



EMA workshop on RNA medicines

Applications of RNA technologies - clinical

RNA targeting for brain disease

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RCSI DEVELOPING HEALTHCARE LEADERS WHO MAKE A DIFFERENCE WORLDWIDE



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AND HEALTH
SCIENCES

Moving from preclinical to early clinical trials

- Brain disease (epilepsy) as a fast-emerging opportunity
- Patient perspectives on RNA medicines
- Opportunities
 - Translational models and first-in-human
- Challenges
 - Delivery to the brain, safety & toxicity
 - Using RNAs as PK/PD biomarkers
- Future perspectives

Disclaimer and conflict of interest: presenter holds patents for the treatment of epilepsies using RNA therapies and has received funding for the development of RNA medicines and biomarkers from commercial sources

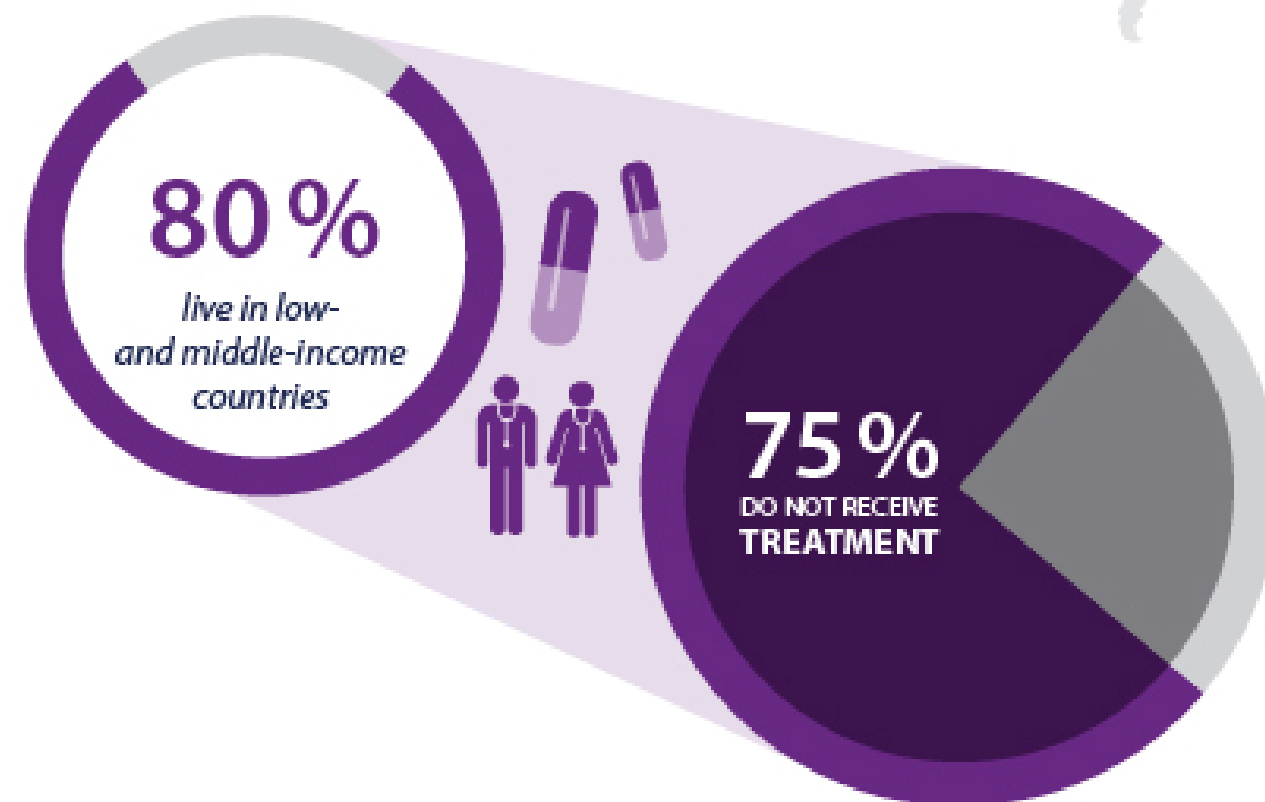
Epilepsy – unmet need and market



Intersectoral Global Action Plan on epilepsy and other neurological disorders 2022 – 2031

50 000 000

More than 50 million people are living with epilepsy globally



CAUSES OF TREATMENT GAP:

- lack of trained staff
- poor access to anti-epileptic medicines
- societal misconceptions
- poverty
- low prioritization for the treatment of epilepsy

3-6 TIMES
GREATER RISK
OF PREMATURE DEATH

Global market for Epilepsy Drugs ~\$5 Billion in the year 2020 (3.3% CAGR)

Why do we need new medicines?

- 1-in-3 patients do not achieve seizure control on current ASMs
- ASMs are not disease-modifying or specific for the underlying pathophysiology

- 40% of severe epilepsies have single gene (monogenic) cause

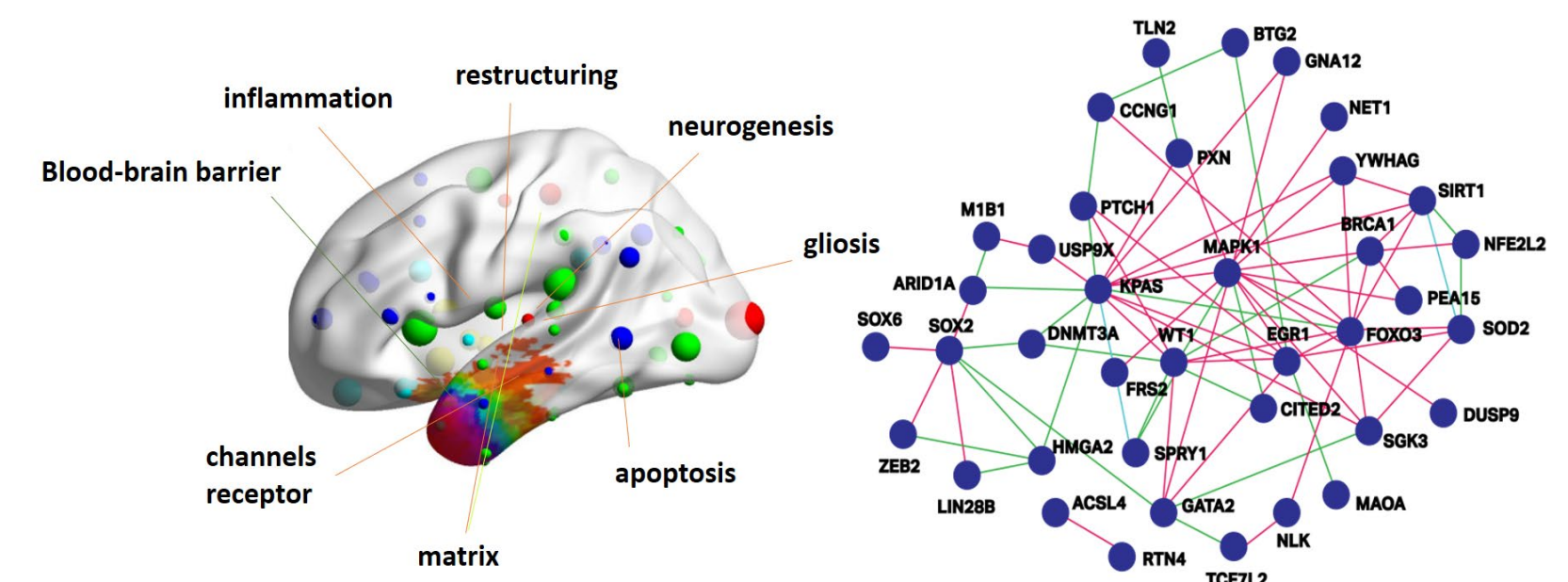


loss and gain of function in Na⁺, K⁺, Ca²⁺ channels, neurotransmitter receptor genes, signaling pathways (mTOR)

