Irish EU Presidency

European Forum on Epilepsy Research

Dublin 25th -27th May 2013

Innovative multidisciplinary approaches and treatment strategies

Merab Kokaia (Sweden)

Innovative approaches

- Gene therapy
- Cell (stem cell) therapy
- Optogenetics

Gene therapy: *in vivo* and *ex vivo*

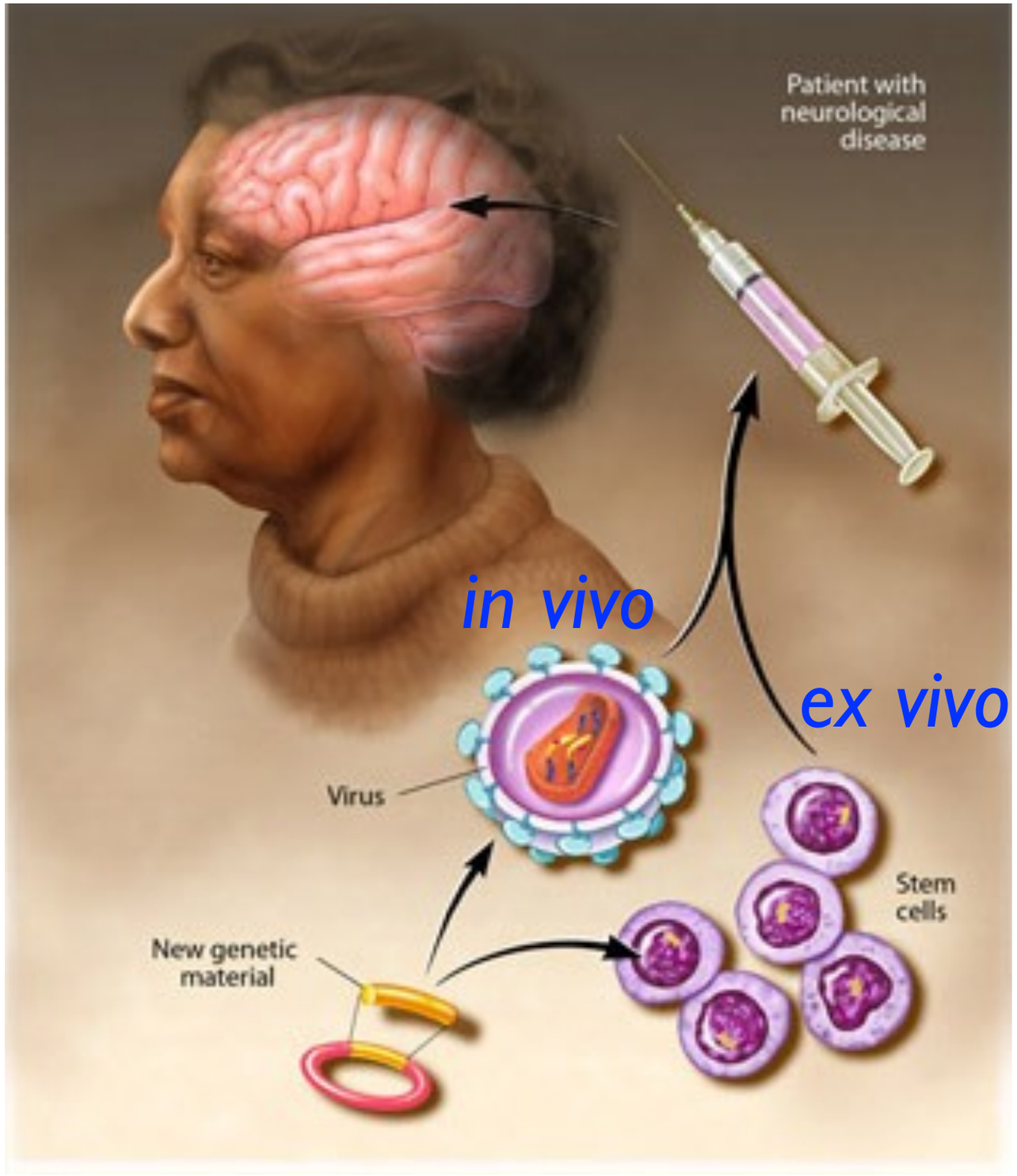
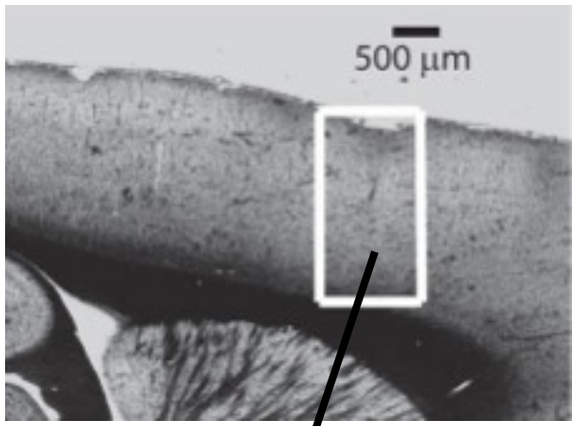


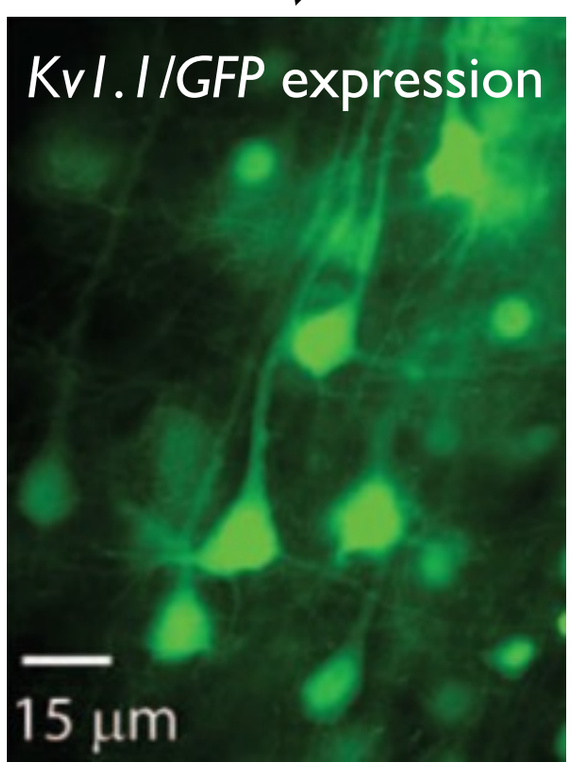
Illustration by Lydia V. Kibiuk, Baltimore, MD; Devon Stuart, Harrisburg, PA

