Innovative gene therapy approaches for brain tumour-related epilepsy

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Professor Mark Cunningham and Dr Kate Connor from Trinity College Dublin discuss the burden of brain tumour-related epilepsy and why novel therapies are urgently needed to improve the quality of life for those affected

Brain tumour-related epilepsy (BTRE) is a unique and devastating condition which embraces two serious pathologies. BTRE incidence is inversely correlated to malignancy, with seizures as the first presenting symptom in 65-85% of patients with low-grade gliomas (LGG) and 30-60% with glioblastoma (GBM). (1)

Seizures often manifest as complications throughout brain tumour evolution. Clinical management via radiotherapy, chemotherapy, and antiepileptic drugs (AEDs) can reduce seizure frequency, but many patients continue to experience seizures following therapeutic intervention. (2) Overall, BTRE is a debilitating and difficult-to-control condition, with seizures closely linked to tumour recurrence and progression.

In all cases, seizures associated with brain tumours significantly impact patients' lives. BTRE is a major risk factor for long-term disability in patients due to the negative impact of seizures on quality of life (QoL) and the side effects of prescribed AEDs. (3) Patients with seizures report reduced physical and mental health, increasing seizure burden and anticonvulsant use associated with reduced cognitive performance. (4)

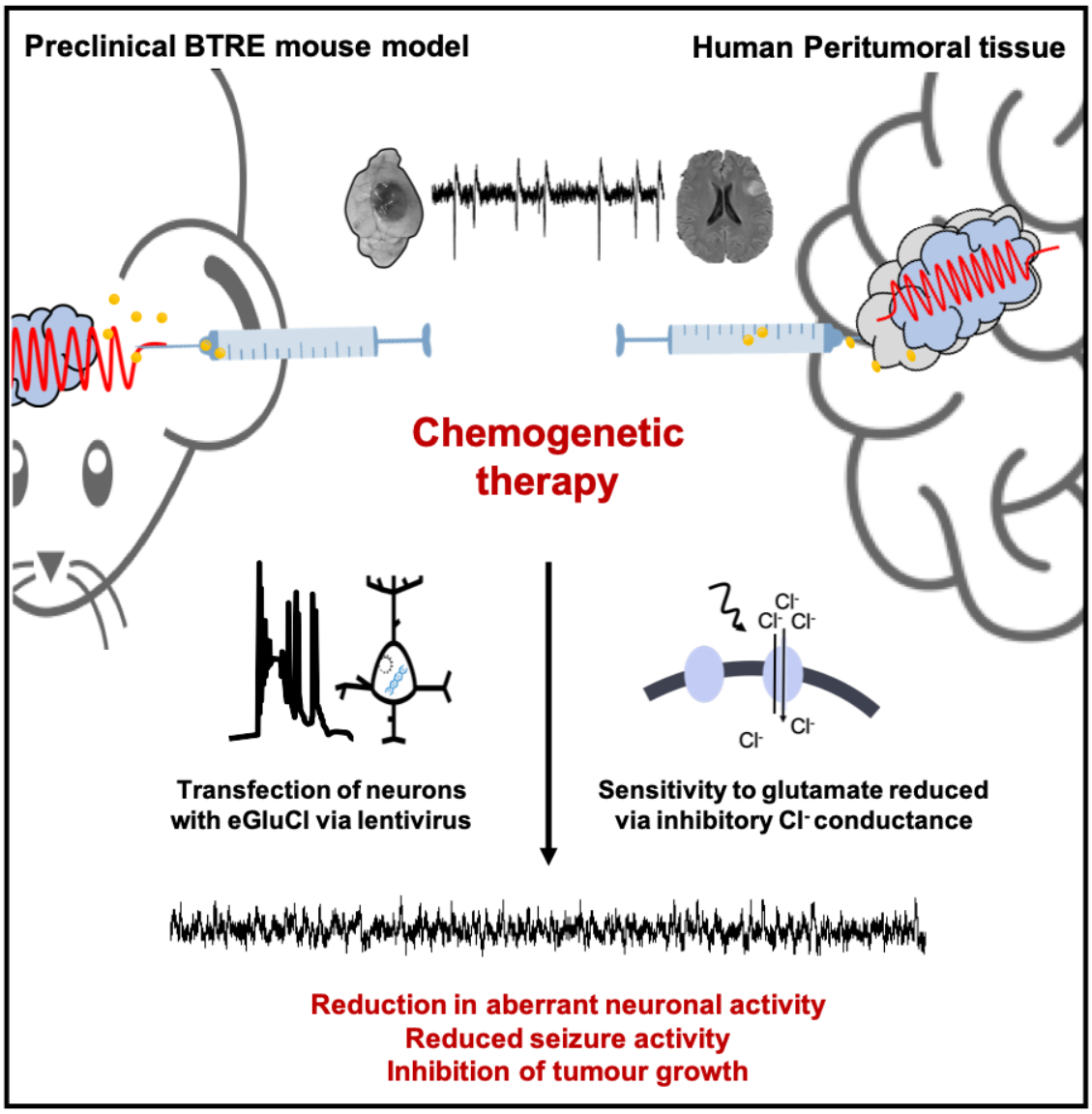
Seizures result in reduced mobility (loss of driving license), contribute to behavioural issues, and increase the risk of death (via uncontrollable seizures). Critically, given the limited efficacy of surgical, oncological, and pharmacological treatments for BTRE, and its significant impact on quality of life, there is an urgent need to expedite the development of novel therapies.