Enhancing productive Scn1a protein by ASO targeting of a natural “decay” signal for **Dravet syndrome**

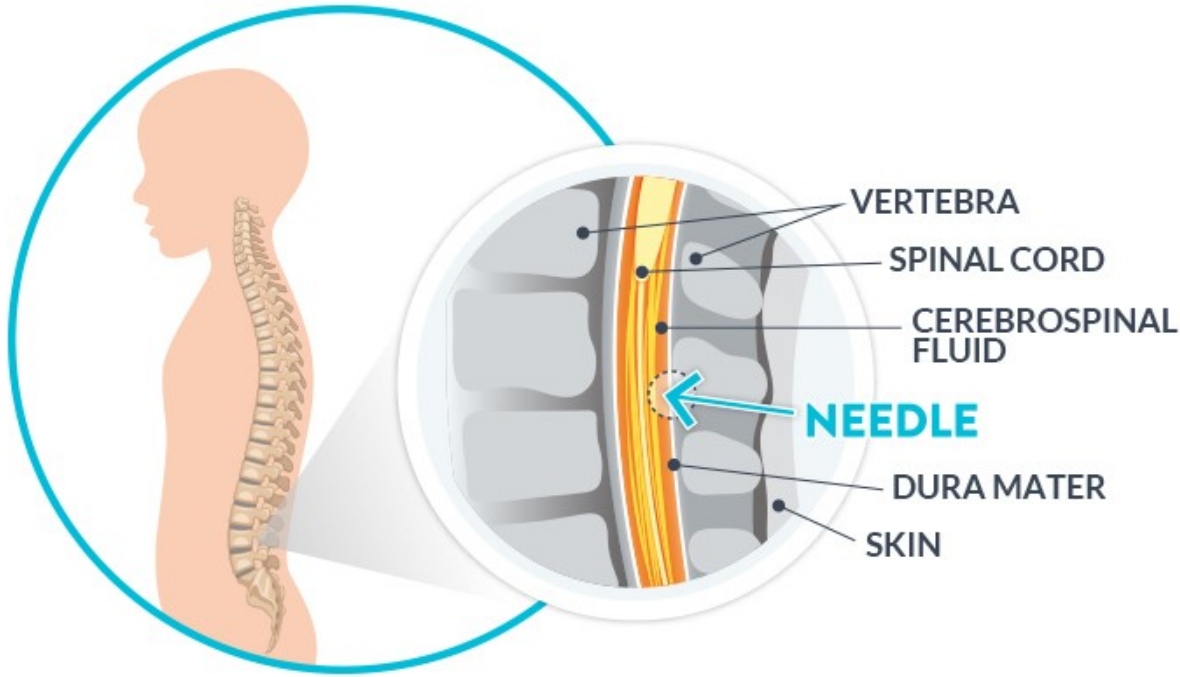
STROKE
THERAPEUTICS
NCT04740476

- Acquired forms of epilepsy
infection, brain injury - multi-pathway causes



What do patients want and what are they afraid of?

Gene and RNA therapies are clinically approved and many more are coming.....



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

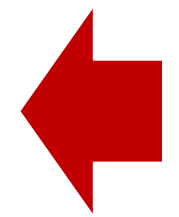
Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkowska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu



>5000 patients consulted - Patient priority setting by ERUK

- 1 What are the causes and contributing factors of epilepsy-related deaths, including Sudden Unexpected Death in Epilepsy (SUDEP), and how can these deaths be prevented?
- 2 What underlying mechanisms cause epilepsy in children and in adults?
- 3 What impact do epilepsy, seizures and anti-seizure medication (ASMs) have on brain health - including cognition, memory, learning, behaviour and mental health?
- 4 How does epilepsy and epilepsy treatment impact neurodevelopment, and can this be managed or prevented?
- 5 How can targeted, personalised medicine, such as gene therapy, be used to treat and/or prevent epilepsy?
- 6 How can tools, devices and biological markers be used to accurately predict and prevent seizures and the onset of epilepsy?
- 7 How do hormonal changes in women throughout the lifespan (puberty, pregnancy, menopause) impact epilepsy, and how can this impact be addressed?
- 8 How can quality of life be improved for people with epilepsy, their families and carers, including those bereaved by epilepsy?
- 9 What causes drug-resistant (refractory) epilepsy, and how can it be best treated?
- 10 How can big data analysis, through artificial intelligence (AI) and machine learning, aid the diagnosis and management of epilepsy?



Patients *want* gene therapies

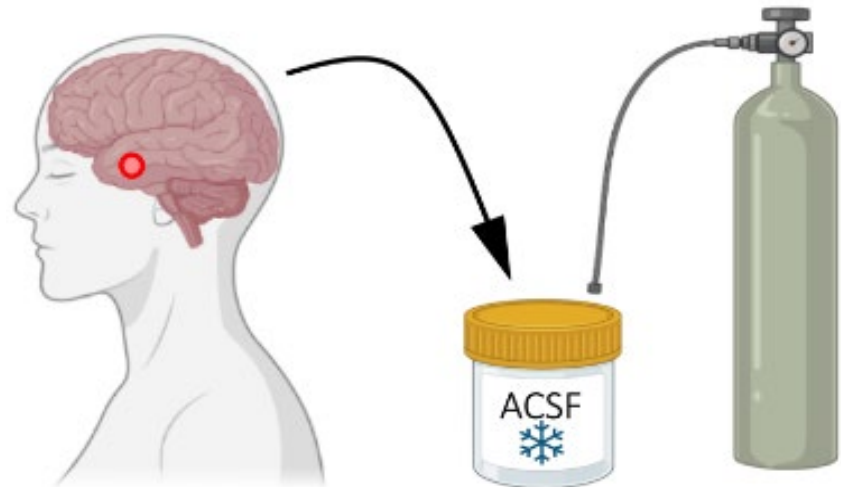
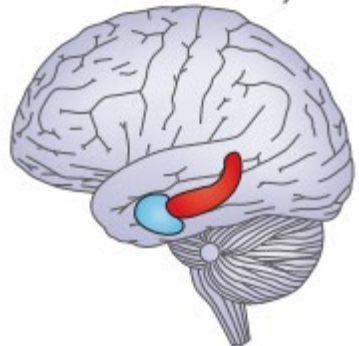
- Potential for cure/disease modification
- No more daily dosing
- Fewer side effects