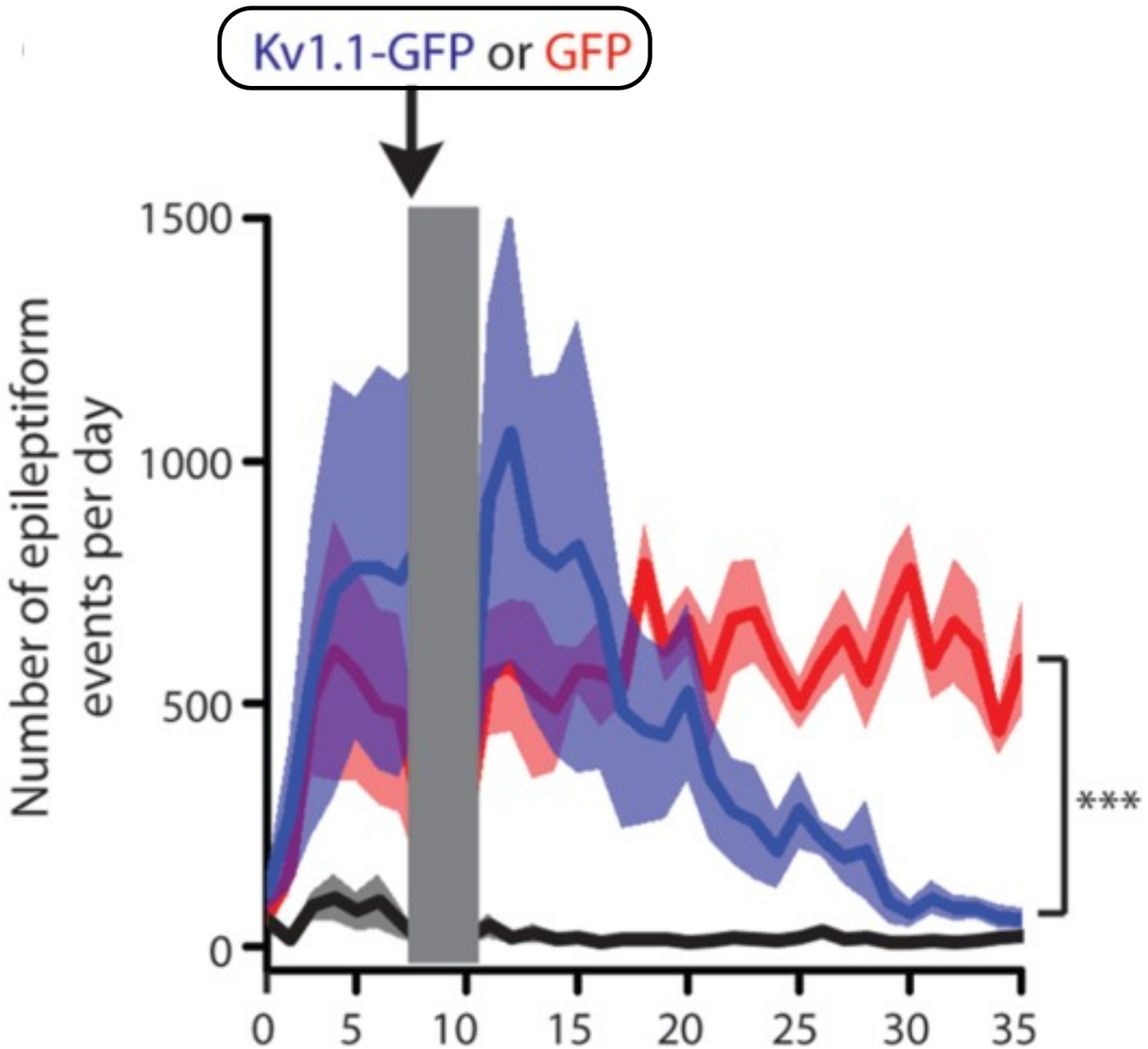
Kv1.1 gene therapy decreases neuronal excitability and epileptiform events in neocortical epilepsy model:

anti-epileptic effect

Tetanus toxin

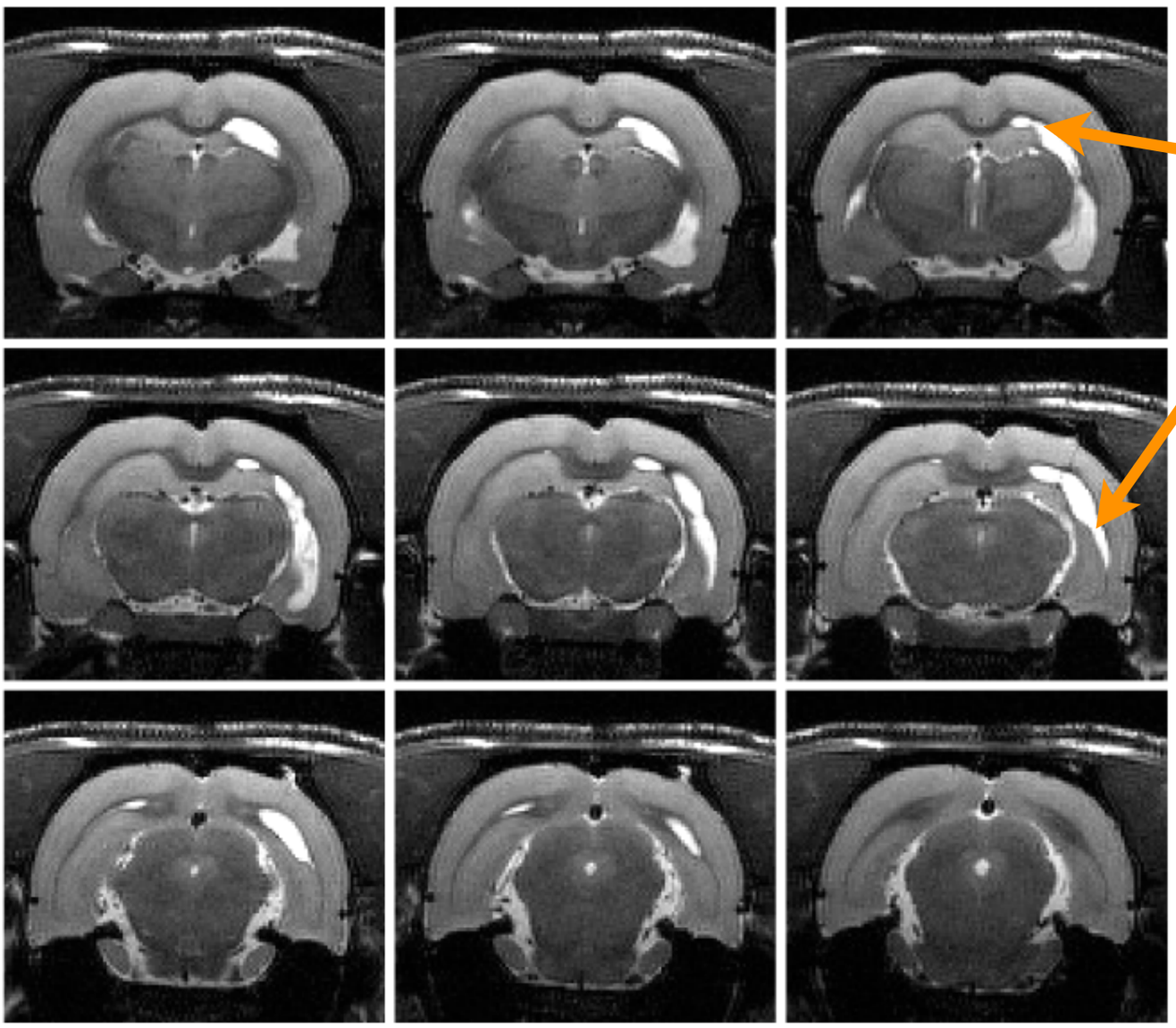




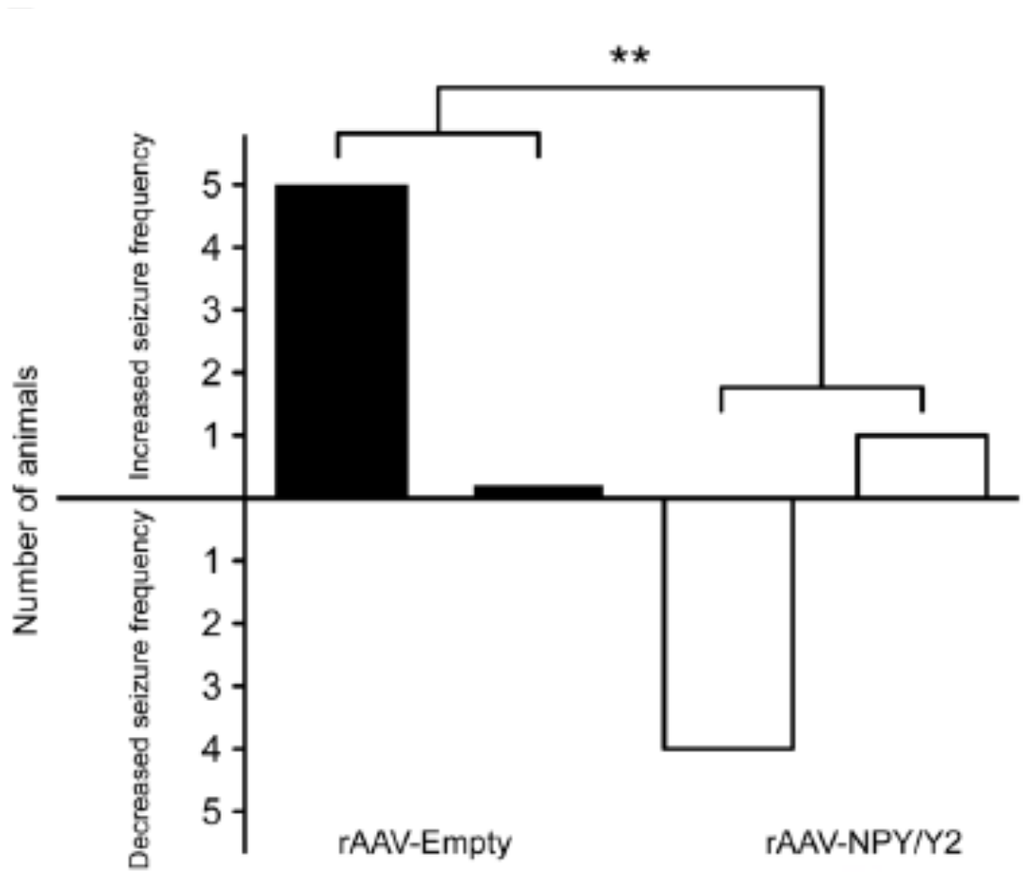


Wykes et al., & Kullmann, Sci.Transl. Med., 2013

MRI of intrahippocampal kainate-treated rat brain



Unilateral *combinatorial* gene therapy of TLE with *neuropeptide Y* and its *receptor Y2*

