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CONCEPTS AND HYPOTHESES

Systemic inflammation as a biomarker of seizure propensity and a target for treatment to reduce seizure propensity

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Abstract

People with diabetes can wear a device that measures blood glucose and delivers just the amount of insulin needed to return the glucose level to within bounds. Currently, people with epilepsy do not have access to an equivalent wearable device that measures a systemic indicator of an impending seizure and delivers a rapidly acting medication or other intervention (e.g., an electrical stimulus) to terminate or prevent a seizure. Given that seizure susceptibility is reliably increased in systemic inflammatory states, we propose a novel closed-loop device where release of a fast-acting therapy is governed by sensors that quantify the magnitude of systemic inflammation. Here, we review the evidence that patients with epilepsy have raised levels of systemic indicators of inflammation than controls, and that some anti-inflammatory drugs have reduced seizure occurrence in animals and humans. We then consider the options of what might be incorporated into a responsive anti-seizure system.

KEYWORDS

biomarkers, closed-loop, epilepsy, inflammation, responsive

1 | INTRODUCTION

Some seizures can be fairly reliably forecasted[1] and even prevented.[2] This usually requires the placement of intracranial electrodes and a responsive neurostimulation system. While non-invasive forecasting of seizures may be feasible in some patients with a combination of neurophysiological and clinical data,[1,3,4] a systemic, chemical marker of seizure propensity is not available. We suggest that a complementary and potentially less invasive approach modeled on the closed-loop systems for release of insulin in response to continuously monitored blood glucose levels might achieve the goals of forecasting and intervention.[5]

In light of evidence that some seizures are associated with inflammation identified peripherally,[6–15] we suggest that a closed-loop system that identifies rising concentrations of an inflammation indicator in a body fluid and delivers an anti-inflammatory agent (either highly specific or broad-spectrum) or more anti-seizure medication[16–18] might be more acceptable than closed-loop electroencephalographic systems requiring a neurosurgical procedure, and may complement other means of non-invasive seizure forecasting, such as clinical information, seizure diaries,

and non-invasive neurophysiological data. We provide more detail about this option.

2 | PREDICTION

We envision two time scales of probability assessment. The shorter time frame is likely seconds or minutes, and the presumed best early indicator of state shift is the EEG.

The longer time frame is likely hours or days, and the frame of reference is "forecasting."[19–21] This orientation takes advantage of the increasing availability of online seizure diaries allowing "cycles" (circadian, multi-day) to be identified,[3,22–25] and machine-learning to be applied to identifying correlates of increased seizure propensity,[4,26,27] similar to what has been done for predicting the likelihood of sustained hypoglycemia.[28] Identification of the trajectory that best describes a child's pre-ictal course would allow an intervention minutes to hours before seizure risk rises rapidly.

3 | PROOF OF CONCEPT

Proof of concept that seizures can be forecasted for up to 3 days comes from a study of EEG and clinical data of 157 adults with drug-resistant focal epilepsy followed at 35 US medical centers.[19] Proof of principle/concept that seizures can be aborted within a very short time through a closed-loop system after receipt of a signal of heightened seizure propensity comes from documentation of the success of neurostimulation.[2,29,30]

4 | INFLAMMATION

A plethora of recent reviews has linked inflammation and epilepsy.[6–15,31,32] Although elevated body temperature is probably the best-known indicator of inflammation that provides predictive information about increased risk of a seizure, we do not know of any study that has assessed how well serum/plasma levels of inflammation-related proteins convey information about impending seizures.

Inflammation-associated hereditary characteristics[33–36] can contribute to epileptogenesis. Later inflammation-related exposures probably account for some of the seizures associated with auto-immune encephalitides,[37] febrile infection-related epilepsy syndrome (FIRES), and new-onset refractory status epilepticus (NORSE),[15] as well as the late seizures that follow head trauma.[38,39] In addition, some/many children and adults with seizures of presumed idiopathic origin are more likely than others

to have genetic propensities to inflammation and other immune-related processes.[40,41]

4.1 | Both "chicken and egg"?

Some of the inflammation associated with seizures might be compensatory, reflecting the recruitment of the "clean-up squad" (e.g., microglia, astrocytes) to remove debris and initiate repair.[42] On the other hand, some reactive glia can contribute to epileptogenesis.[10] Although sterile inflammation of the brain need not require white cell infiltration,[43–46] activated peripheral mononuclear immune cells can contribute to seizure generation.[47]

In addition, pre-clinical studies document that the inflammation can come before, during, and after the seizure.[48] Studies in humans are needed to determine to what extent inflammation precedes seizures, and what biomarkers of inflammation are an appropriate signal for intervention. While inflammation may not be the sole predictor of seizures in all patients, evaluation of the contribution of inflammation, including the gain of additional predictive information for seizures, is crucial.