But they have *concerns*

- Can it be switched off?
- Invasive/painful injections

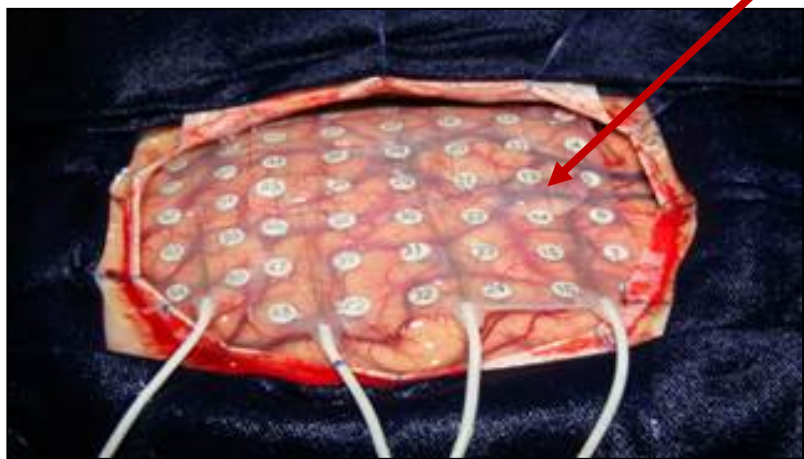
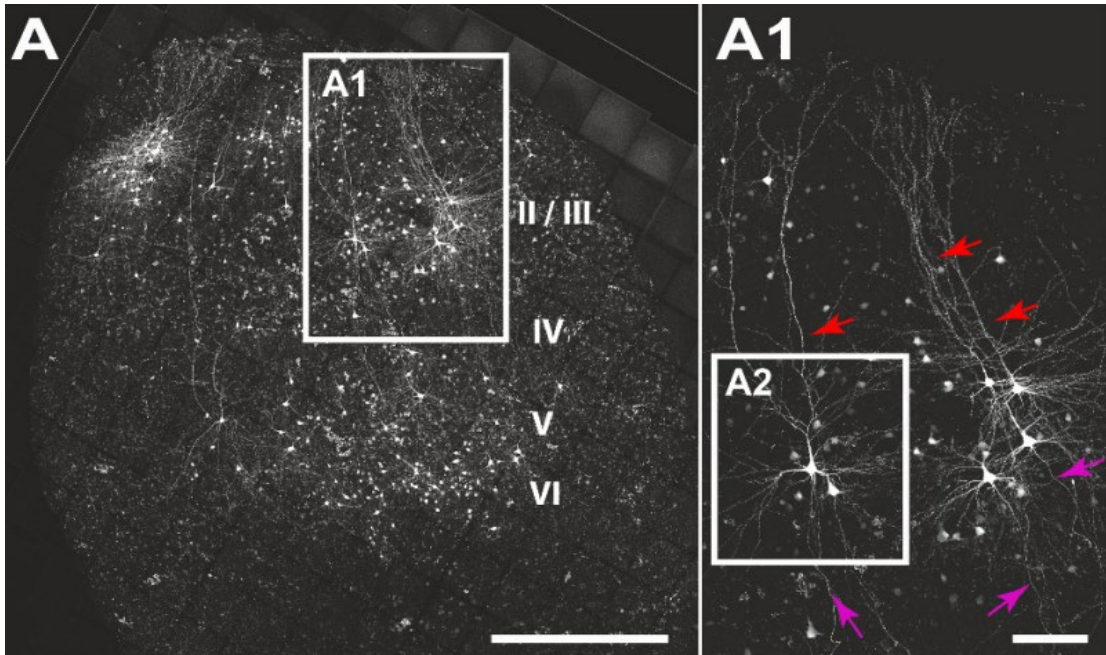
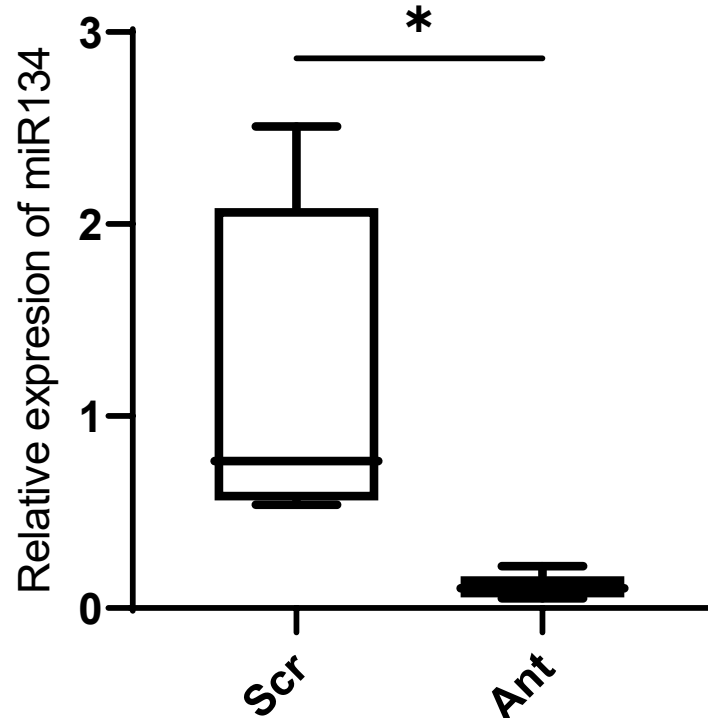
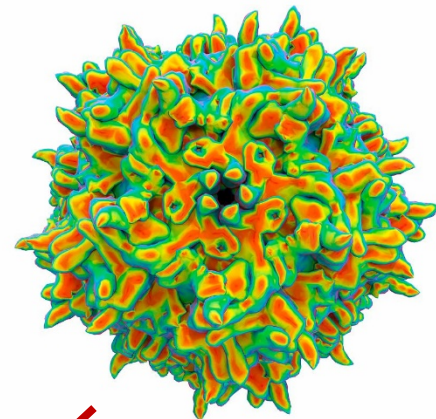
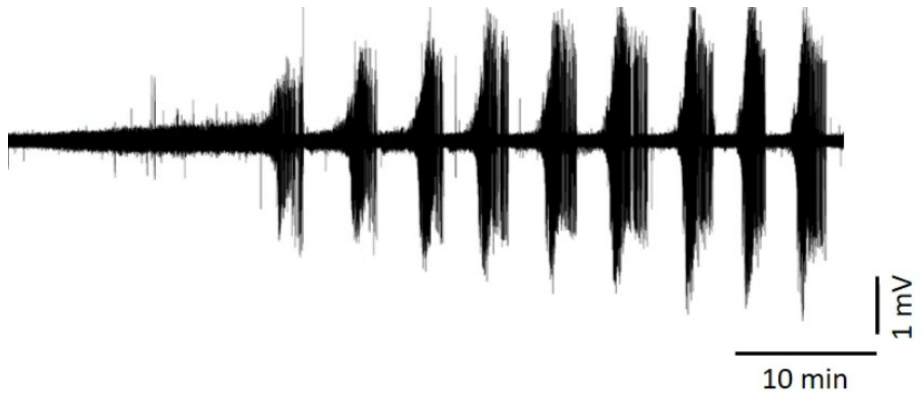
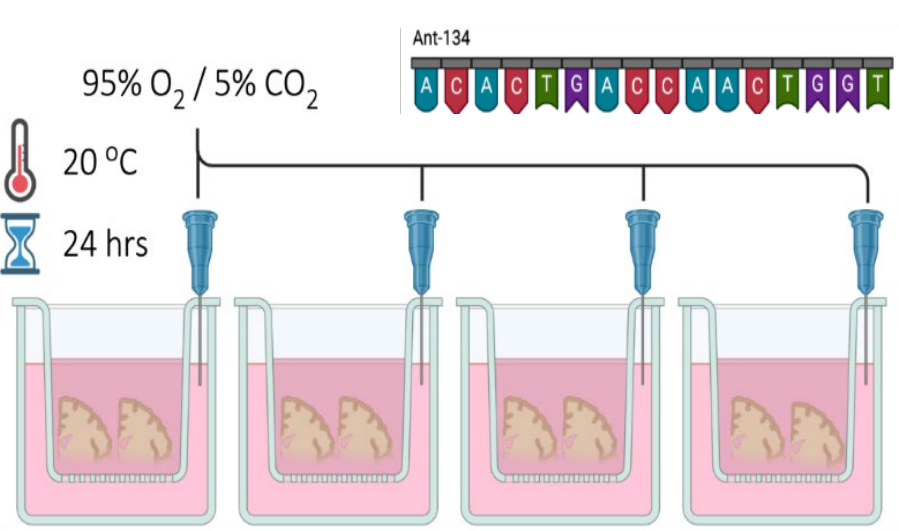
Opportunities for clinical translation

