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Removing obstacles in translation of preclinical discoveries to clinic: focus on finding cures for epilepsy

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The unmet need

30% of people with epilepsy do not respond well to AEDs

Opportunities to interfere with early stages of epileptogenesis are limited

What can be offered to patients with established drug-resistant epilepsy?

- New small molecule treatments

  (new drugs have not had much impact on refractoriness in the last 20 years)
- Surgical resection

  (only where epileptogenic zone remote from eloquent cortex)
- Vagal nerve stimulation (weak evidence, uncertain effectiveness)
- Ketogenic diet (evidence mainly in children, poor compliance)
- Brain cooling (experimental)
- Brain stimulation (experimental)
- Stem cells (experimental)
- Gene therapy (experimental)

Gene therapy is the most promising prospect for a long-lasting reduction in seizures

- Rational design to decrease circuit excitability
- Regional specificity
- Cell-type specificity
- (Temporal specificity)
- Advances in vectors and promoters
- 2012: first gene therapy licensed for lipoprotein lipase deficiency

Prelinical research efforts

Choice of vector:

- Lentivirus
- AAV
- HSV
- …

Choice of cargo:

- Overexpression of native proteins
- Expression of non-native proteins
- RNA interference
- …

Choice of preclinical model:

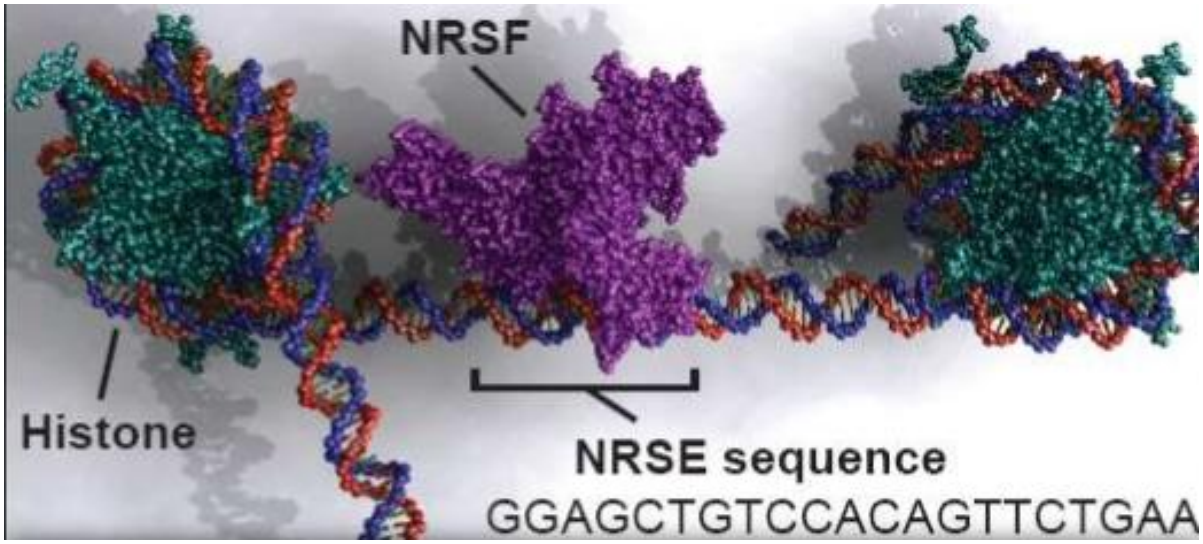
- Limbic epilepsy
- Focal neocortical epilepsy
- Thalamocortical epilepsy
- Models of epilepsy associated with malformations

Early preclinical data

Promising results in recent years:

- Epigenetic repression
- MiRNA silencing
- Neuropeptide overexpression
- Neurotrophin overexpression
- Potassium channel overexpression
- Optogenetics