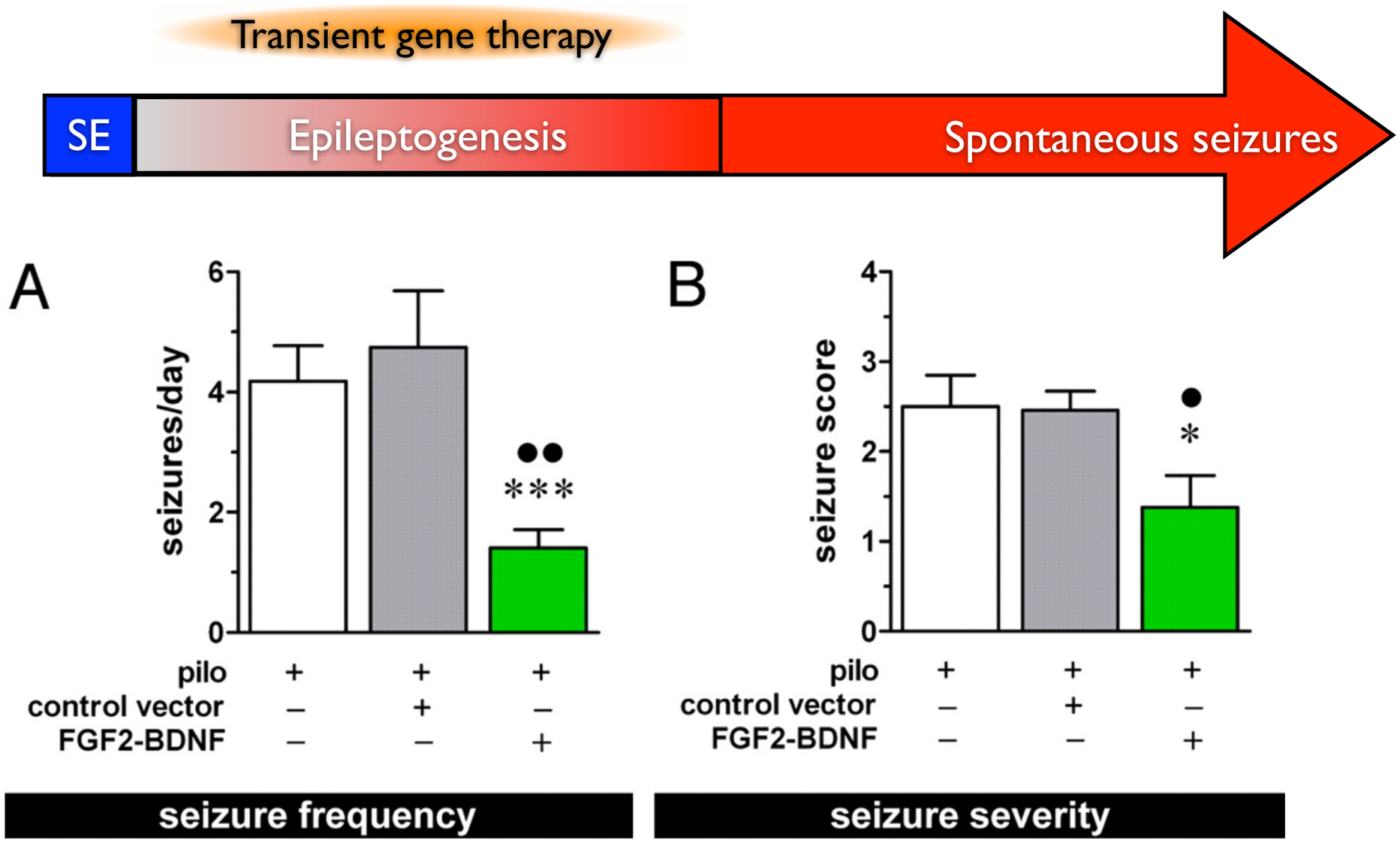


gene therapy

SE | Epileptogenesis | Spontaneous seizures

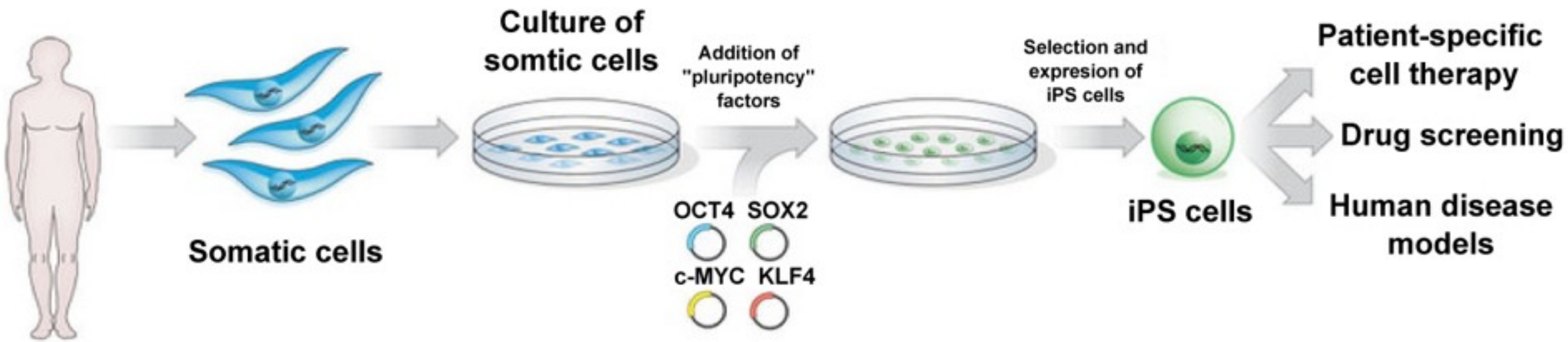
Nikitidou et al., & Kokaia, 2013, submitted

Combinatorial gene therapy with *FGF-2 and BDNF* during early epileptogenesis decreases seizure frequency and severity: *anti-epileptogenic effect*



Paradiso et al., & Simonato, PNAS, 2009

Induced pluripotent stem (iPS) cell-derived neurons for epilepsy treatment

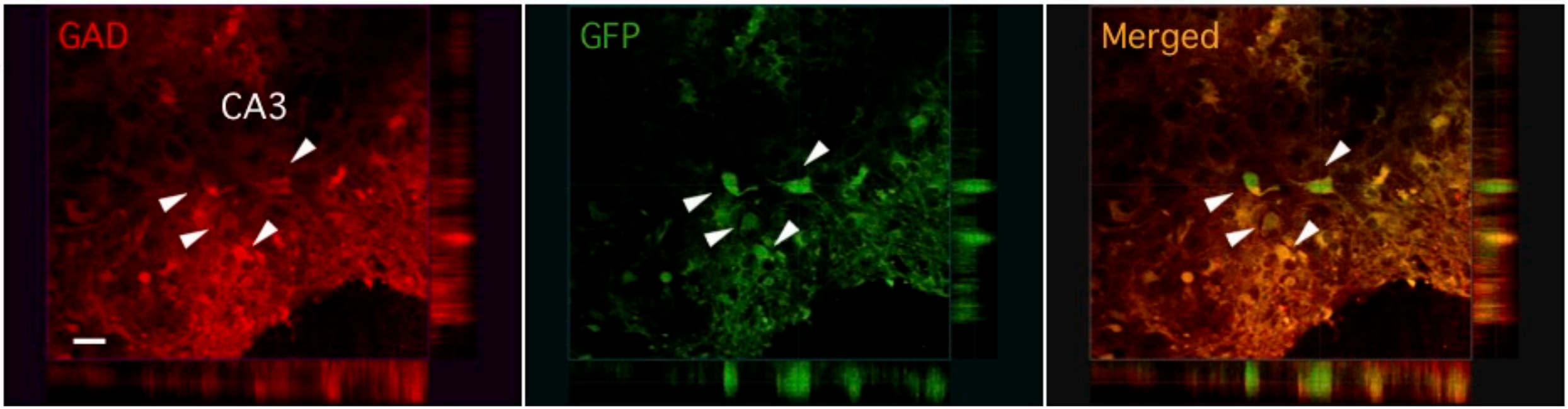


Advantages of iPS cells:

- No immune rejection
- No ethical issues
- Patient-specific cell therapy
- Drug screening
- Human disease models

Are these cells truly neuronal?

Human iPS cells differentiate into GABAergic neuronal phenotype: *could be used for cell therapy in epilepsy?*

