

# Collaboration with Dr Stephen Waxman of Yale University to Evaluate Pharmacology of Nav1.7 Mutations in Chronic Pain Disorders

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## **Agreement follows a very successful preceding collaboration with Dr Waxman with findings due to be presented at IASP 2014**

Convergence Pharmaceuticals Holdings Limited ("Convergence"), the company focused on the development of novel and high value analgesic medicines for the treatment of chronic pain via a pharmacologically and genetically defined approach, today announces a collaboration with Dr Stephen Waxman, the Bridget Flaherty Professor of Neurology, Neurobiology, and Pharmacology at Yale University. The collaboration aims to identify patient groups likely to respond to Nav1.7 blockers and ultimately initiate clinical studies. Today's broader and more closely linked strategic collaboration follows an earlier one between Convergence and Dr Waxman, findings from which will be presented at The International Association for the Study of Pain via a poster in Buenos Aires, Argentina, October 6-11, 2014.

A pharmacological evaluation of Nav1.7 gain of function mutations identified in patients suffering from chronic paroxysmal pain disorders such as erythromelalgia, small fibre neuropathy and paroxysmal extreme pain disorders[1], will be performed to discover selective drug therapy matched to a pain genotype. The ground breaking research conducted by Dr Waxman's laboratory has pioneered the field by showing that many Nav1.7 gain of function mutations lead to cellular hyper excitability which is an underlying cause of pain in patients with paroxysmal pain disorders[1]. The collaboration will study existing mutations and identify novel pathogenic mutations in ion channels associated with chronic pain phenotypes.

By screening a range of novel proprietary molecules from the Convergence pipeline, and also existing sodium channel blockers currently used in clinical practice to treat neuropathic pain, this collaborative venture will build a rationale for future clinical studies, through pharmacological validation of genetically defined patient groups.

The first sodium channel blocker to be evaluated will be CNV1014802 which has shown outstanding efficacy and safety in a recent Phase II trigeminal neuralgia study run by Convergence. This work will lay the ground for future proof-of-concept studies with CNV1014802 in paroxysmal pain disorders.

In the preceding collaboration between Dr Waxman and Convergence, findings showed that Convergence's compounds demonstrate preferential activity against patient-derived Nav1.7 gain of function mutations that have previously been linked by Dr. Waxman and his co-workers to human pain disorders.

**Valerie Morisset, VP and Head of Biology for Convergence, commented:** "Dr Steve Waxman is a world-renowned leader in the field of sodium channel mutations and we are incredibly excited to be working with him. Paroxysmal pain disorders are notoriously difficult to treat in the clinic because current therapies show sub-optimal efficacy and have a poor tolerability profile. We hope, therefore, that by using genetics to stratify these patients, we can discover novel and more effective methods of treatment with minimal side effects. Data so far has been exciting and so now we will embark upon a broader and more closely linked strategic collaboration with Dr Waxman."

**Dr Stephen Waxman, the Bridget Flaherty Professor of Neurology, Neurobiology, and Pharmacology at Yale University, said:** "I have been impressed with the rigor and novelty of the work Convergence has done in this area, particularly by the recent Phase II results of its novel sodium channel blocker CNV1014802 for trigeminal neuralgia. I strongly believe that genotyping will provide the answers to finding optimal treatments for patients with paroxysmal pain disorders and I am looking forward to continuing and building on our existing strong and exciting collaboration."

#### **About Dr Stephen Waxman**

Dr Waxman served as Chairman of Neurology at Yale from 1986 until 2009. He founded and is Director of the Neuroscience & Regeneration Research Center at Yale. Prior to moving to Yale, Dr. Waxman worked at Harvard, MIT, and Stanford. Dr. Waxman's research has defined the ion channel architecture of nerve fibers, and demonstrated its importance for axonal conduction (*Science*, 1985). He demonstrated increased expression of sodium channels in demyelinated axons (*Science*, 1982), identified the channel isoforms responsible for this remarkable neuronal plasticity which supports remission in multiple sclerosis (*PNAS*, 2004), and delineated the roles of sodium channels in axonal degeneration (*PNAS*, 1993). He has made pivotal discoveries on pain after nerve injury. In translational leaps from laboratory to humans, he carried out molecule-to-man studies combining molecular genetics, molecular biology, and biophysics to demonstrate the contribution of ion channels to human pain (*Trends in Molec. Med*, 2005; *PNAS*, 2006), led an international coalition that identified sodium channel mutations as causes of peripheral neuropathy (*PNAS*, 2012) and has used atomic-level modeling to advance pharmacogenomics (*Nature Comm.*, 2012).