1). Epilepsy surgery provides access to live human tissue to test RNA medicines



2). Innovative trials for RNA/gene therapies

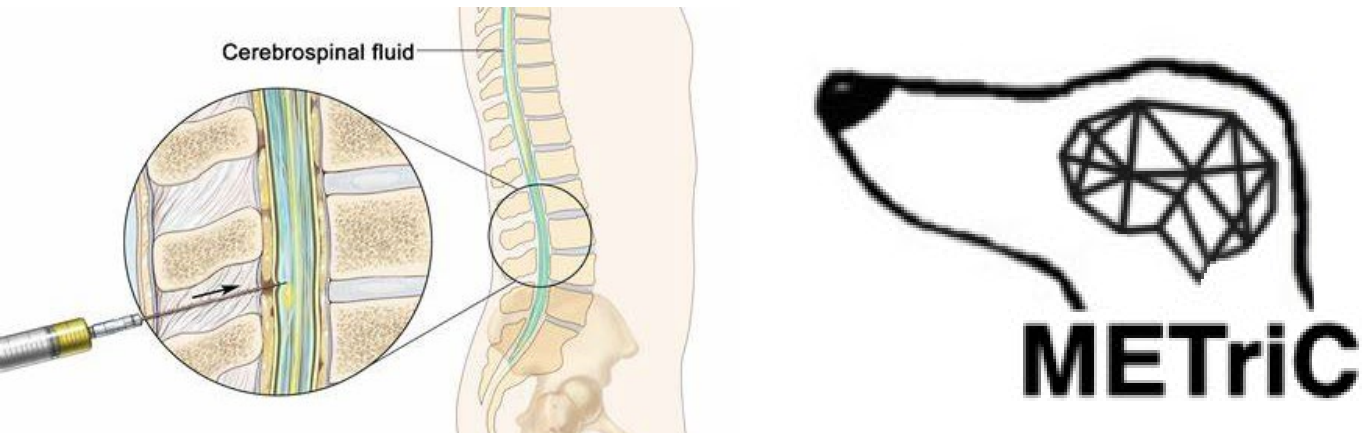
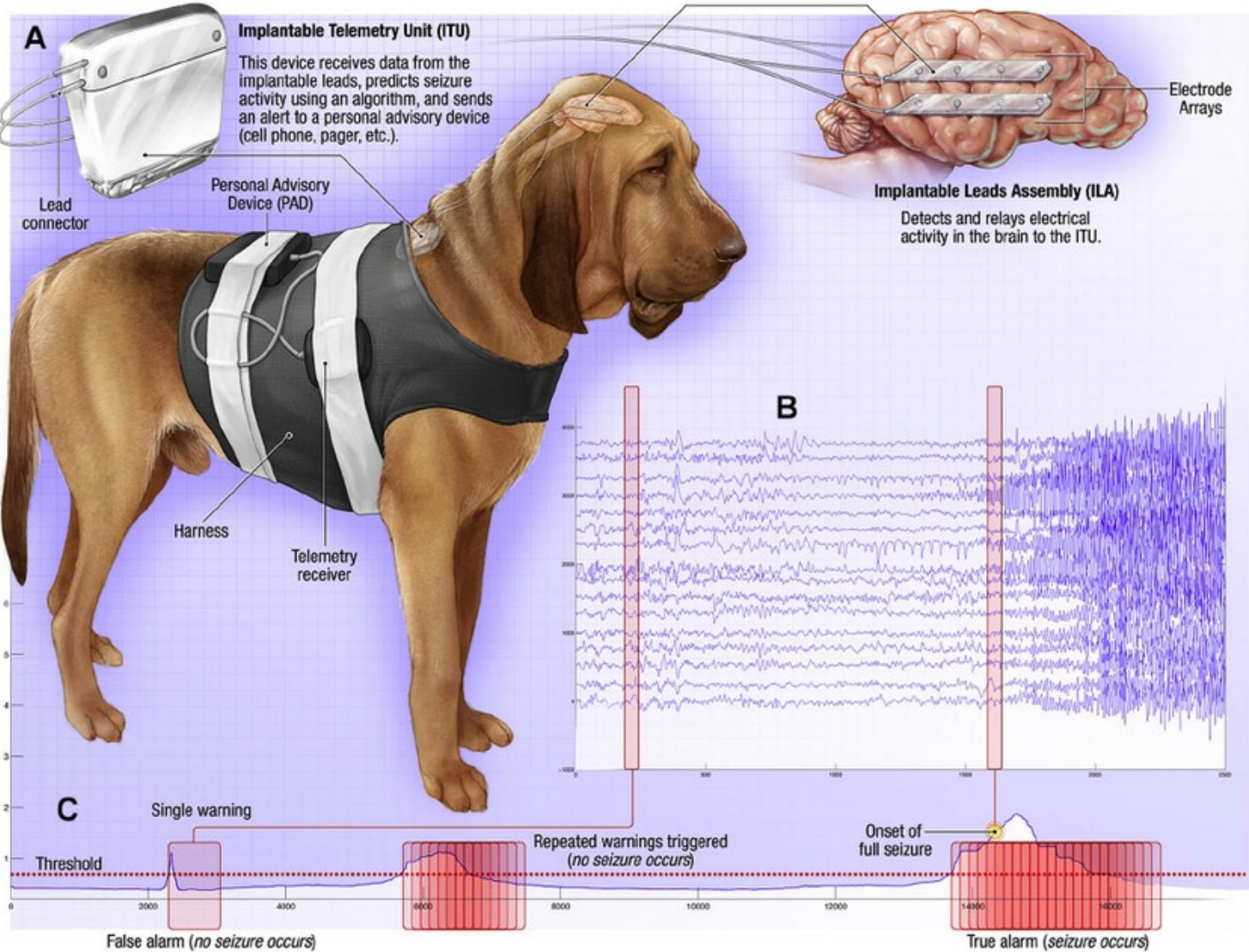
- Surgery already planned. RNA therapy injected into tissue scheduled for resection
- = de-risking RNA medicines trials for CNS