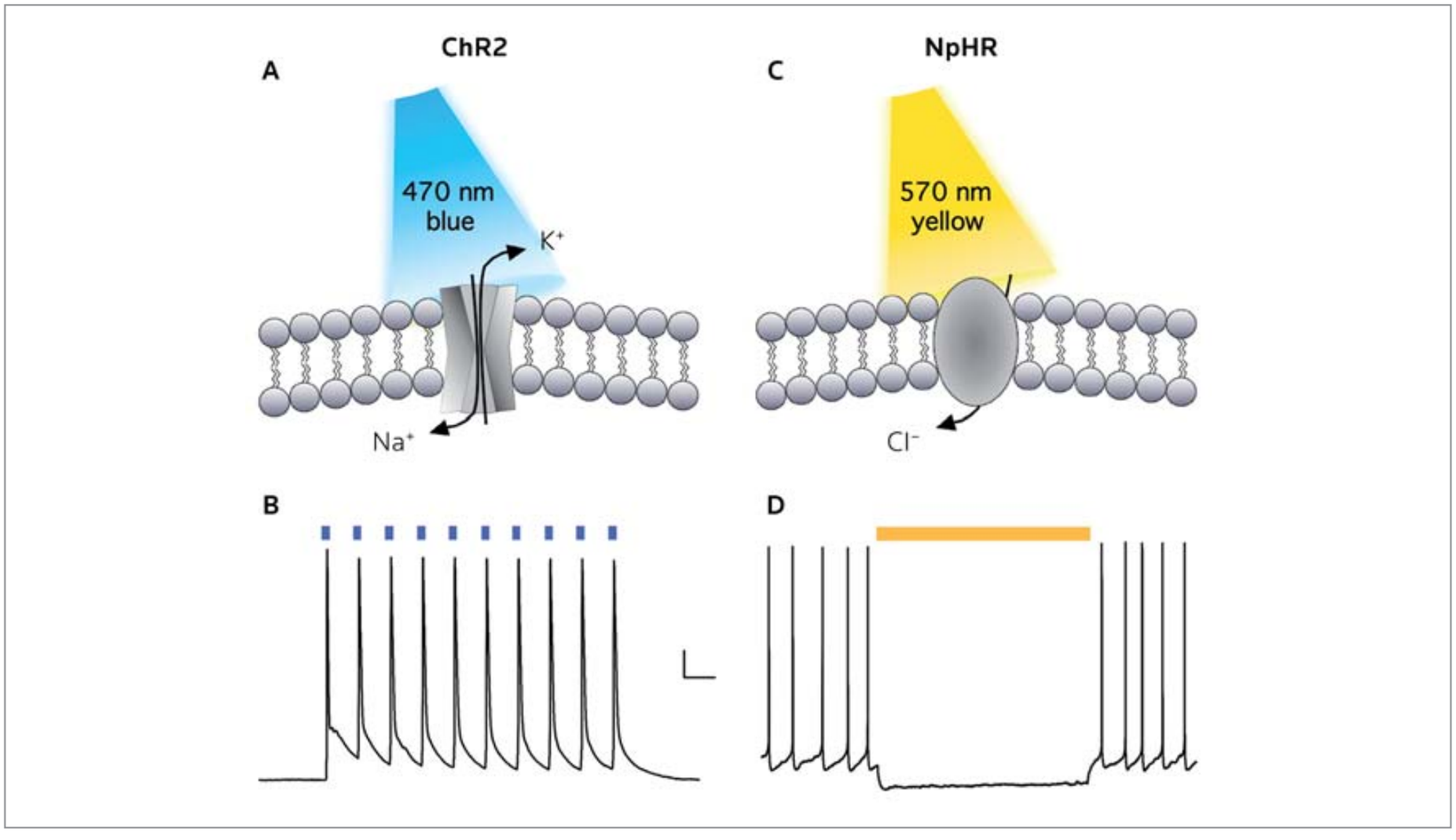


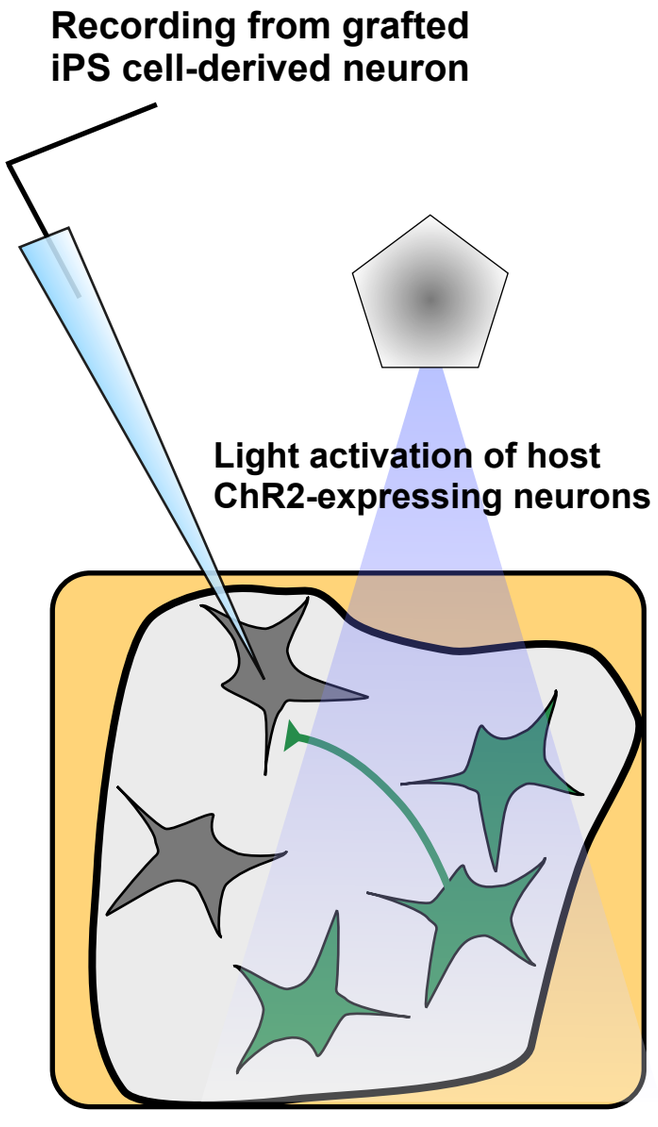
Avaliani et al., & Kokaia, 2013, submitted

Do these cells synaptically integrate into the host circuitry?