4.2 | NLRP3 inflammasome

Inflammasomes are multiprotein complexes that promote the availability of pro-inflammatory cytokines, such as interleukin-1β and interleukin-18.[49,50] Among various inflammasome complexes, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome can contribute to secondary brain damage[51] and is activated in rodent models of epilepsy,[52–57] and in humans with a seizure disorder.[36,57–61] A recently-published review provides additional details,[62] and another suggests inflammasomes might be good targets for therapeutic intervention.[63]

4.3 | Non-inflammatory stimuli that induce inflammation-related epileptogenesis

Support for the hypothesis that inflammation contributes to ictogenesis comes from rodent models of pilocarpine-induced, kainic acid-induced, and pentylenetetrazole-induced seizure propensities that include a robust inflammatory response.[64–70] Anti-inflammatory approaches involving inhibition of prostaglandin EP2 receptors,[65,66] inhibition of mTOR signaling,[64] and inhibition of neurotensin receptor 2 reduce the inflammation-associated phenomena (including seizure occurrence) attributed to pilocarpine, and thus offer support for the hope that these

anti-inflammatory approaches might reduce seizure occurrence in humans.

5 | MEASUREMENT OF INFLAMMATION—WHAT TO MEASURE?

The first decision point is whether the biomarker should be a general indicator of inflammation or one more specific to an individual patient.

If a general indicator will do, perhaps the least invasive way to identify a systemic inflammatory process contributing to seizure onset is to measure body temperature continuously with a wearable device. We are not aware of any assessments of the value measuring body temperature continuously. Most likely this reflects the previous unavailability of non-invasive wearable devices capable of measuring a surrogate for body temperature. Wristbands are now available that can continuously measure and record skin temperature.[1,4] Their usefulness for identifying heightened risk of a seizure, however, remains to be determined.

Tables 1 and 2, which list inflammation-related biomarkers that have been measured in human peripheral blood near the time of a seizure, include broad-spectrum indicators of inflammation along with specific cytokines, chemokines, adhesion molecules, growth factors, and other biomarkers of inflammation.

5.1 | High-sensitivity C-reactive protein

Serum levels of high-sensitivity C-reactive protein, (hs-CRP), apparently the most frequently studied inflammation biomarker in people with epilepsy,[71] not only convey information about acute inflammation but can also provide information about chronic processes.[103–108]

The five identical monomers (mCRP) of the circulating pentameric (pCRP) are capable of activating the complement cascade, and thereby able to amplify inflammation.[109] This recognition has led to the exploration of ways to minimize the inflammatory capabilities of mCRP.[110]

A meta-analysis of 16 case-control studies (comprised 1918 individuals) found that the CRP blood levels "were significantly increased in epileptic patients compared to healthy controls, indicating a significant association between inflammation and epilepsy."[71] Subsequent individual studies have confirmed this.[72–75,111]

5.2 | Procalcitonin

Procalcitonin (PCT), another frequently studied inflammation biomarker of seizures,[112,113] is now considered superior to CRP for evidence of infection and inflammation.[114–116] Nevertheless, its specificity is also less than desired.[114,117] Decreases in elevated PCT levels were once thought to mirror improvement so well that they could be a source of information for decisions about whether or not to discontinue antibiotic treatment.[118] This approach, however, is now viewed with some skepticism.[119]

5.3 | Other biomarkers of inflammation

Among the more interesting candidates are microRNA (miRNA)[120–123] and circular RNA (circRNA),[124,125] which

TABLE 1 Products of inflammation documented repeatedly in the peripheral blood of patients with recurrent seizures in reports published since a 2016 review[7]

CRP	Various seizure disorders	Case-control	Children, adults	[71–76]
IL-6	Various seizure disorders	Case-control	Children, adults	[58, 72, 77–81]
HMGB-1	Various seizure disorders	Case-control	Children	[82–85]
IL-1β	Various seizure disorders	Case-control	Children, adults	[58, 77, 82, 85]
TNF-α	Various seizure disorders	Case-control	Children, adults	[82, 86, 87]
interferon-γ	Various seizure disorders	Case-control	Children, adults	[80, 87, 88]
miRNAs	Temporal lobe epilepsy	Case-control	Children, adults	[84, 89, 90]
IL-17A	Various seizure disorders	Case-control	Adults	[80, 87]
MMP-9	TLE + Generalized Seizures	Case-control	Children, adults	[72, 73]
prolactin	TLE and febrile seizures	Case-control	Children, adults	[73, 91]
Caspase 3	Generalized Seizures	Case-control	Adults	[77, 86]

Abbreviations: CRP, C-Reactive Protein; HMGB-1, High Mobility Group Box 1; IL, Interleukin; miRNA, micro-ribonucleic acids; MMP, Matrix-MetaloProtein; TLE, Temporal Lobe Epilepsy; TLE-hs, Temporal Lobe Epilepsy with hippocampus sclerosis; TNF-α, Tumor necrosis factor-alpha.