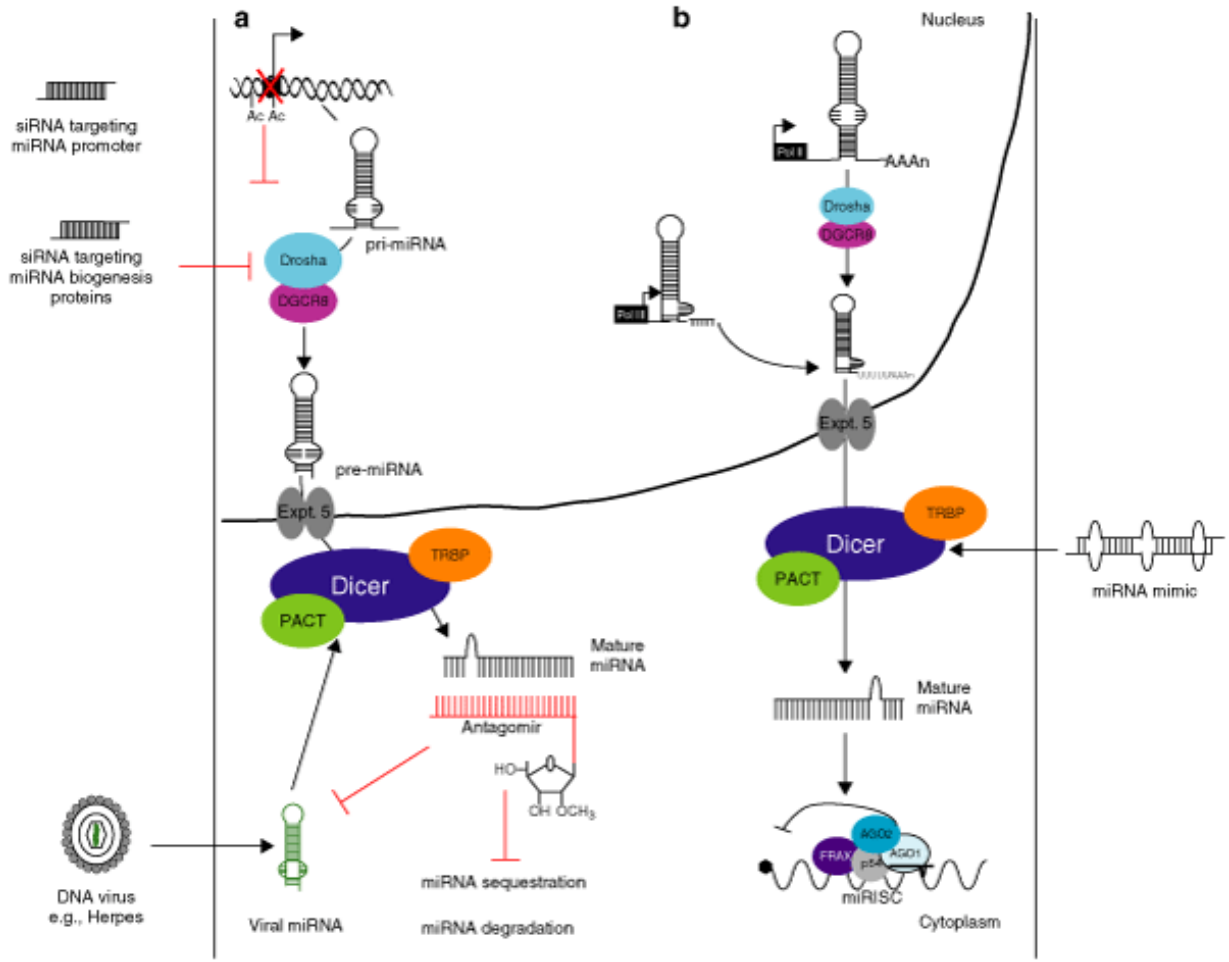
Manipulation of epigenetic repression



Neuron-restrictive silencer factor

McClelland et al (2011) *Ann Neurol* 70, 454–465

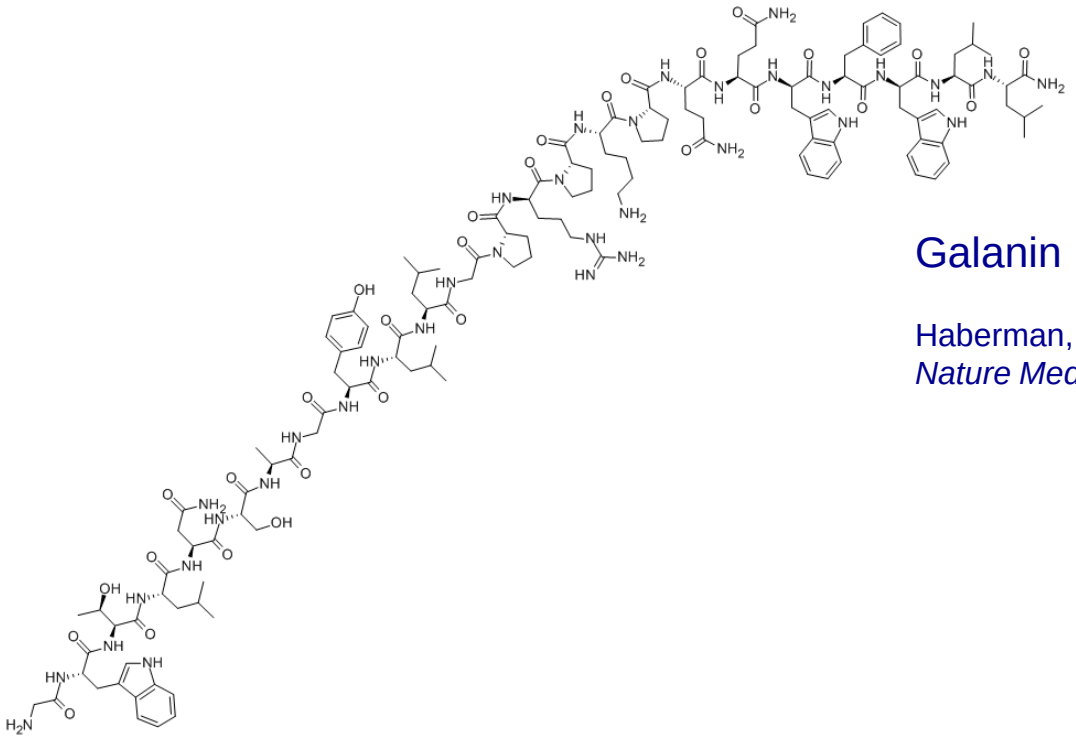
MicroRNA silencing



Antagomir-mediated silencing of MiRNA-134

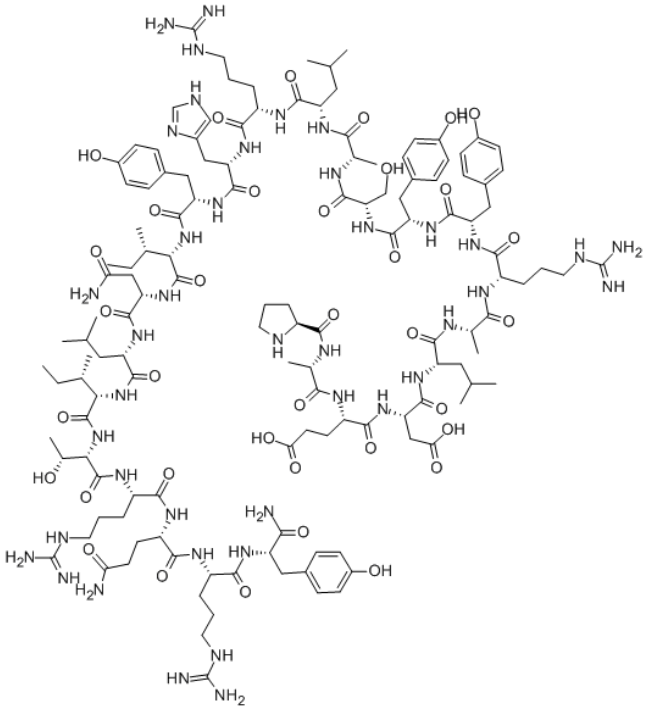
