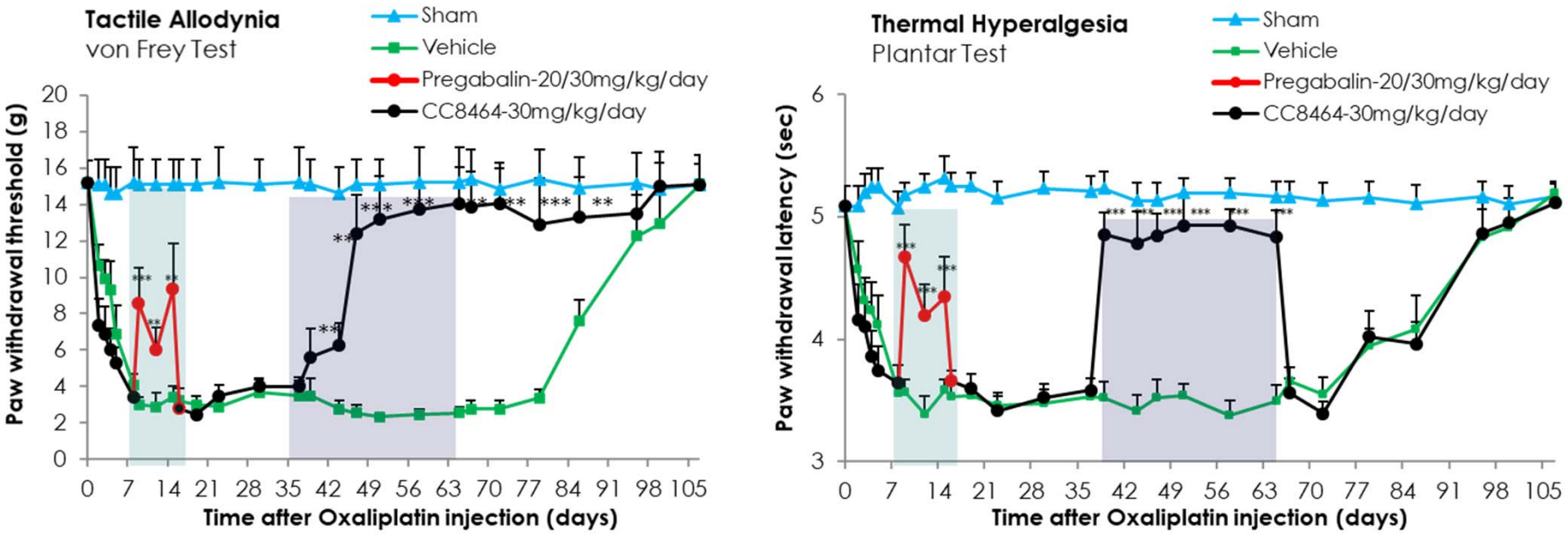
CC8464 Efficacy in Treatment of Pain in the Rat Model of Oxaliplatin-Induced Peripheral Neuropathy (CIPN)



In an Oxaliplatin-induced CIPN pain model (5 doses of 4 mg/kg Oxaliplatin given intraperitoneally), a stable and robust pain phenotype develops by day 8. Pregabalin was self-administered in drinking water: 20mg/kg day 8-11, and 30mg/kg day 12-16. After a 20-days washout period, the same animals received CC8464 30mg/kg in drinking water *ad libitum* for 4 weeks. Data are presented as mean +/- SEM; n=9-10, **p<0.01, ***p<0.001.

> CC8464 significantly reduces established neuropathic pain in a CIPN model with no tachyphylaxis