TABLE 2 Products of inflammation measured in peripheral blood reported since publication of a review[7] in 2016. Elevated concentrations of these analytes have been associated with seizures in single reports only

IL-R1	Refractory seizures	Case-WCE control	Children	[82]
IL-5	drug-resistant TLE	Case-control	Adults	[79]
IL-8	Generalized Seizures	Case-control	Adults	[92]
IL-10 (lower levels)	TLE-hs	Case-other sz	Adults	[93]
IL-18 + IL-18BP	Generalized Seizures	Case-control	Adults	[94]
IL-22	Drug-resistant epilepsy	case-WCE control	Adults	[87]
IL-33	Epilepsy	Case-control	Adults	[95]
sTNFr2	Epilepsy	Case-control	Adults	[96]
TRAIL	Generalized Seizures	Case-control	Teens, adults	[13]
TLR4	Refractory seizures	Case-WCE control	Children	[82]
NLRP3[a]	Febrile Seizures	Case-feb control	Children	[97]
ICAM-1	Generalized Seizures	Case-control	Teens, adults	[13]
MCP-2	Generalized Seizures	Case-control	Teens, adults	[13]
Eotaxin (CCL11)	Refractory seizures	Case-control	Children	[98]
NFκB mRNA[a]	Focal seizures	Case-control	Adults	[58]
tRNA	Focal epilepsy	Case-control	Adults	[99]
BDNF	Epilepsy	Case-control	Adults	[96]
GMCSF	Drug-resistant epilepsy	Case-WCE control	Adults	[87]
NGF	Epilepsy	Case-control	Adults	[96]
NT3	Epilepsy	Case-control	Adults	[96]
Caspase 1	Generalized Seizures	Case-control	Adults	[77]
AACT	New onset epilepsy	Case-control	Children	[85]
homocysteine	Symptomatic epilepsy	Case-control	Adults	[72]
kallikrein	Temporal lobe epilepsy	Case-control	Adults	[74]
bradykinin	Temporal lobe epilepsy	Case-control	Adults	[74]
α-synuclein	Generalized seizures[b]	Case-control	Children	[100]
CD4 + CD38+[c]	drug-resistant TLE	Case-control	Adults	[79]
Adiponectin	Febrile seizures	Case-control	Children	[81]
Copeptin	Febrile seizures	Case-control	Children	[81]
GDF-15	Status with fever	Case-control	Children	[101]
Zfas1	Temporal lobe epilepsy	Case-control	Adults	[102]
P2X7R	Temporal lobe epilepsy	Case-control	Adults	[76]

Note: blood CD14+ mononuclear cells. AACT α1-antichymotrypsin. Zfas1 long non-coding RNA Zfas1. P2X7R P2X7 receptor.

Abbreviations: BDNF, Brain-Derived Neurotrophic Factor; GDF-15, Growth/differentiation factor-15 (macrophage inhibitory cytokine-1); GMCSF, Granulocyte-Macrophage Colony-Stimulating Factor; ICAM-1, intercellular adhesion molecule 1; IL, Interleukin; MCP-2, monocyte chemoattractant protein-2; mRNA, micro-ribonucleic acids; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells mRNA measured in peripheral; NGF, Nerve Growth Factor; NLRP3, nucleotide-binding domain, leucine-rich repeat family, pyrin-domain containing 3 inflammasome; NT3, Neurotrophic Factor-3; sTNFr2 soluble TNF-α, Tumor necrosis factor-receptor; TLE, Temporal Lobe Epilepsy; TLE-hs, Temporal Lobe Epilepsy with hippocampus sclerosis; TLR4, Toll-Like Receptor-4; TRAIL, Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand; tRNA, transfer RNA; WCE, well-controlled epilepsy.

[a]measured in peripheral blood mononuclear cells and not in serum or plasma.

[b]and an acquired demyelinating disorder.

[c]T and B regulatory cells.

can play a prominent role in regulating the immune system.[121,126,127] In vivo measurement capabilities are not yet available.