Jimenez-Mateos et al (2012) *Nature Medicine* 18, 1087–1094

Neuropeptide overexpression



Galanin

Haberman, R.P.; Samulski, R.J.; McCown, T.J (2003) *Nature Medicine* 9(8), 1076-1080.



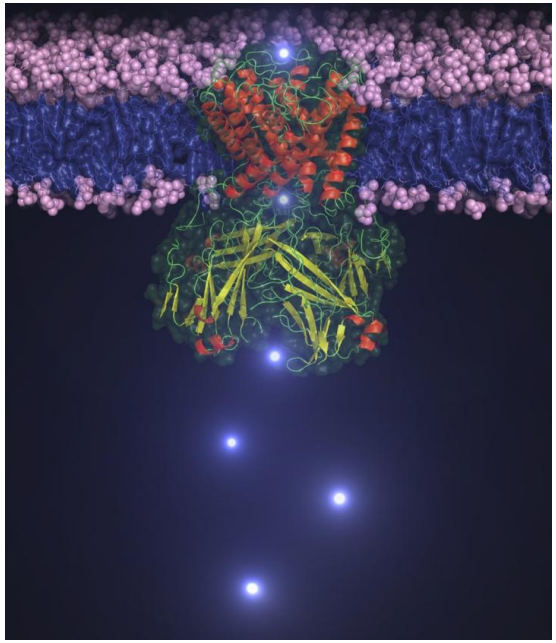
NPY overexpression

Richichi et al. (2004) *J Neurosci.* 24:3051-9.