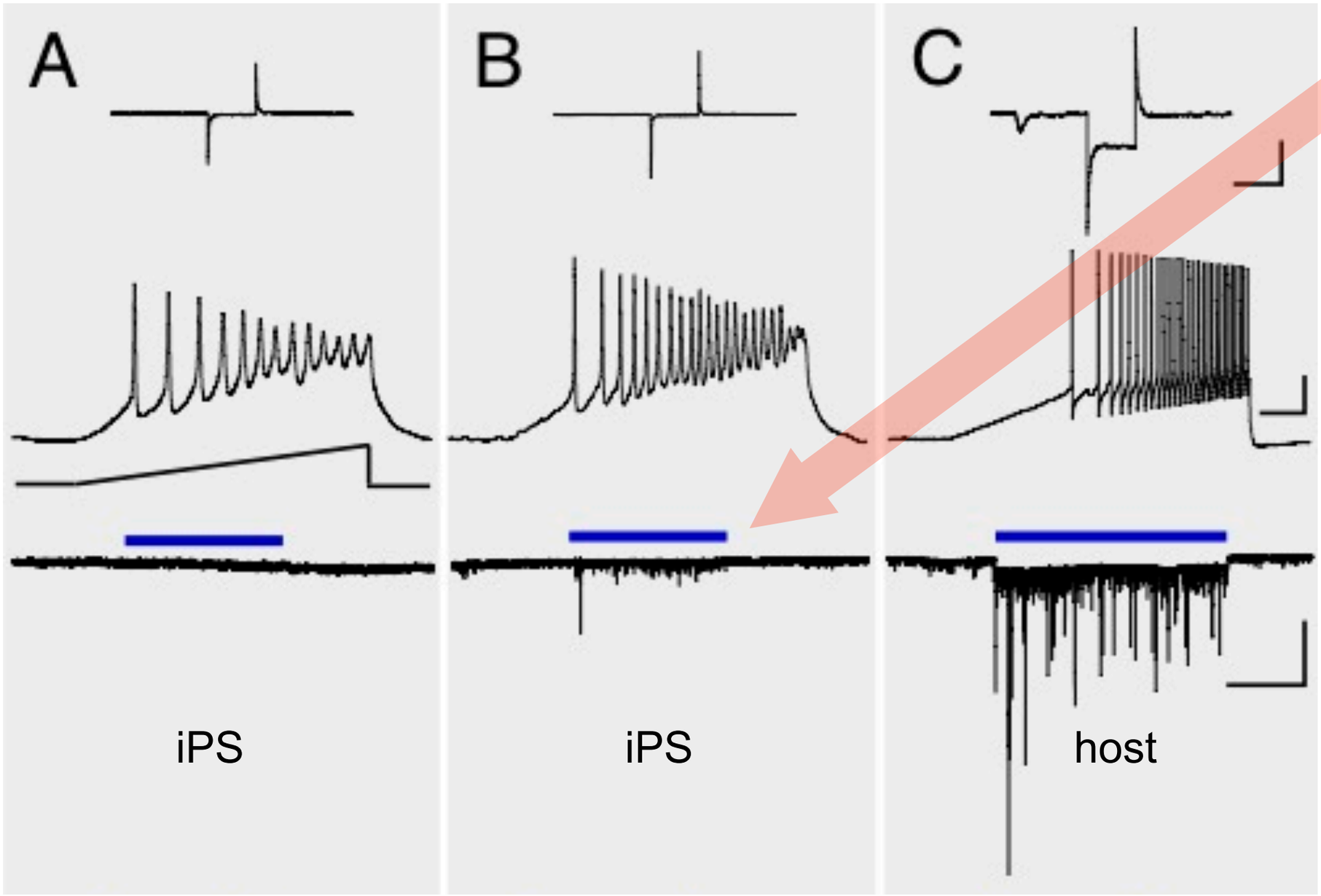
Optogenetic tools

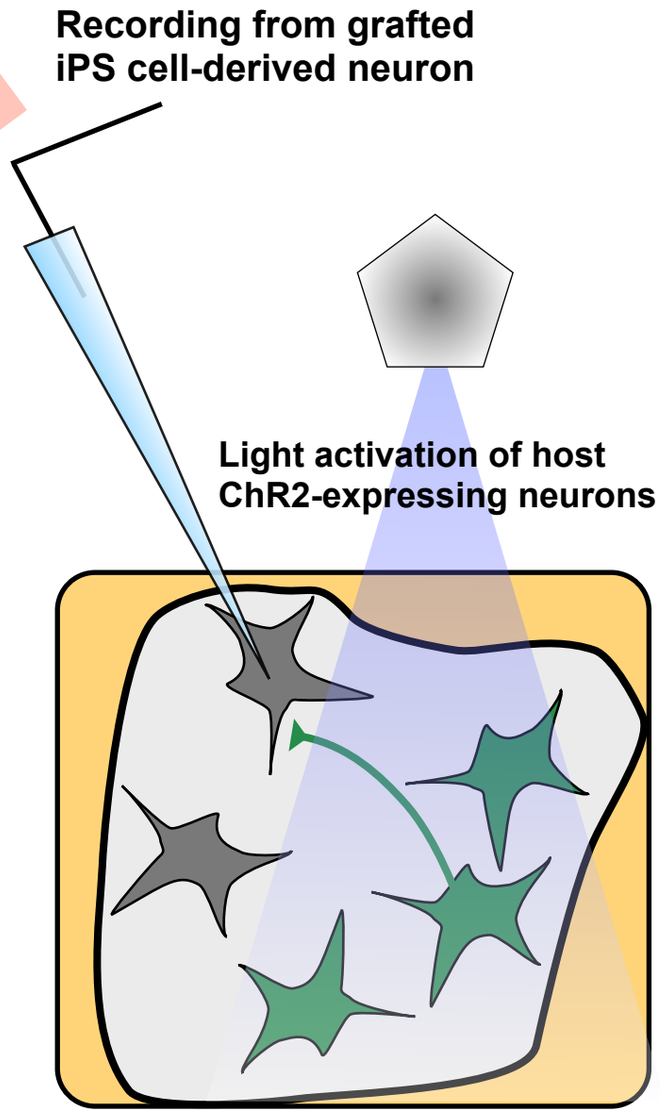
bacterial membrane channels and pumps





Grafted iPS cells differentiate into functional neurons and receive afferent inputs from host



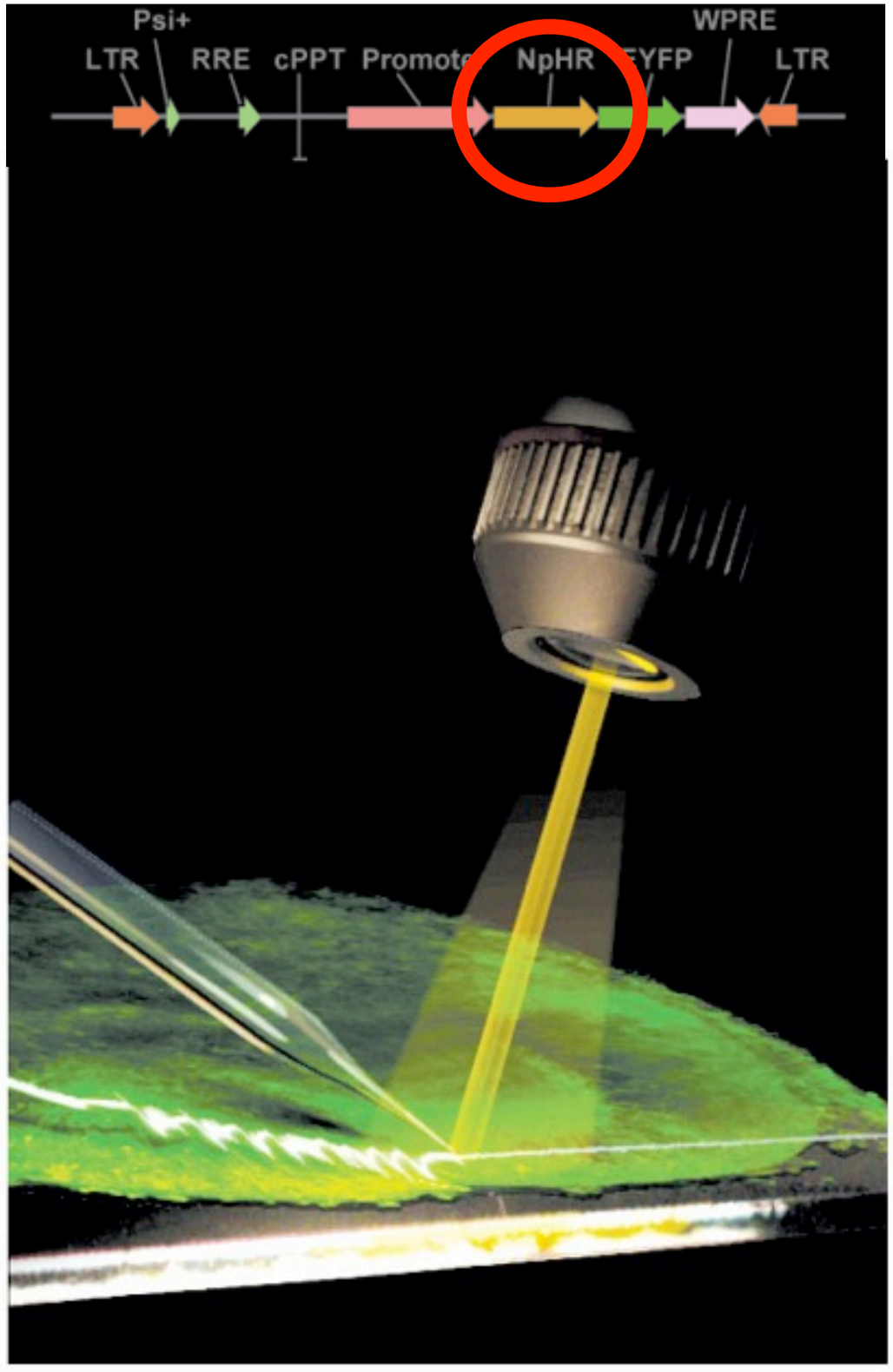


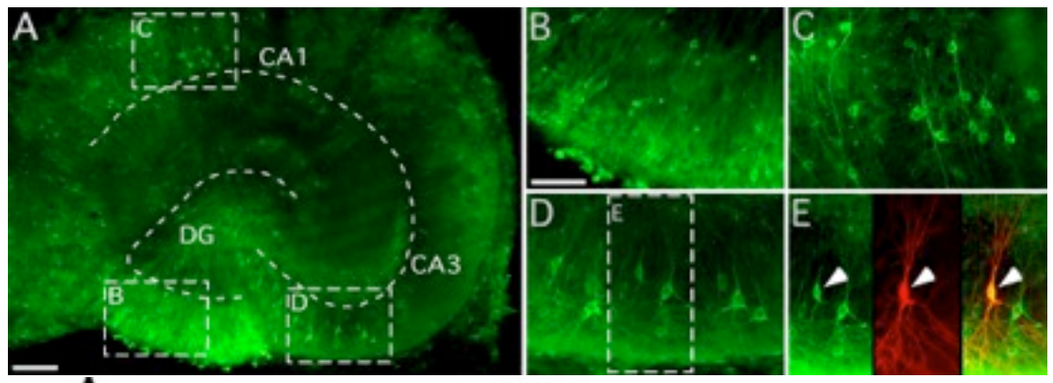
Avaliani et al., & Kokaia, 2013, submitted