Transfer RNAs (tRNAs) constitute another group of candidates.[128,129] tRNAs function as adaptor molecules that help ribosomes decode messenger RNA (mRNA), transfer amino acids, and synthesize proteins,[130] and are therefore capable of influencing inflammatory processes. Pre-seizure plasma samples obtained from patients with focal epilepsy had higher levels of three tRNA fragments than did plasma

from healthy controls.[99] A point-of-care electrochemical system that measures three specific tRNA fragments is likely to be available to patients and their families very soon.[131]

6 | MEASUREMENT OF INFLAMMATION—HOW TO MEASURE IN VIVO?

To identify changes in seizure propensity as soon as they happen requires continuous surveillance. The surveillance we consider most appropriate for the most rapid identification of a change in seizure propensity is an EEG.[132,133] Integrating EEG and inflammation signals has the potential to enhance progress in working out the best signals for initiating prophylaxis.

Forecasting for less urgent intervention might not need to rely on electrophysiologic indicators. Surveillance for this task might do as well, or potentially better, relying on frequent assessments of a circulating indicator of inflammation. The closest analogy of the ideal we envision is the continuous measurement of blood glucose by a sensor attached to an insulin pump worn by some people who have relatively unstable diabetes mellitus.[134] By adjusting drug release in response to a biosignal, such closed-loop delivery strategies are designed to approximate homeostasis.[16–18]

Although frequent intermittent static assessments ("snapshots") might be adequate, they are less desirable than continuous assessments ("video"), which can identify fluctuations over time from a given baseline, and also identify periodic patterns.[135] The best candidate for this task remains to be determined.

Proof of concept that systemic inflammation is associated with seizure propensity comes from literature reviews[6–15] and Tables 1-3, which were prepared to provide more recently published support for inflammation in peripheral blood accompanying or soon following seizures.

Proof of concept that "prodromal biomarkers" … [might] be used to predict seizure risk comes from a report that concentrations of a marker of systemic inflammation (e.g., tRNA fragments) are higher before a seizure than afterward.[99]

Proof of concept that seizures can be predicted based on rising concentrations of an inflammation biomarker is not yet available.

7 | TIMING

Almost all the reports documenting circulating indicators of inflammation in people with epilepsy provide measurements after a recent or remote seizure. Indeed, ongoing systemic inflammation (elevated CXCL8 [IL-8]

concentrations) has been documented in adults a week after the last overt seizure,[75] and even months later.[92]

Levels of tRNA fragments were higher in pre-seizure plasma than in plasma collected soon after the seizure.[99] This is the only evidence that suggests inflammation predates seizure onset in humans. But even this would not be enough. Documentation is needed that levels of inflammation indicators increase prior to seizure onset.

Missing are reports of increasing concentrations of an inflammation indicator preceding a seizure.[121] Without this type of information everything presented here is rather indirect support for the putative benefits of a closed-loop system. Consequently, studies documenting increasing concentrations of a biomarker of inflammation is essential.

8 | HOW BEST TO INTERVENE

8.1 | Closed-loop systems

8.1.1 | The sensor

The first closed-loop system for seizures we know of delivered an anti-seizure medication in response to EEG discharges.[179] The closed-loop system we envision will work best if measurements of inflammation indicators are made continuously in vivo.

Although cytokines and other proteins are now measured ex vivo as part of a panel,[13,180,181] potentially wearable nanosensors offer the promise of continuous measurement in vivo.[182,183] The availability of fluorescence sandwich immunoassays for **continuous** measurements/detection of cytokines and other proteins in the blood[184] adds to the hope of being able to continuously measure what conveys helpful information about seizure propensity.

Just as efforts are underway to create a bionic pancreas,[185] in which beta cells sense glucose levels, the hope is that implanted inflammation-sensitive cells that sense inflammation might be able to function as the ideal sensors and responsive interventions.

8.1.2 | Set points

The level of inflammation that best triggers prophylaxis probably needs to be determined for each patient individually. Some propose variable setpoints, at least initially.[186]

The information collected by a sensor provides current data, but does not provide any information about the occurrence of a subsequent event. The closed-loop system we consider most appropriate also needs to have the capability of taking the sensor-collected data and anticipating a delayed future event.