NPY + Y2 receptor overexpression

Noè F, et al (2008) *Brain* 131:1506-15.

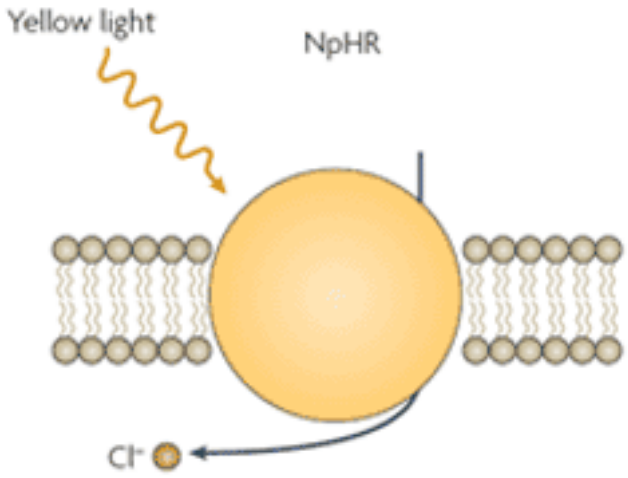
Potassium channel overexpression



Kv1.1

Wykes et al (2012) *Sci Transl Med* 4:161ra152..

Optogenetics



Halorhodopsin, channelrhodopsin

Tønnesen et al (2009) *PNAS* 106:12162-7
Wykes et al (2012) *Sci Transl Med* 4:161ra152.
Krook-Magnuson et al (2012) *Nat Commun.* 4:1376.
Paz et al (2013) *Nat Neurosci* 16:64-70.

Prevention or cure?

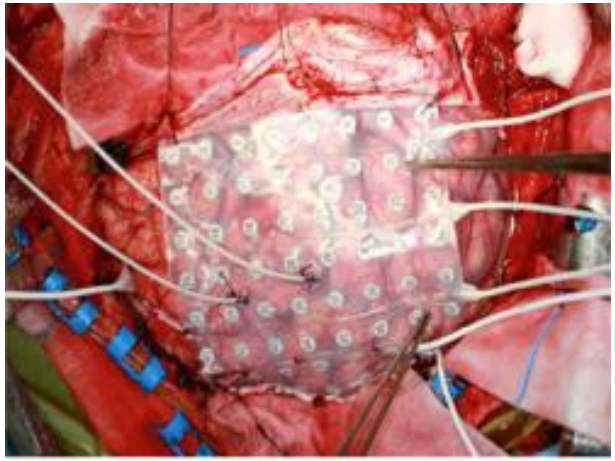
	Antiepileptogenic	Antiepileptic / disease modifying
NRSF manipulation	+	?
Antagomir	+	?
Galanin	+	?
NPY (+ Y2)	+	(+)
Potassium channel overexpression	+	+
Optogenetics	-	-

How to move from the lab towards clinical trials?

- Consolidate evidence of preclinical effectiveness
- Anticipate structure of clinical trials
- Meet regulatory requirements

Anticipate the structure of a clinical trial

What might a phase I/II trial of an antiepileptic treatment for drug-resistant epilepsy look like?



Current practice: Identify epileptogenic zone → ± Resect

Clinical trial: Focal gene therapy

European legislative framework surrounding gene therapy

- Clinical trials: Directive 2001/20/EC
- Definition of medicinal product: Directive 2001/83/EC
- Regulation on Advanced Therapy Medicinal Products: Regulation (EC) 1394/2007)
- Genetically Modified Organisms: Directive 2001/18/EC or Directive 2009/41/EC

Regulatory framework surrounding clinical translation

A new medicine or medical device is allowed on to the market with a licence or CE-mark only if there is enough evidence that the potential benefits will outweigh the likely risks.