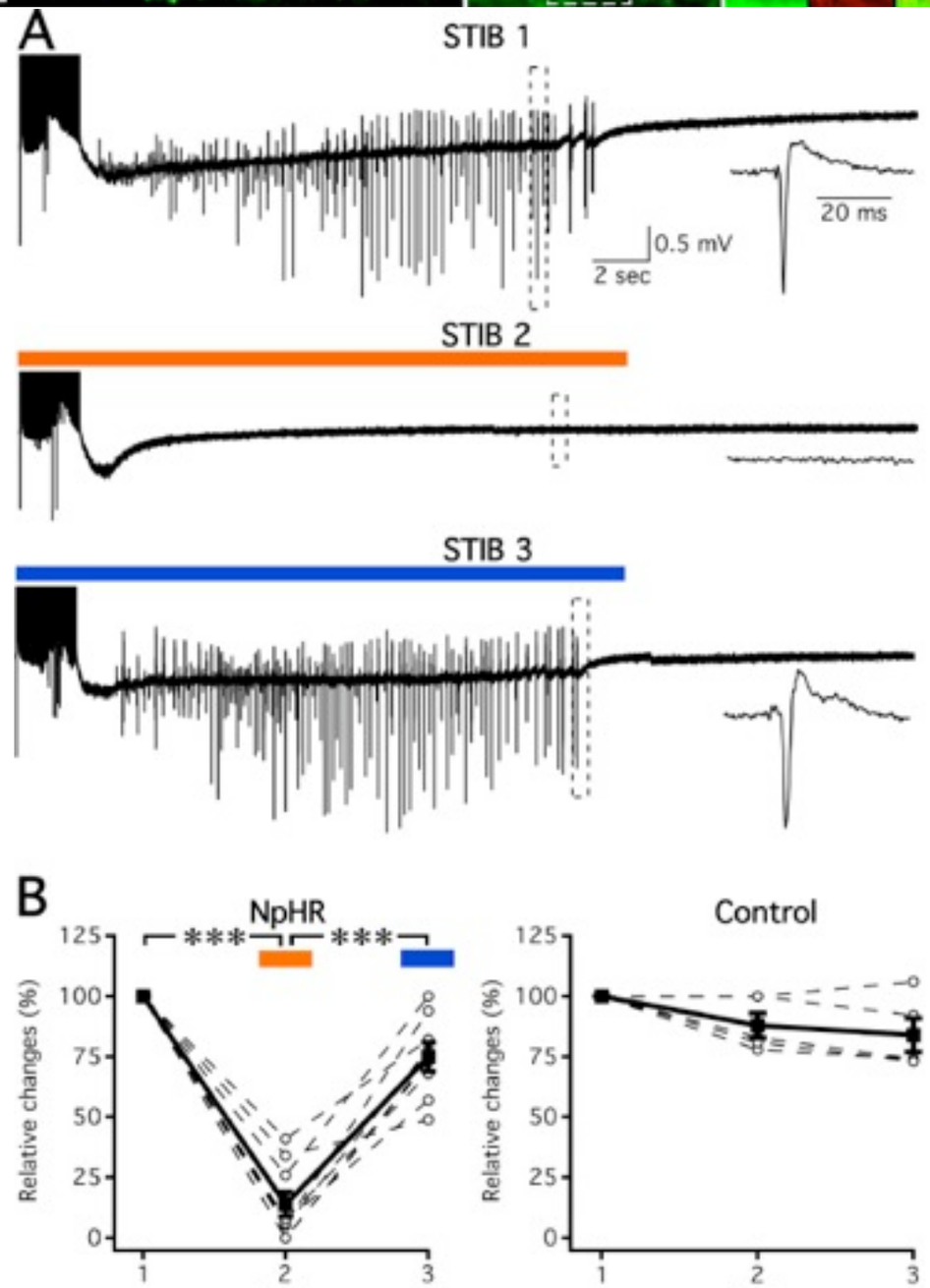
Optogenetics control seizures

Tonnesen et al., & Kokaia, PNAS, 2009

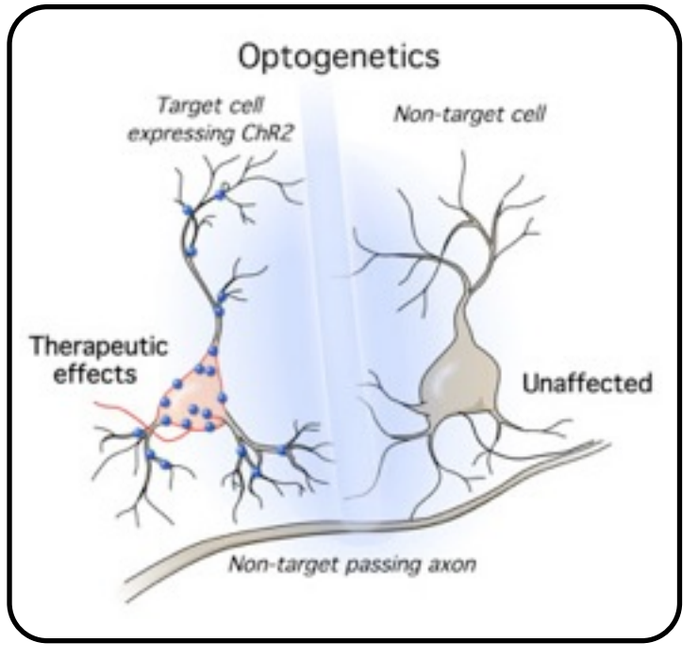
Lentiviral vector



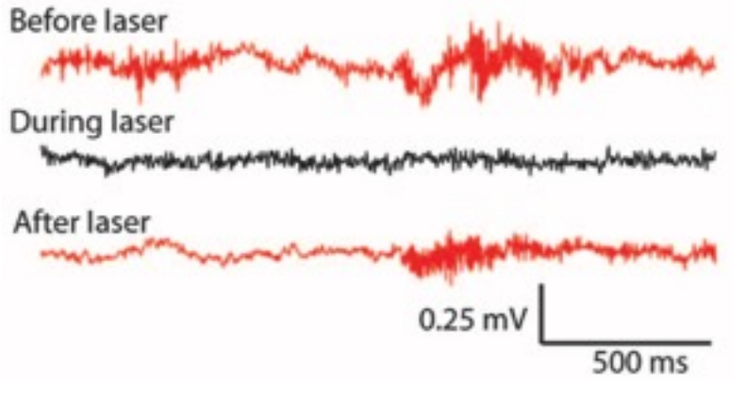


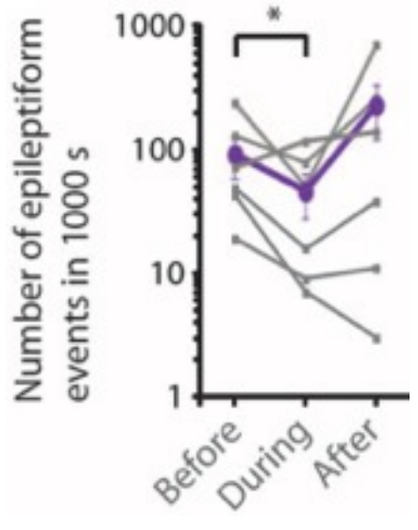


Optogenetics control seizures



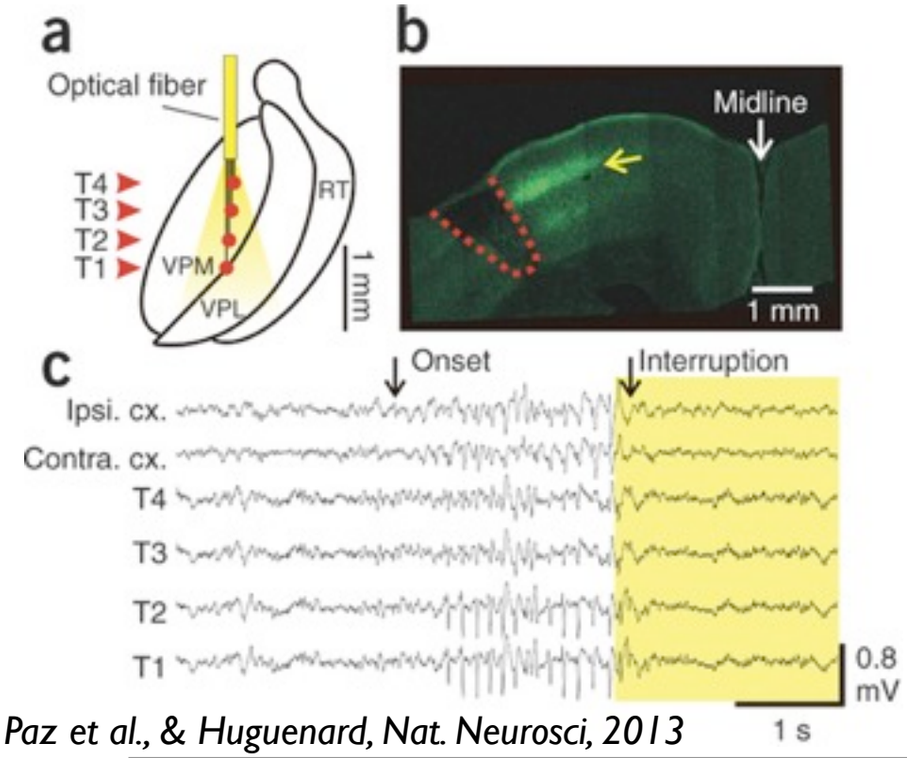
NpHR in neocortical epilepsy: optogenetics inhibit epileptiform activity





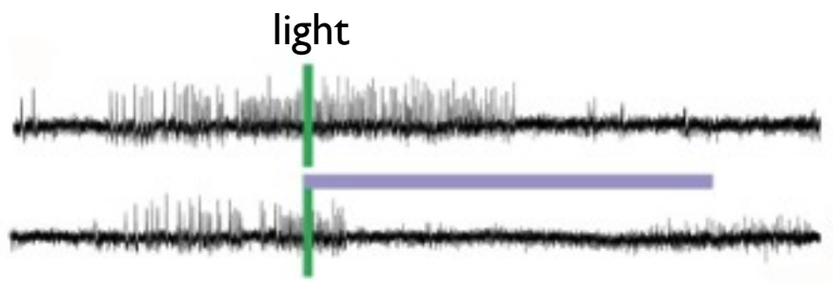
Wykes et al., & Kullmann, Science Transl. Med., 2013