TABLE 3 Potential anti-inflammation therapies intended to reduce seizure occurrence reported since a 2016 review[7]

Focus	Drug	Disorder	Recipients	Reference
Human				
IL-1	Anakinra	NORSE, FIRES	Children	[136–144]
		Rasmussen's	Children	[145]
	Rilonacept	CAPS	Children	[34]
	Canakinumab	CAPS	Children	[35, 36]
IL-6	Tocilizumab	FIRES	Children	[146–154]
IL-6, CRP	Statins	Post-stroke szs	Adults	[155–159]
IL-6, IL-2, CRP	VPA + LEV	Epilepsy	Children	[160]
TNF-α	Adalimumab	Rasmussen's	Children	[161]
HMGB1	Melatonin	Epilepsy	Adults (+rodents)	[162]
α-4 integrin	Natalizumab	Drug-resistant	Adults	[163]
NMDAR antibody	Rituximab	NMDARE	Children + adults	[164, 165]
COX-2	Aspirin	Sturge-Weber	Children	[166–171]
		Focal seizures	Adults	[172]
Pre-clinical				
microRNA	ASOs	Drug-resistant	Rats + mice	[173]
HMGB1	mAb	Epilepsy	Rats + mice	[174]
PGE2	PGE2 RA	Status epilepticus	Rats + mice	[171]
IL-1β and IL-6	Lacosamide	LPS + pilocarpine	Mice	[175]
IL-1β and IL-6	serotonin	PTZ-induced	Rats	[176]
	PEA	Multiple models	Mice and rats	[177]
	Minocycline	Multiple models	Mice and rats	[178]

Abbreviations: ASOs, Anti-Sense Oligonucleotides (antagomirs); CAPS, Cryopyrin-Associated Periodic Syndrome; CD20, Cluster of differentiation 20; FIRES, Febrile Infection-Related Epilepsy Syndrome; LEV, levetiracetam; mAb, monoclonal antibody; NMDAR, N-methyl-d-aspartate receptor; NMDARE, N-methyl-d-aspartate receptor (NMDAR) antibody encephalitis; NORSE, New Onset Refractory Status Epilepticus; PEA, palmitoylethanolamide; PGE2 RA, Prostaglandin EP2 Receptor Antagonist; PTZpentylenetetrazole; VPA, valproate.

Most attempts to predict seizure occurrence utilize information extracted from electroencephalograms.[187] We are not aware of any report of efforts to predict seizure occurrence based on the concentration of any blood component. Consequently, the most appropriate model for doing so would seem to come from the literature about predicting sustained hypoglycemia based on blood glucose levels collected continuously by an in situ sensor.[188,189] In essence, machine-learning algorithms would determine the magnitude or slope of concentration changes of the inflammation biomarker that best predicts/anticipates the next seizure.[190]

9 | CANDIDATES FOR DELIVERY

9.1 | Broad spectrum

Anti-inflammatory treatments are applied in clinical practice, and albeit the working mechanism may not be solely tied to anti-inflammatory properties, reduction of inflammation may play a role. This includes steroid application in epilepsy syndromes such as infantile spasms, Landau-Kleffner Syndrome, Continuous Spikes and Slow Waves during Sleep, or Lennox Gastaut syndrome,[191] potential anti-inflammatory properties of vigabatrin[192] and metformin[64] through their effects on the mTOR pathway, anti-inflammatory properties of the ketogenic diet,[193] or use of (broad-spectrum) immunomodulatory drugs (as outlined in Table 3).[194]

9.2 | Specific anti-inflammatory drugs

Recent reviews and Table 3 document inflammation pathways activated in drug-resistant epilepsy,[11] and provide proof of concept that anti-inflammatory agents and strategies can reduce seizure occurrence.[48]

The more specific, the more personalized the approach,[195,196] the closer the realization of "precision medicine."[197] In the spirit of "one size does not fit all," we offer as candidates the anti-inflammatory agents first those listed in Table 2, but consider other options that have yet

to be tested. This personalized approach may also entail application of anti-seizure or anti-inflammatory interventions only when needed. Some might appear to target specific steps in the inflammatory process. However, inflammatory cascades are complex incorporating interconnected sets of networks.[50,198] Consequently, interfering in the function of just one component can sometimes appreciably reduce the extent and severity of inflammation.[199]

More than a decade ago, antibodies that neutralize a single cytokine were known to have broad anti-inflammatory effects.[199,200] More recently, small-molecule kinase inhibitors were shown to have broad anti-inflammatory effects.[201] With the multiple effects of inflammasomes,[202,203] anti-inflammasome drugs have the potential to affect several targets,[63] each with some potential to initiate an inflammatory cascade.[49,204] Thus, single-target drugs, or those expected to have limited effects sometimes/often achieve their broad potential by limiting inflammation in multiple ways.[205]

Because some/many of the inflammation-related biomarkers of seizure risk are not specific, and because some/many children with epilepsy might not have appreciable change in any of them as seizure risk rises, our vision might have limited application.

