OXFORD UNIVERSITY INNOVATION

Gene therapy for chronic pain and epilepsy

OUI Project 13911

Summary

- Gene therapy for chronic pain and epilepsy (secondary opportunity)
- AAV vector delivering transgene encoding a modified CASPR2 polypeptide
- Preliminary *in vivo* efficacy data
- Further research ongoing
- Available for partnering now

Chronic pain and epilepsy

Unmet clinical needs remain

- Chronic pain, including neuropathic pain ("NP")
  - 22% of the world's primary care population suffers chronic debilitating pain (WHO)
  - 9.8% community prevalence of NP in over-30s (Yawn *et al* (2009); study in MN, US)
    - Based on 'gold standard' clinical examination; assessment by other methods gave estimates of 3.0% to 12.4%
  - Detrimental to sufferer's QoL; huge economic cost – US$635bn in US alone (based on 2008 data)
  - Current therapies (e.g. NSAIDs and opioids) lack efficacy (especially for NP) and/or have side-effects
  - Global NP drugs market expected to reach US$8bn by 2023 (at ~6% CAGR) (Market Research Future)
- Epilepsy (secondary market opportunity)
  - Prevalence – 5-10 per 1,000 in the UK (i.e. up to 680K sufferers); incidence – 50 per 100,000/yr (NICE)
  - Anti-epileptic drugs ("AEDs") include sodium valproate, carbamazepine and lamotrigine
    - Some AEDs are also used to treat NP, e.g. gabapentin and pregabalin
    - AEDs provide adequate control for two-thirds of people with active epilepsy (NICE)
    - Poor side-effect profiles, especially at the start of treatment
  - Global AED drugs market expected to reach US$5.5bn by 2021 (DPI Research)

Oxford's research-stage GT

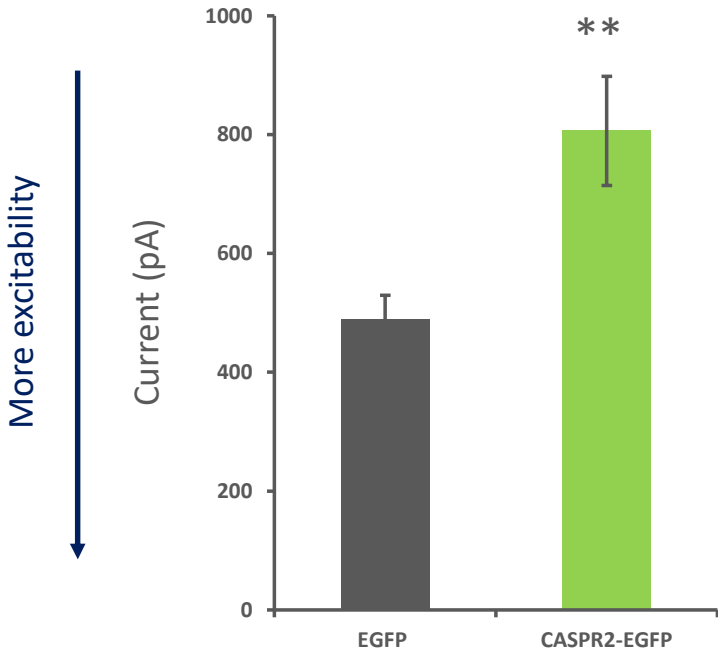
Potentially an innovative new therapeutic option

- **AAV-based GT to *over*express a modified CASPR2 (contactin-associated protein 2) polypeptide in sensory neurons**
- Neuronal hyperexcitability is a key feature underlying NP as well as epilepsy
- CASPR2 regulates the function of potassium channels (specifically, through its inter-action with the VGKC complex), which are key determinants of neuronal excitability
- Autoantibodies against CASPR2 are associated with NP and epilepsy
  - Patients can be successfully treated with immunotherapies that reduce antibody levels
  - Also note: genetic ablation of CASPR2 causes pain hypersensitivity and sensory neuronal excitability
- Therapeutic rationale: *increasing* CASPR2 levels should reduce neuronal hyper-excitability and thus potentially provide therapeutic benefit in NP and/or epilepsy
- Envisaged GT delivers a gene encoding a modified form of the CASPR2 polypeptide for overexpression in the target sensory neurons