➔ Histology on resected tissue (and monitor for changes to seizures)
Or if it “works” do not proceed to surgery

Opportunities for clinical translation

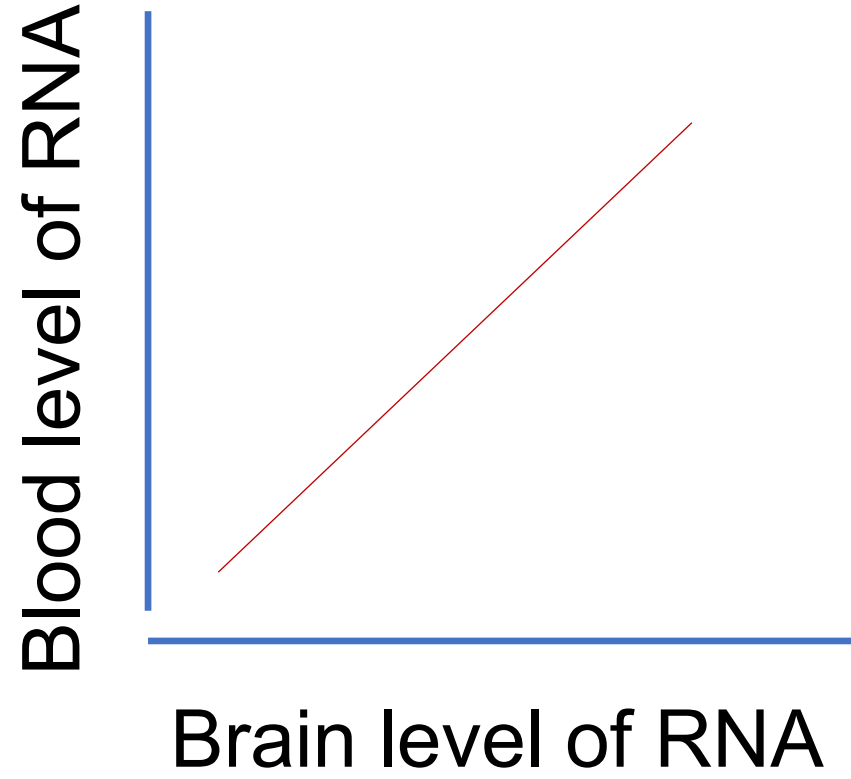
3). Other translational models for pre-human testing of RNA therapies



4). Companion biomarkers: Circulating RNAs could support selection of patients or PK/PD.



e.g. Mirxes' GASTROClear

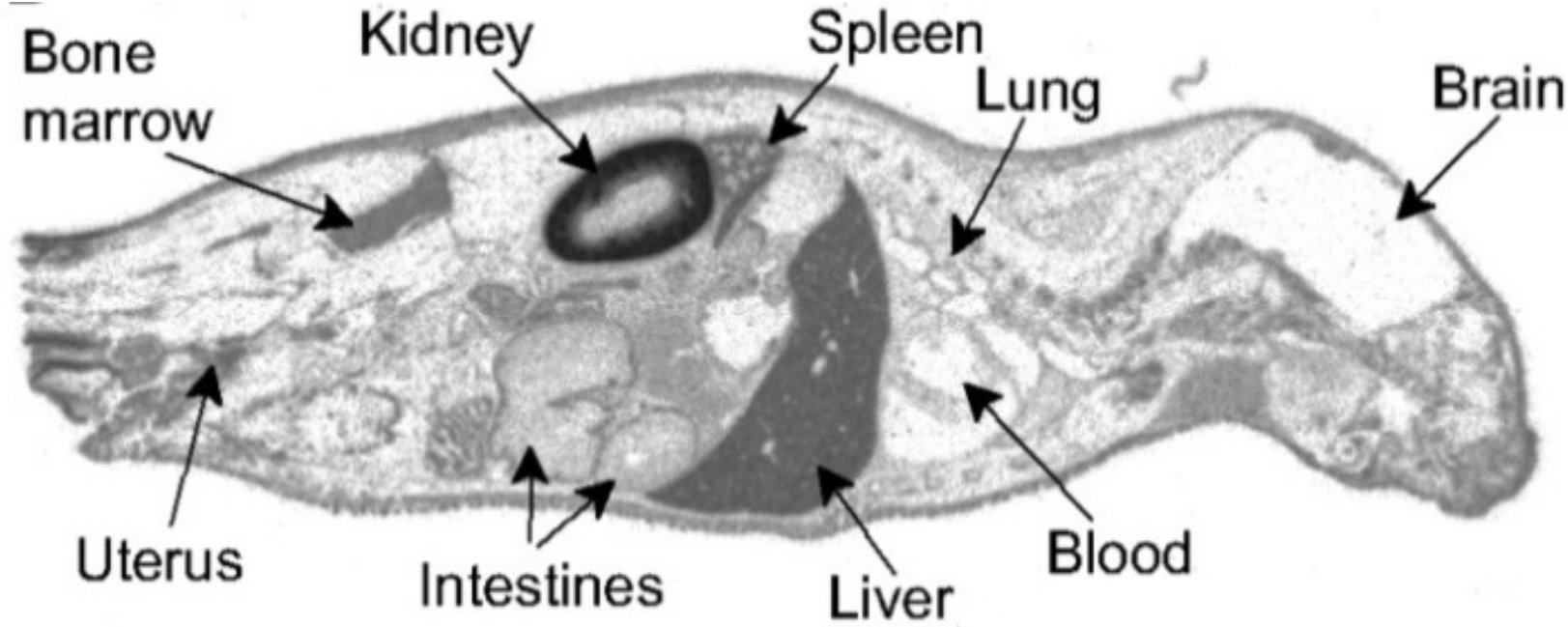


They could:

- Monitor target engagement
- Monitor change in symptoms (e.g. seizures)
- Easy detection with PCR-type point-of-care (POC) technology

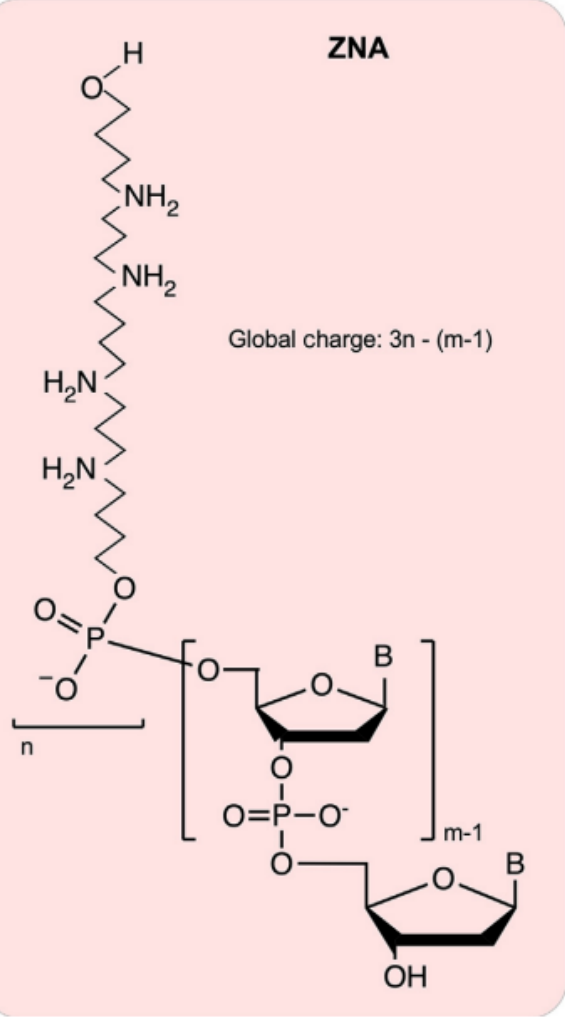
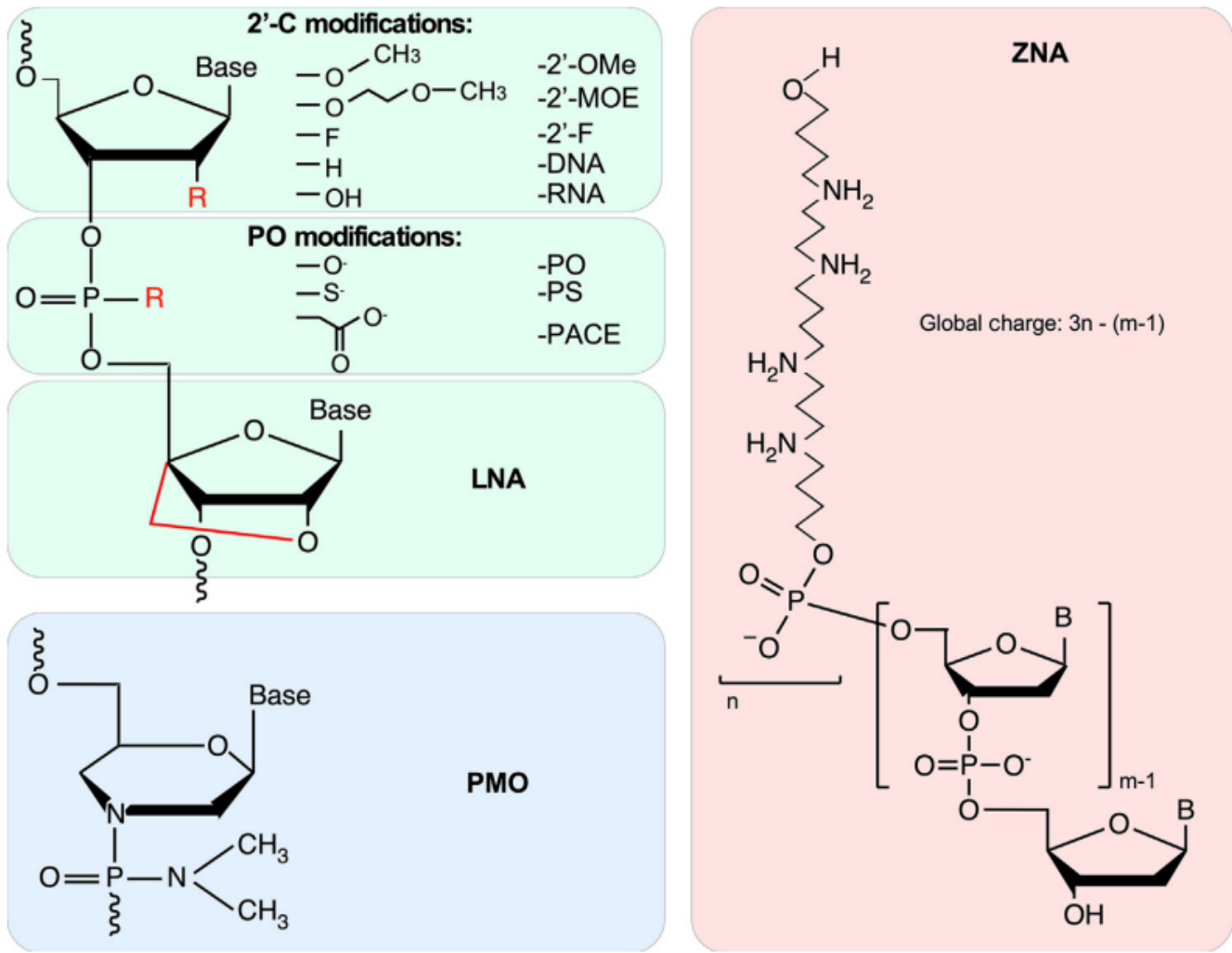
Challenges with RNA therapies