9.3 | The future

A recently proposed roadmap for biomarker research has five phases.[206] Tables 1 and 2 and related text document some of the progress made in four of the phases in identifying and quantifying circulating biomarkers of seizure diathesis. These four phases include preclinical exploratory studies (phase 1), initial clinical assessments (phase 2), retrospective studies of data in repositories (phase 3), and prospective studies to determine diagnostic accuracy (phase 4). The main component of phase five is assessing the reduction in mortality, morbidity, and disability associated with biomarker testing and the therapeutic intervention. Table 3 offers guidance about potential therapeutic interventions. However, we are not aware of any study that has assessed to what extent an anti-inflammation intervention in response to an elevated blood concentration of a biomarker of inflammation before a seizure occurs reduces the probability of a seizure.

10 | CONCLUSION

We have gathered support for our vision that people with epilepsy will be able to benefit from a wearable closed-loop system similar to those that benefit people with "difficult-to-control" epilepsy. This has included documentation

that epilepsy is associated with inflammation, that both specific and broad-spectrum anti-inflammatory therapies have reduced seizure occurrence, that a wearable closed-loop system might be capable of identifying increasing concentrations of inflammation indicators in the blood or other sources, and that machine learning programs have the potential to identify the slope of these increasing levels of inflammation proteins most predictable of an impending seizure.

Yet, despite all this support, what is missing is documentation that circulating concentrations of an inflammation biomarker increase shortly before an impending seizure. Until indwelling inflammation biomarker sensors are available, this documentation will most likely come from animals whose blood is sampled sequentially.

AUTHOR CONTRIBUTIONS
Alan Leviton prepared the first draft; Coral Stredny, Alexander Rotenberg, and Tobias Loddenkemper then provided multiple edits iteratively. All authors read and approved the final draft.

CONFLICT OF INTEREST
The authors declare that they wrote this essay in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Coral Stredny is on the advisory board of the NORSE Institute and receives active research support from the Pediatric Epilepsy Research Foundation. Alexander Rotenberg is co-founder of Prevep Inc. and Neuromotion Labs, is on the advisory boards of Gamify and Neurorex, and has active research support or consulting agreements with Biomarin, CRE Medical, Encoded, Loulou Foundation, National Football League, Neuroelectrics, Roche and Praxis. Tobias Loddenkemper discloses pending and approved patents and intellectual property related to epilepsy management, seizure detection and prediction, device loans from Empatica, and receives active research support from Upsher-Smith.

ETHICS STATEMENT
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Nasseri M, Pal Attia T, Joseph B, Gregg NM, Nurse ES, Viana PF, et al. Ambulatory seizure forecasting with a wrist-worn device using long-short term memory deep learning. Scientific reports. 2021;9(11):21935.

2. Ryvlin P, Rheims S, Hirsch LJ, Sokolov A, Jehi L. Neuromodulation in epilepsy: state-of-the-art approved therapies. The Lancet Neurology. 2021;20(12):1038–47.

3. Brinkmann BH, Karoly PJ, Nurse ES, Dumanis SB, Nasseri M, Viana PF, et al. Seizure diaries and forecasting with wearables: epilepsy monitoring outside the clinic. Front. neurol. 2021;12:690404 Review.

4. Meisel C, El Atrache R, Jackson M, Schubach S, Ufongene C, Loddenkemper T. Machine learning from wristband sensor data for wearable, noninvasive seizure forecasting. Epilepsia. 2020;61:2653–66.

5. Zhang J, Xu J, Lim J, Nolan JK, Lee H, Lee CH. Wearable glucose monitoring and implantable drug delivery systems for diabetes management. Adv Healthc Mater. 2021;10(17):e2100194.

6. Terrone G, Balosso S, Pauletti A, Ravizza T, Vezzani A. Inflammation and reactive oxygen species as disease modifiers in epilepsy. Neuropharmacology. 2020;167:107742.

7. de Vries EE, van den Munckhof B, Braun KP, van Royen-Kerkhof A, de Jager W, Jansen FE. Inflammatory mediators in human epilepsy: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2016;63:177–90.

8. van Vliet EA, Aronica E, Vezzani A, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy. Nat Rev Neurol. 2018;44:91–111.

9. Bosco DB, Tian DS, Wu LJ. Neuroimmune interaction in seizures and epilepsy: focusing on monocyte infiltration. FEBS J. 2020;287:4822–37. Review.

10. Sanz P, Garcia-Gimeno MA. Reactive glia inflammatory signaling pathways and Epilepsy. Int J Mol Sci. 2020;21(11):4096.

11. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nature reviews Neurology. 2019;15:459–72.