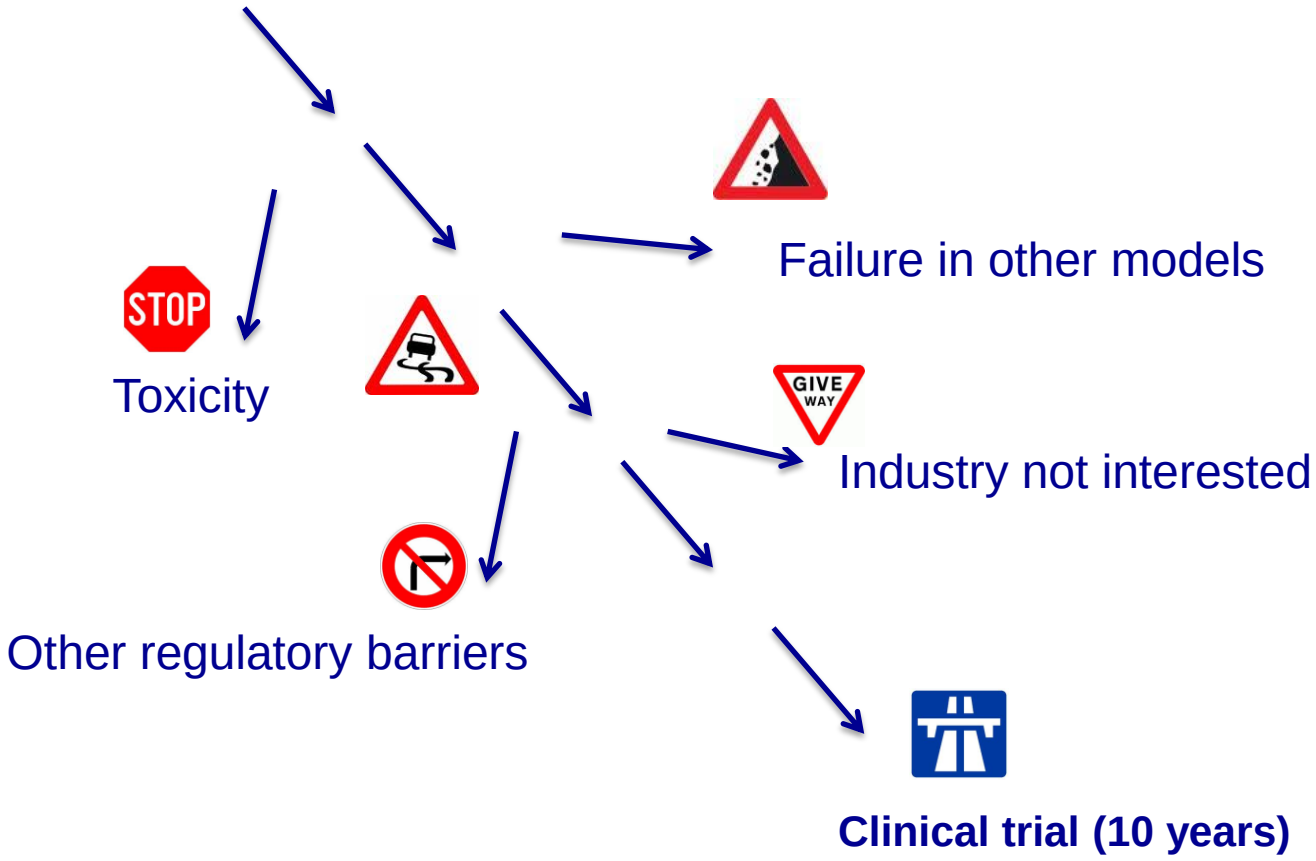
Practical obstacles to translation

Anticipated challenges

- Minimise effects on normal circuit function
- Minimise long-term toxicity:
  - off-target effects
  - insertional mutagenesis
  - Immunogenicity of non-mammalian proteins including fluorescent reporters
- Control biodistribution:
  - spread of the virus
  - level of expression of transgene
- Proof of concept in other models and other species
- Meet cost of making viruses to GMP standards
- Licensing
  - Navigate IP landscape

What does the roadmap look like now?

Now: limited preclinical data, usually limited to only one rodent model, one time point



Research priorities

- Which vector?
  - Predictable expression, reduced risk of insertional mutagenesis, refined promoter design
- Which payload?
  - Reliable effect, absence of adverse effects, selective for abnormal vs normal activity
- Which preclinical model?
  - Relevant to several forms of epilepsy, across different ages, effective in the long term
- Which target population?
  - Improved understanding of epilepsy mechanisms
- How to run a trial?
  - Multi-centre patient recruitment, define outcome