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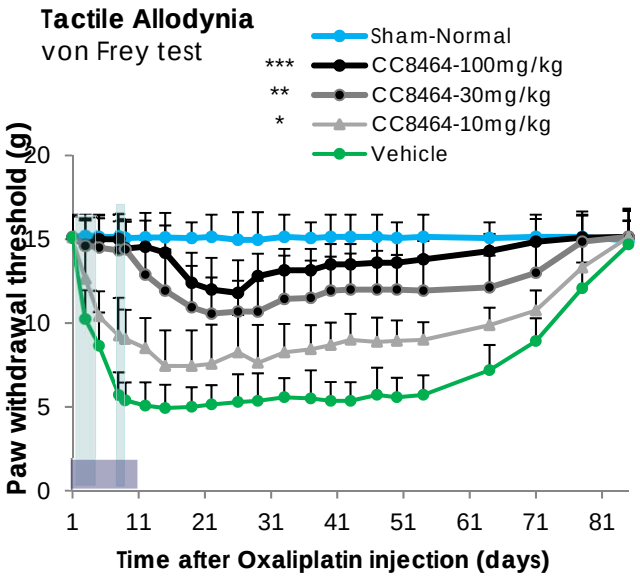
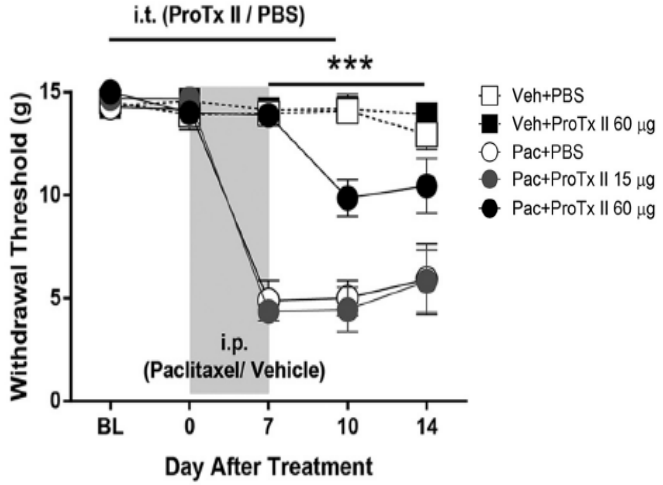
Comparison CC8464 and ProTx-II Pharmacology for Prevention of Pain in the Rat Models of Chemotherapy-Induced Peripheral Neuropathy





- CC8464 dose dependently reduces measures of CIPN pain
- Concomitant administration of CC8464 during Oxaliplatin treatment prevents CIPN pain
- Dose-dependent reduction in CIPN pain persists after discontinuation of CC8464
- Data on CC8464 in the oxaliplatin rat model of CIPN pain appears to replicate published data produced using a potent NaV1.7 toxin (ProTx II) in paclitaxel rat model of CIPN pain Li Y et al. J Neurosci. 2018;38 (5) 1124-1136

> Replication of the published ProTx II data using a different CIPN model strongly suggests target engagement and the potential of $Na_V1.7$ inhibition for the treatment and prevention of CIPN

CC8464 Toxicology Program Summary

CC8464 did not exhibit genotoxicity in an in vivo micronucleus assay in rats, a bacterial reverse mutation assay or an in vitro mammalian cell gene mutation test (L5178Y/TK+/- mouse lymphoma assay)

A full toxicological evaluation of CC8464 was conducted in

- 28-day and **91-day** repeat dose toxicity studies in rats
- 28-day repeat dose toxicity study in dogs
- 14-day and **91-day** repeat dose toxicity studies in minipigs

The potential reproductive and developmental toxicity effects of CC8464 have been evaluated in three pivotal studies:

- Fertility (male and female, rats)
- Embryo fetal development (rats and rabbits)

Safety Pharmacology:

- a cardiovascular and pulmonary safety study in dogs
- a Functional Observational Battery (FOB) study in rats

> CC8464 toxicology data supports up to 3-month dosing in human clinical trials

CC8464 Clinical Summary

A total of 177 healthy subjects have been dosed orally with CC8464 in four Phase 1 studies:

1. **CC8464-1001** SAD/MAD, once a day (QD) administration
2. **CC8464-1002** relative bioavailability (suspension vs solid form capsule)
3. **CC8464-1003** relative bioavailability (solid form capsule vs tablet)
4. **1807-CL-0102** Drug-Drug Interaction (DDI) study, first administration of CC8464 as a BID regimen

- Phase 1 SAD/MAD completed with good tolerability:
  - No dose escalation stopping criteria were fulfilled
  - No significant dose related trends or apparent differences compared to placebo in laboratory assessments, vital signs or ECG
- Bioavailability of single 200mg dose of the solid form/capsule is ~2-fold greater than from the same dose of the suspension capsule
- Tablet is bioequivalent to the solid form in a capsule; PK data support the use of all three strengths of the tablet in Phase 2
- Clinical data supports initiation of Phase 2a/POC studies in chemotherapy-induced peripheral neuropathy and neuropathic pain in 2019-2020

Chromocell's Therapeutics Pipeline

Asset	Indication	Development Status
CC8464	**Acute and chronic pain**	**Phase 2**
$Na_V1.7$ selective back-ups	Acute and chronic pain	Lead molecules identified
$Na_V1.8$ selective blockers	Acute and chronic pain	Lead scaffold identified
Dual $Na_V1.7$ + $Na_V1.8$ blockers	Acute and chronic pain	Discovery
ENaC modulators	Cystic Fibrosis Polycystic kidney disease	Discovery
GABA(A) subtype specific modulators	Anxiety, learning, depression	Discovery platform
Na_V isoforms stable cell lines	Acute and chronic pain, epilepsy, skeletal muscle dysfunction	Discovery platform
CFTR stable cell lines	Cystic Fibrosis	Discovery platform

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