1). Requires direct delivery to CNS



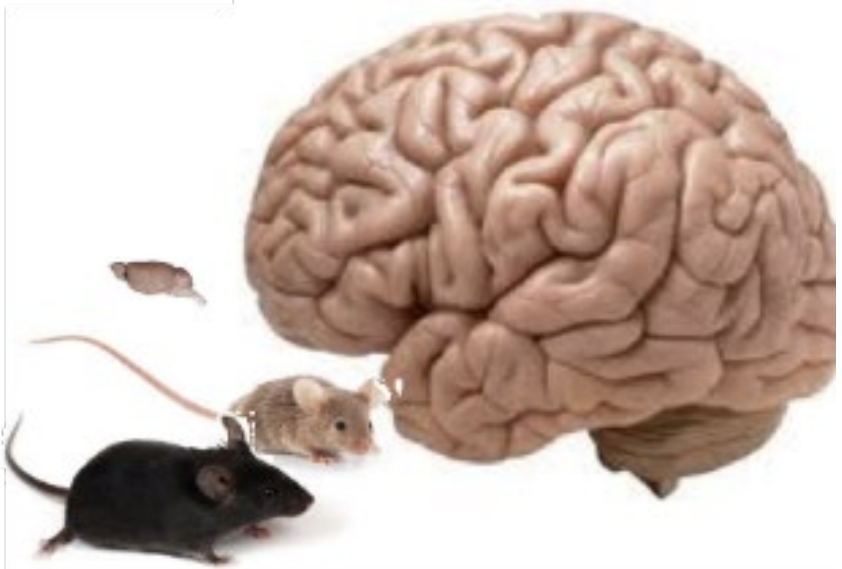
Straarup et al. *Nucl Acid Res*2010

2). Optimal chemistry (backbone, sequence....)



Morris et al *Trends Pharmacol Sci* (2021)

3). How good are rodent models at predicting “off-target” and long-term effects?



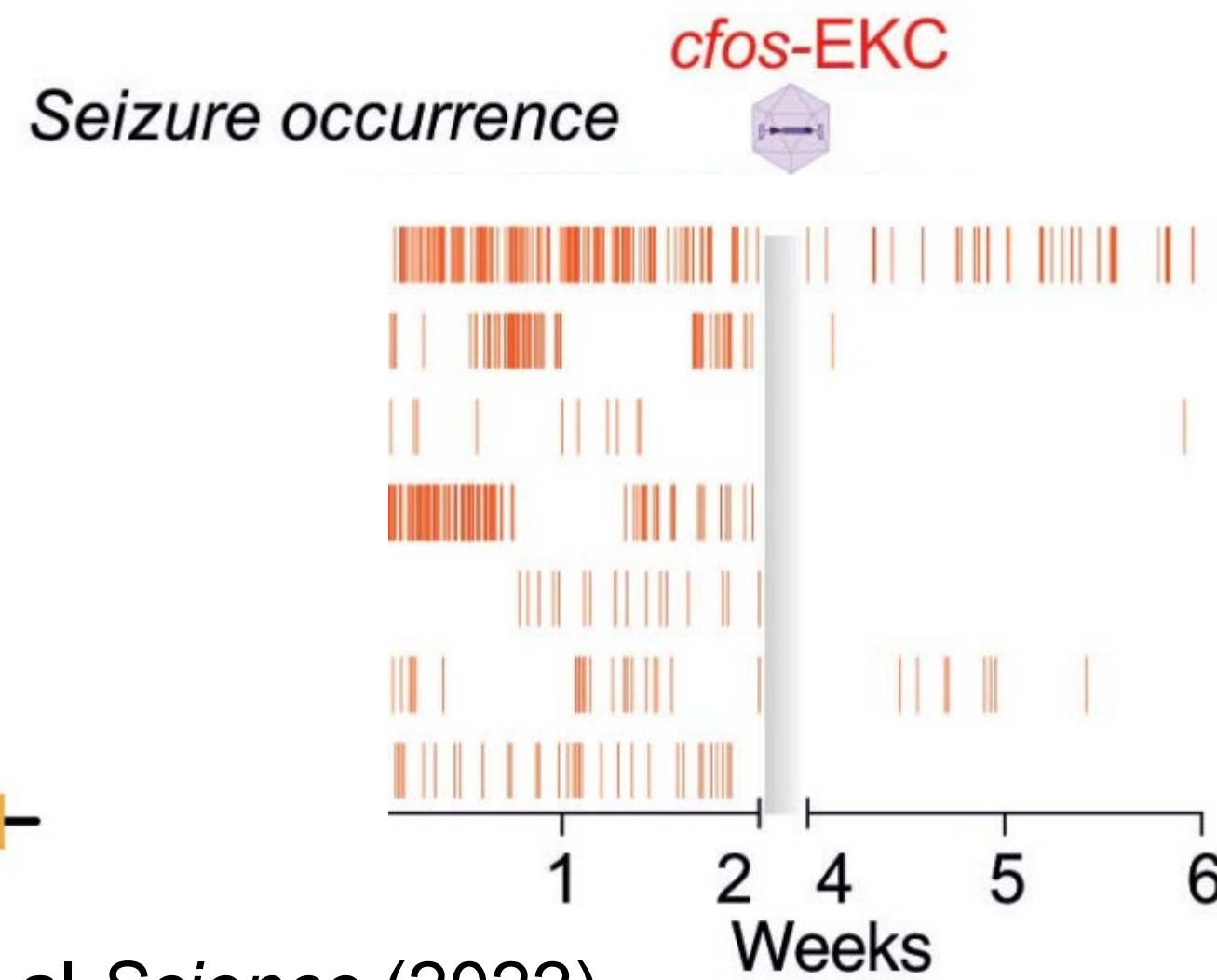
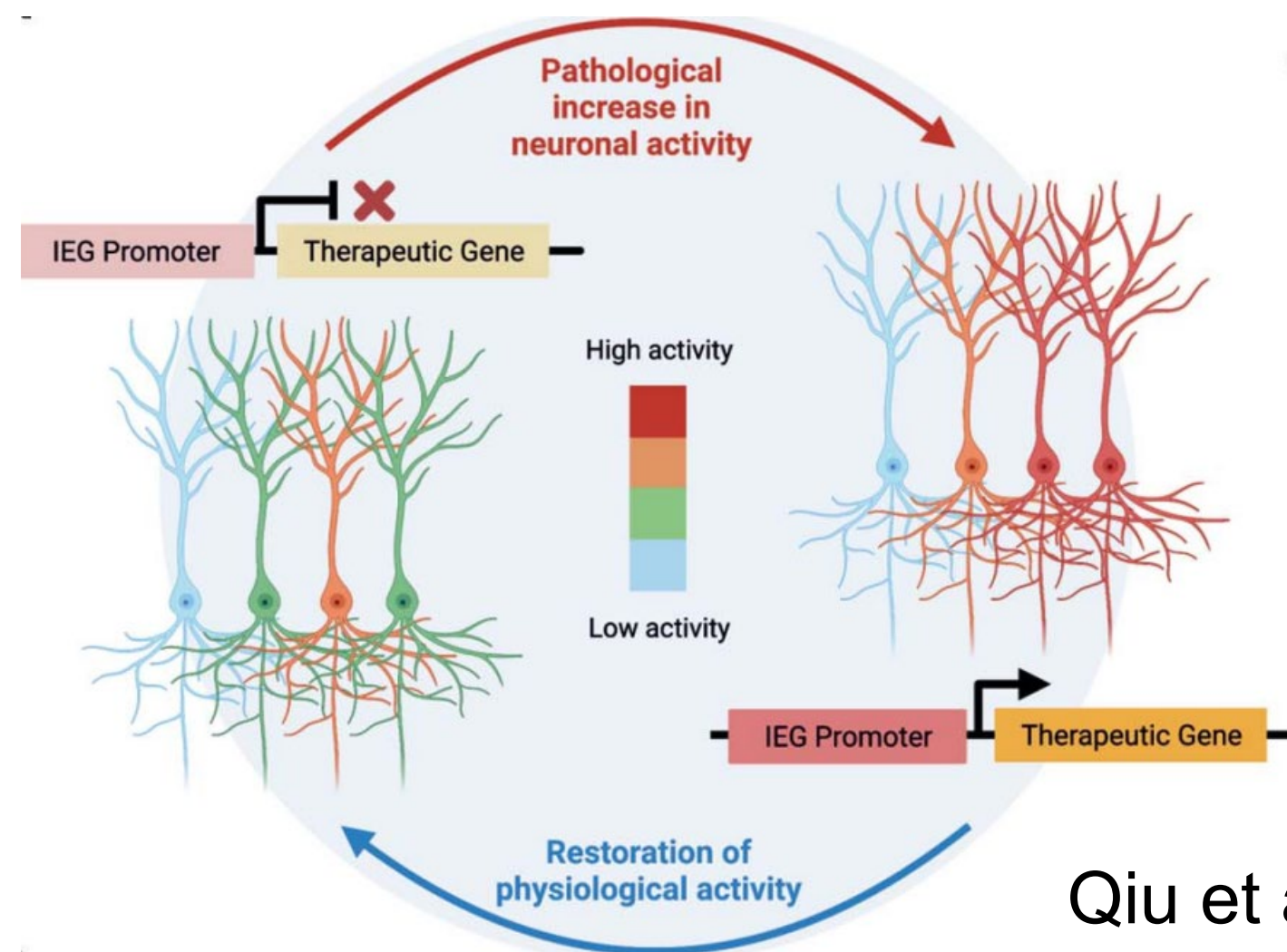
4). Will RNA therapy interact with current treatment?