Dr. Waxman has published more than 600 scientific papers and has edited nine books. He has trained more than 200 academic neurologists and neuroscientists who lead research teams around the world.

### **About Convergence Pharmaceuticals**

Convergence Pharmaceuticals is an independent biotechnology company focused on the development of novel analgesics with potentially commercially attractive efficacy, responder-rate and side effect profiles. The Company, led by CEO, Clive Dix, was formed in October 2010 following the acquisition of certain neuroscience clinical assets from GlaxoSmithKline ("GSK"). The Company has a pipeline of differentiated clinical-stage compounds targeting the points of convergence in chronic pain signalling through modulation of specific ion-channels.

Convergence Pharmaceuticals is well funded and raised US\$35.4 million, in Series A financing from a syndicate of leading European and US financial institutions. For more information please go to the Company's website at <http://www.convergencepharma.com>.

### **About Paroxysmal Pain Disorders**

Paroxysmal pain disorders refer to disorders which are characterised by severe attacks of pain. Such disorders include trigeminal neuralgia, inherited erythromelalgia, paroxysmal extreme pain disorder and small fiber neuropathy. The severity of pain and its unpredictability results in profound effects on the quality of life of these patients and new treatments are desperately needed.

The International Association for the Study of Pain defines trigeminal neuralgia as sudden, severe, brief, stabbing, recurrent episodes of pain usually on one side of the face. Trigeminal neuralgia currently affects approximately 50,000 people in the USA alone and can affect people of any age. Trigeminal neuralgia peak onset is between 50 and 70 years of age, and the condition worsens over time. Current guidelines recommend sodium channel blockers, such as carbamazepine or oxcarbazepine, as the first-line treatment. However, the currently available drugs are often associated with poor tolerability resulting in sub-optimal pain control.

Erythromelalgia is characterized by episodes of searing burning pain and redness, on the distal extremities, precipitated by warmth and exercise. It is a rare disease; approximately 15% of EM have been associated with Nav1.7 gain of function mutations[2].

Paroxysmal extreme pain disorder is a very rare disorder characterized by perirectal, periocular or perimandibular pain, which has been directly linked to Nav1.7 gain of function mutations.

Small Fiber Neuropathy affects thinly myelinated and unmyelinated peripheral nerve and is characterized by ongoing neuropathic pain with paroxysmal episodes and autonomic symptoms. The diagnosis of can be confirmed by demonstration of reduced nerve fiber density on skin biopsy and/or abnormal quantitative sensory testing. There is a strong association with diabetes and a clear link with Nav1.7 gain of function mutation in approximately 30% of idiopathic Small Fiber Neuropathy[4].

## About chronic pain

Currently, more than 1.5 billion people worldwide suffer from chronic pain of varying degrees. Among all types of chronic pain, neuropathic pain stands out with approximately 3-4.5% of the global population affected, with incidence rate increasing in line with increased age of the population. With the unmet clinical need so high, the demand for better pain management therapies, addressing acute and chronic pain, is on the rise. The global pain management market is set to reach US\$60 Billion by 2015[5].

The Pain therapeutic area encompasses any disease where pain is a major symptom. The unmet medical need for patients in pain is enormous, with the greatest need being for a more effective therapy that is well tolerated and safe over a long period of time. Within the pain marketplace, current pain treatments are unsatisfactory; overall efficacy is poor (typically 1-2 point reductions on a 10 point scale) and satisfactory to less than 50% of patients. Whilst treatments, such as opioids and non-steroidal anti-inflammatory drugs, are available on the market, many patients obtain little or no relief from these existing analgesics and often such drugs are associated with adverse events, side effects and addiction concerns.

## References:

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[http://www.strategyr.com/Pain\\_Management\\_Market\\_Report.asp](http://www.strategyr.com/Pain_Management_Market_Report.asp)

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