Selected data (i)

Reduction of neuronal hyperexcitability *in vitro*

Overexpression of the modified CASPR2 polypeptide *in vitro* reduces the excitability of sensory neurons



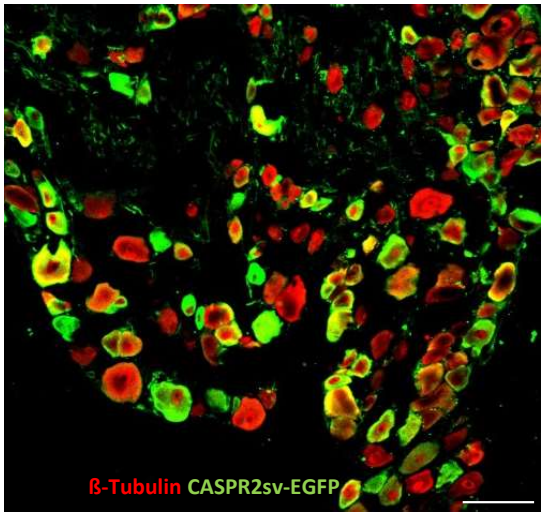
The graph shows the average rheobase that is the threshold for neuronal firing.

Increased threshold = reduced excitability

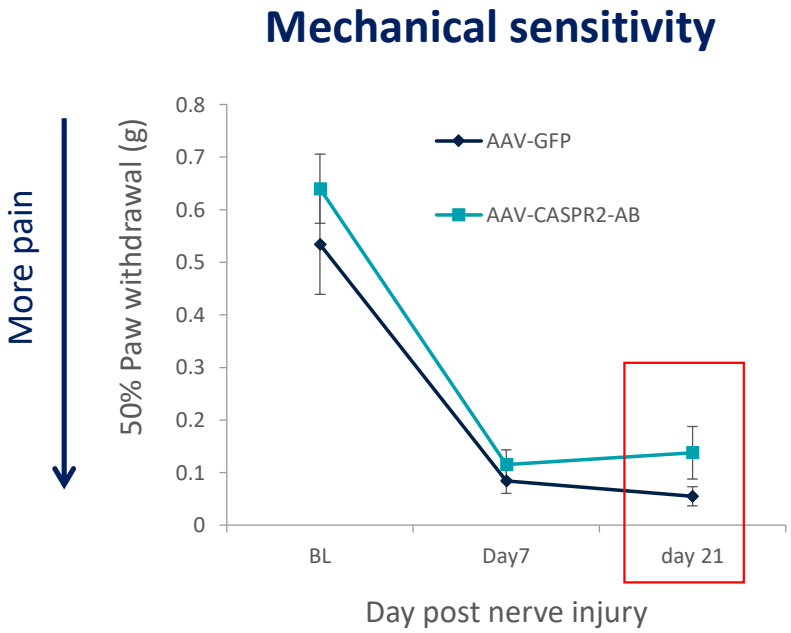
Selected results (ii)

Reduction of neuropathic-like pain behaviour in mouse model

A clear effect is demonstrated even without optimisation of the experimental protocol



CASPR2 is overexpressed in mouse sensory neurons *in vivo*



CASPR2 overexpression reduces neuropathic-like pain behaviour in a pre-clinical mouse model, the spared nerve injury ("SNI") model

Intellectual property

- PCT application published as WO 2018/060712
- Claim 1

  A method for the treatment or prevention of pain, or excessive neuronal activity, or epilepsy in an individual in need thereof, the method comprising overexpression of a CASPR2 polypeptide in sensory neurons of the individual.

- 'Clean' ISR & WO
- Regional/national applications pending in Europe and the US

- Fully owned by, and all rights assigned to, OUI

Further development and partnering

- Further *in vivo* studies ongoing
  - Examination of earlier administration of GT (*vs*. 1 week prior to nerve injury in the initial SNI study)
  - Monitoring response over a longer time-scale (*vs*. 21 days in the initial SNI study)

- Available for commercial partnering, e.g. via:
  - Option or licence
  - Translational collaboration
  - Spin-out formation

Any questions?

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