Future perspectives

1). RNA therapy that responds only to “active” pathology

NEUROSCIENCE

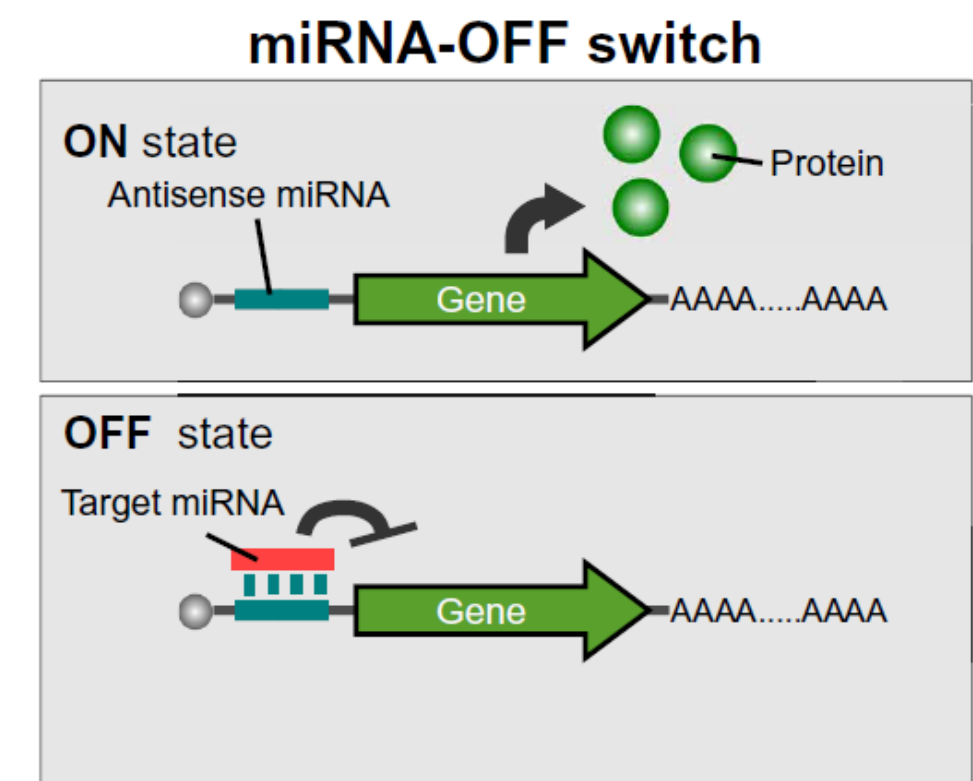
On-demand cell-autonomous gene therapy for brain circuit disorders



Qiu et al *Science* (2022)

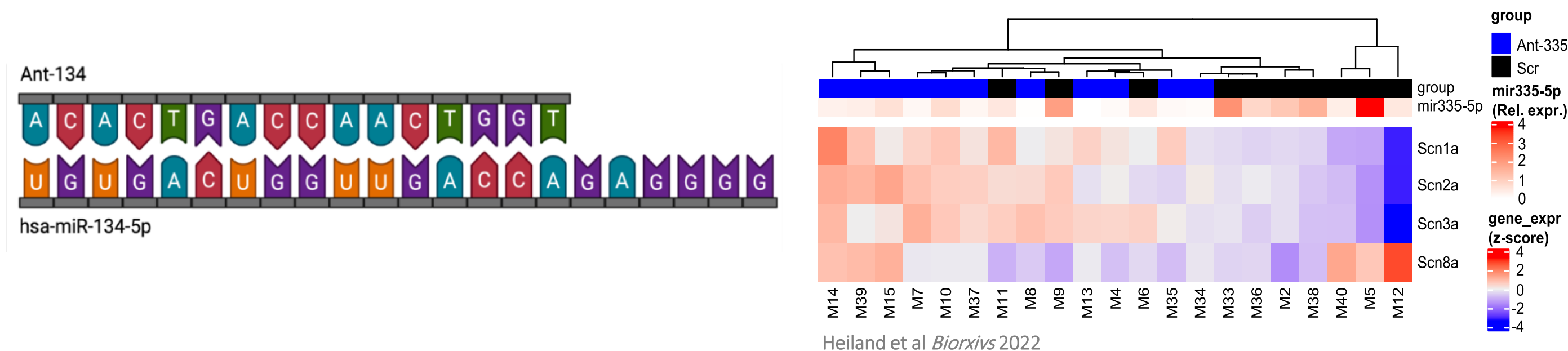
2). Engineering “On” and “Off” switches for gene therapies

SCIENCE ADVANCES | RESEARCH ARTICLE



Fujita et al *Sci Adv* (2022)

3). “Network” molecules such as microRNAs as ASO targets



Heiland et al *Biorxivs* 2022

4). Cell-directed targeting of ASOs?