12. Kamali AN, Zian Z, Bautista JM, Hamedifar H, Hossein-Khannazer N, Hosseinzadeh R, et al. The potential role of pro-inflammatory and anti-inflammatory cytokines in epilepsy pathogenesis. Endocr Metab Immune Disord Drug Targets. 2021;21(10):1760–74.

13. Gledhill JM, Brand EJ, Pollard JR, St Clair RD, Wallach TM, Crino PB. Association of Epileptic and Nonepileptic Seizures and changes in circulating plasma proteins linked to neuroinflammation. Neurology. 2021;9(96):e1443–52.

14. Granata T, Fusco L, Matricardi S, Tozzo A, Janigro D, Nabbout R. Inflammation in pediatric epilepsies: Update on clinical features and treatment options. Epilepsy behav. 2021;15:107959.

15. Tan TH, Perucca P, O'Brien TJ, Kwan P, Monif M. Inflammation, ictogenesis, and epileptogenesis: An exploration through human disease. Epilepsia. 2021;62:303–24.

16. Sharma R, Singh D, Gaur P, Joshi D. Intelligent automated drug administration and therapy: future of healthcare. Drug Deliv Transl Res. 2021;11(5):1878–902.

17. Yu J, Zhang Y, Yan J, Kahkoska AR, Gu Z. Advances in bioresponsive closed-loop drug delivery systems. Int J Pharm. 2018;544(2):350–7.

18. Aicua-Rapun I, Andre P, Novy J. Closed-loop neuropharmacology for Epilepsy: distant dream or future reality? Curr Neuropharmacol. 2019;17:447–58.

19. Proix T, Truccolo W, Leguia MG, Tcheng TK, King-Stephens D, Rao VR, et al. Forecasting seizure risk in adults with focal epilepsy: a development and validation study. Lancet Neurol. 2021;20(2):127–35.

20. Payne DE, Dell KL, Karoly PJ, Kremen V, Gerla V, Kuhlmann L, et al. Identifying seizure risk factors: A comparison of sleep, weather, and temporal features using a Bayesian forecast. Epilepsia. 2021;62(2):371–82.

21. Chiang S, Moss R, Black AP, Jackson M, Moss C, Bidwell J, et al. Evaluation and recommendations for effective data visualization for seizure forecasting algorithms. JAMIA open. 2021;4(1):ooab009.

22. Karoly PJ, Cook MJ, Maturana M, Nurse ES, Payne D, Brinkmann BH, et al. Forecasting cycles of seizure likelihood. Epilepsia. 2020;61(4):776–86.

23. Goldenholz DM, Goldenholz SR, Romero J, Moss R, Sun H, Westover B. Development and validation of forecasting next reported seizure using e-diaries. Ann Neurol. 2020;88(3):588–95.

24. Karoly PJ, Eden D, Nurse ES, Cook MJ, Taylor J, Dumanis S, et al. Cycles of self-reported seizure likelihood correspond to yield of diagnostic epilepsy monitoring. Epilepsia. 2021;62(2):416–25.

25. Stirling RE, Cook MJ, Grayden DB, Karoly PJ. Seizure forecasting and cyclic control of seizures. Epilepsia. 2021;62(S1):S2–S14.

26. Cousyn L, Navarro V, Chavez M. Preictal state detection using prodromal symptoms: A machine learning approach. Epilepsia. 2021;62:e42–7.

27. Stirling RE, Maturana MI, Karoly PJ, Nurse ES, McCutcheon K, Grayden DB, et al. Seizure forecasting using a novel subscalp ultra-long term EEG monitoring system. Front Neurol. 2021;12:713794.

28. Mujahid O, Contreras I, Vehi J. Machine learning techniques for hypoglycemia prediction: trends and challenges. Sensors (Basel). 2021;21(2):546.

29. Ali I, Houck K. Neuromodulation in pediatric epilepsy. Neurol Clin. 2021;39(3):797–810.

30. Rincon N, Barr D, Velez-Ruiz N. Neuromodulation in drug resistant epilepsy. Aging Dis. 2021;12(4):1070–80.

31. Aguilar-Castillo MJ, Cabezudo-Garcia P, Ciano-Petersen NL, Garcia-Martin G, Marin-Gracia M, Estivill-Torrus G, et al. Immune mechanism of epileptogenesis and related therapeutic strategies. Biomedicines. 2022;10(3):716.

32. Costagliola G, Depietri G, Michev A, Riva A, Foiadelli T, Savasta S, et al. Targeting inflammatory mediators in epilepsy: a systematic review of its molecular basis and clinical applications. Front Neurol. 2022;13:741244.

33. Sanz P, Serratosa JM. Neuroinflammation and progressive myoclonus epilepsies: from basic science to therapeutic opportunities. Expert Rev Mol Med. 2020;22:e4.

