A NEW TARGET FOR SPASTICITY
A REVIVAL FOR PHENOTHIAZINES

BACKGROUND
Spasticity is a common consequence of spinal cord injury (75% of patients) or cerebrovascular accidents that significantly affects patient’s quality of life.
Over 4 million people suffer from spasticity induced by spinal cord injury.
Baclofen is commonly used for treating severe spasticity: administered to patients with an implanted pump when the oral route is inefficient or has too many side effects.
Treatments using baclofen are very expensive, even without counting the surgery act for implantation of the pump.

HOW IT WORKS
KCC2 protein expression (potassium-chloride co-transporter 2) decreases after spinal cord injury and is responsible of spasticity (Boulengez & al., Nature Medicine, 2010).
Screening of The Prestwick Chemical Library® performed in vitro: identification of some phenothiazine as able to penetrate into the CNS and to activate KCC2.

RESULTS

Phenothiazine compound 10 µ/kg iv

Baclofen 2 mg/kg iv

In vivo efficacy on a spasticity model (complete transection of spinal cord)
Phenothiazine compound shows a comparable effect to baclofen, at a 200-fold lower dose, on mice

KEY BENEFITS
• KCC2 is a new validated molecular target on spasticity
• Repositioning of drugs already approved for CNS disorders (for antipsychotic & antiemetic indications) to replace or combine with baclofen
• These drugs are administered by oral route in human
• Efficient at very low doses to treat spasticity, with reduced side-effects risks

APPLICATIONS
Generalized and regional spasticity (orphan drug designation) due to spinal cord injury (SCI)
Potential therapy for spasticity caused by multiple sclerosis (MS), stroke, cerebral palsy, traumatic brain injury...