NpHR in post-stroke epilepsy: seizures are stopped by closed-loop optogenetics

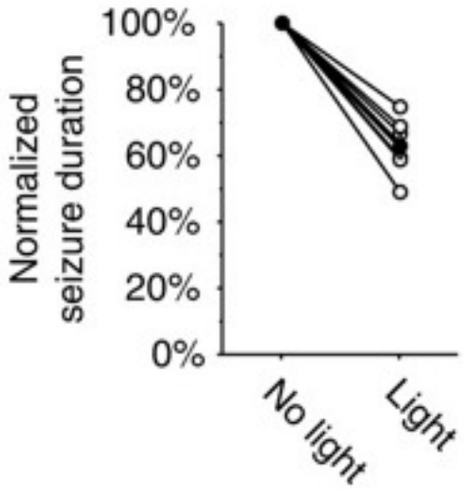


Paz et al., & Huguenard, Nat. Neurosci, 2013

ChR2-PV interneurons in TLE: seizures are stopped by closed-loop optogenetics



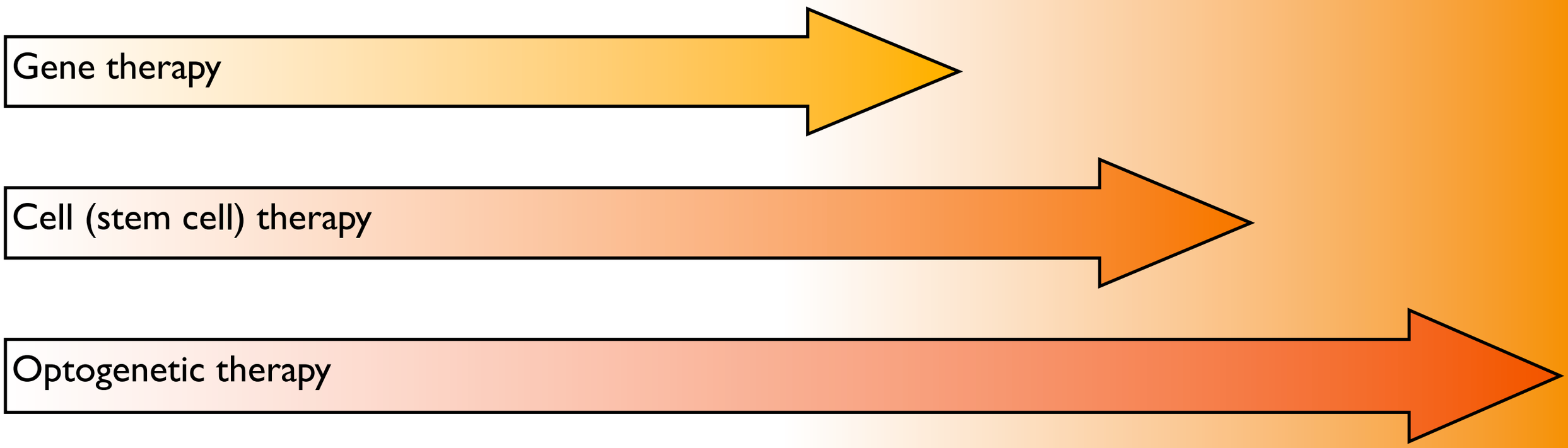
Krook-Magnusson et al., & Soltesz, Nat. Com., 2013



Expected translational time-line:
first clinical trial milestone

Within next 5 years

Beyond next 5 years



Appropriate EU-wide multidisciplinary collaborations and allocation of resources is necessary to achieve expected milestones