Glutamatergic mechanisms in brain tumour-related epilepsy

Epilepsy is fundamentally characterised by aberrant neuronal excitability. Notably, glutamate (the major excitatory neurotransmitter in the central nervous system) within the peritumoural microenvironment is a key contributor to malignant tumour growth and seizure generation. (5)

Specifically, abnormal glutamate expression (i.e., elevated extracellular levels of glutamate and excessive glutamate receptor activation) leads to uncontrolled neuronal excitability, promoting synchronous neuronal epileptic discharges. (6) Glutamate induces calcium-dependent depolarisation of post-synaptic neurons, causing excitotoxicity and

subsequent neuronal cell death. [7] This dynamic and destructive process promotes tumour growth and glioma cell infiltration into the surrounding brain parenchyma. The critical role glutamate plays in glioma growth and epileptogenesis highlights the glutamate system as a powerful therapeutic target [8] and biomarker [9] for BTRE treatment.



Innovative therapeutic approaches for BTRE

To date, attempts to treat BTRE have yielded disappointing clinical results. Nevertheless, chemogenetics (gene therapy whereby proteins are engineered to interact with small chemical actuators) has the potential to overcome the limitations of pharmacological interventions. Notably, one such form of chemogenetics is an engineered glutamate-gated chloride (GluCl) channel. [10]

Activation of the GluCl receptor results in chloride influx, leading to neuronal hyperpolarisation and overall suppression of neuronal firing. Importantly, recent data has shown that an enhanced version of GluCl (eGluCl) can decrease seizure activity in rodent

epilepsy models. [11] Therefore, given the central role of glutamate in BTRE pathogenesis, there is a unique opportunity to avail of this biochemical autoregulatory gene therapy approach to improve treatment options for brain tumour-related epilepsy.

Research towards the future of BTRE

The Cunningham Laboratory research group aims to understand the basis of neurological and psychiatric disease at the level of the neuronal microcircuit. In particular, our research seeks to understand physiological and pathological electrical activity generated in various disease states. In the BTRE context, our research aims to employ the previously described eGluCl chemogenetic approach to prevent seizure generation and propagation in brain tumour-related epilepsy.

Here, we use closed-loop chemogenetic approaches and wireless electrocorticogram (ECoG) recording methods in a syngeneic orthotopic glioma model. Complementary *in vitro* brain slice electrophysiological methods (extracellular local field potential (LFP) and whole-cell patch clamp recordings) are employed to study eGluCl treatment effects on harvested peritumoral tissue.

Finally, *ex vivo* organotypic human peritumoral slices will be generated and used (inter-ictal and ictal activity analysed following treatment) to develop eGluCl to clinical translation. We anticipate this technology will address a significant unmet clinical need, providing effective therapeutic options in drug refractory BTRE patients.

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