Crosstalk Rebuttal to JP-CT-2022-282185R1

Authors: Amy Richardson[1], Gareth Morris[2]

[1]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, United Kingdom

[2]Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom

**Correspondence:*

Written: Gareth Morris, Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom, WC1E 6BT.

Email: gareth.morris@ucl.ac.uk

ORCID: 0000-0003-2469-5102

Manuscript details: Words: 390; References: 10; Figures: 0; Tables: 0;

Manuscript #: JP-CT-2022-283577

Prof Cunningham (Cunningham, 2022) succinctly argues that erroneous extrapolation between rodent and human brain tissues may underlie the well-documented clinical treatment gap for epilepsy, where approximately one third of patients continue to experience seizures, even with optimal medications (Janmohamed *et al.*, 2020). Prof Cunningham argues that reliance on animal models has not delivered drugs that differentiate from older therapies, and that network signals from animal brain slices, including pathological HFOs, do not provide insights into circuit mechanisms underlying these oscillations. Here, we provide brief counterarguments to these ideas.

In terms of small molecule drug development, it is true that current approaches have not necessarily reduced the percentage of pharmacoresistant cases. However, we argue that newer generation anti-seizure medications (ASMs) are typically associated with fewer adverse effects. Furthermore, animal models are currently yielding promising novel treatments for pharmacoresistant seizures which include genetic therapies (Morris *et al.*, 2021; Morris & Schorge, 2022) – clinical trials for a leading gene therapy, developed in animal models, will begin in the near future (Kullmann *et al.*, 2014; Snowball *et al.*, 2019). Many of these preclinical therapies have been tested in multiple animal models, capturing a variety of epileptogenic mechanisms, in order to maximise their applicability in the diverse range of clinical pharmacoresistant epilepsies.

Regarding circuit mechanisms, there are examples in the literature where brain slices from chronically epileptic animals have been used to study the cellular correlates of (patho)physiological HFOs (Morris *et al.*, 2016), unveiling new mechanistic insights. These oscillations have good face value as a model of human HFOs, though as Prof Cunningham states, they usually must be evoked pharmacologically (Raimondo *et al.*, 2017) and do not occur spontaneously, as may be desirable for a model of epilepsy.

We do however concede that animal models cannot capture the full complexity of the human brain. There are examples of biophysical phenomena (e.g. (Gidon *et al.*, 2020)) and cell types (e.g. (Boldog *et al.*, 2018)) which are unique to the human brain and were discovered using resected human tissues (NB – the later study excluded tissues from people with a history of epilepsy). These are likely responsible at least in part for the more complex integration of information in the human brain. Ultimately, the choice of tissue and model system must be weighed up for each experiment, taking into account model validity, scientific, ethical, logistical and biosafety considerations.

Boldog E et al. (2018). Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type. *Nature Neuroscience* **21,** 1185–1195.

Cunningham MO (2022). CrossTalk proposal: Human-derived brain tissue is a better epilepsy model than animal-based approaches. *The Journal of Physiology*.

Gidon A, Zolnik TA, Fidzinski P, Bolduan F, Papoutsi A, Poirazi P, Holtkamp M, Vida I & Larkum ME (2020). Dendritic action potentials and computation in human layer 2/3 cortical neurons. *Science* **367,** 83–87.

Janmohamed M, Brodie MJ & Kwan P (2020). Pharmacoresistance – Epidemiology, mechanisms, and impact on epilepsy treatment. *Neuropharmacology* **168,** 107790.

Kullmann DM, Schorge S, Walker MC & Wykes RC (2014). Gene therapy in epilepsy—is it time for clinical trials? *Nature Reviews Neurology* **10,** 300–304.

Morris G, Jiruska P, Jefferys JGR & Powell AD (2016). A new approach of modified submerged patch clamp recording reveals interneuronal dynamics during epileptiform oscillations. *Frontiers in Neuroscience*; DOI: 10.3389/fnins.2016.00519.

Morris G, O'Brien D & Henshall DC (2021). Opportunities and challenges for microRNA-targeting therapeutics for epilepsy. *Trends in Pharmacological Sciences* **42,** 605–616.

Morris G & Schorge S (2022). Gene Therapy for Neurological Disease: State of the Art and Opportunities for Next-generation Approaches. *Neuroscience*; DOI: 10.1016/j.neuroscience.2022.03.010.

Raimondo J v., Heinemann U, de Curtis M, Goodkin HP, Dulla CG, Janigro D, Ikeda A, Lin CCK, Jiruska P, Galanopoulou AS & Bernard C (2017). Methodological standards for in vitro models of epilepsy and epileptic seizures. A TASK1-WG4 report of the AES/ILAE Translational Task Force of the ILAE. *Epilepsia* **58,** 40–52.

Snowball A, Chabrol E, Wykes RC, Shekh-Ahmad T, Cornford JH, Lieb A, Hughes MP, Massaro G, Rahim AA, Hashemi KS, Kullmann DM, Walker MC & Schorge S (2019). Epilepsy gene therapy using an engineered potassium channel. *Journal of Neuroscience* **39,** 3159–3169.

Additional Information

Data availability statement

N/A

Competing interests

The authors declare no competing interests.

Author contributions

Both authors conceived, wrote and finalised the manuscript. The authors contributed equally to this publication.

Funding

AR is supported by the Wellcome Trust (grant number 212285/Z/18/Z). GM is supported by an Emerging Leader Fellowship Award from Epilepsy Research UK (grant reference F2102 Morris).