34. Giat E, Lidar M. Cryopyrin-associated periodic syndrome. Isr Med Assoc J. 2014;16:659–61.

35. Paim-Marques LB, Cavalcante A, Castro C, Muskardin TLW, de Oliveira JB, Niewold TB, et al. Novel mutation in the NRLP3 manifesting as an intermediate phenotype of cryopyrinopathies. Rheumatol Int. 2021;41:19–225.

36. DeSena AD, Do T, Schulert GS. Systemic autoinflammation with intractable epilepsy managed with interleukin-1 blockade. J Neuroinflammation. 2018;15(1):38.

37. Yeshokumar AK, Pardo CA. Autoimmune epilepsies. Semin Pediatr Neurol. 2017;24(3):161–7.

38. Therajaran P, Hamilton JA, O'Brien TJ, Jones NC, Ali I. Microglial polarization in posttraumatic epilepsy: Potential mechanism and treatment opportunity. Epilepsia. 2020;61(2):203–15.

39. Eastman CL, D'Ambrosio R, Ganesh T. Modulating neuroinflammation and oxidative stress to prevent epilepsy and improve outcomes after traumatic brain injury. Neuropharmacology. 2020;172:107907.

40. Fu Y, Wu Z, Guo Z, Chen L, Ma Y, Wang Z, et al. Systems-level analysis identifies key regulators driving epileptogenesis in temporal lobe epilepsy. Genomics. 2020;112(2):1768–80.

41. Rawat C, Kushwaha S, Srivastava AK, Kukreti R. Peripheral blood gene expression signatures associated with epilepsy and its etiologic classification. Genomics. 2020;112(1):218–24.

42. Alam A, Thelin EP, Tajsic T, Khan DZ, Khellaf A, Patani R, et al. Cellular infiltration in traumatic brain injury. J Neuroinflammation. 2020;17(1):328.

43. Gilles FH, Averill DR Jr, Kerr CS. Neonatal endotoxin encephalopathy. Ann Neurol. 1977;2:49–56.

44. Gilles FH, Leviton A, Kerr CS. Endotoxin leucoencephalopathy in the telencephalon of the newborn kitten. J Neurol Sci. 1976;27:183–91.

45. Yamanaka G, Takata F, Kataoka Y, Kanou K, Morichi S, Dohgu S, et al. The neuroinflammatory role of pericytes in epilepsy. Biomedicines. 2021;9(7):759.

46. Matsumoto J, Dohgu S, Takata F, Machida T, Bolukbasi Hatip FF, Hatip-Al-Khatib I, et al. TNF-α-sensitive brain pericytes activate microglia by releasing IL-6 through cooperation between IkappaB-NFkappaB and JAK-STAT3 pathways. Brain Res. 2018;1692:34–44.

47. Librizzi L, Vila Verde D, Colciaghi F, Deleo F, Regondi MC, Costanza M, et al. Peripheral blood mononuclear cell activation sustains seizure activity. Epilepsia. 2021;62(7):1715–28.

48. Ravizza T, Vezzani A. Pharmacological targeting of brain inflammation in epilepsy: Therapeutic perspectives from experimental and clinical studies. Epilepsia open. 2018;3:133–42.

49. Ismael S, Ahmed HA, Adris T, Parveen K, Thakor P, Ishrat T. The NLRP3 inflammasome: a potential therapeutic target for traumatic brain injury. Neural Regen Res. 2021;16(1):49–57.

50. Cornut M, Bourdonnay E, Henry T. Transcriptional Regulation of Inflammasomes. Int J Mol Sci. 2020;21(21):8087.

51. O'Brien WT, Pham L, Symons GF, Monif M, Shultz SR, McDonald SJ. The NLRP3 inflammasome in traumatic brain injury: potential as a biomarker and therapeutic target. J Neuroinflammation. 2020;17:104.

52. Shen K, Jiang W, Zhang C, Cai L, Wang Q, Yu H, et al. Molecular mechanism of a specific NLRP3 inhibitor to alleviate seizure severity induced by pentylenetetrazole. Curr Mol Pharmacol. 2020;14(4):579–86.

53. Liu R, Wu S, Guo C, Hu Z, Peng J, Guo K, et al. Ibuprofen exerts antiepileptic and neuroprotective effects in the rat model of pentylenetetrazol-induced Epilepsy via the COX-2/NLRP3/IL-18 pathway. Neurochem Res. 2020;45:2516–26.

54. He Q, Jiang L, Man S, Wu L, Hu Y, Chen W. Curcumin reduces neuronal loss and inhibits the NLRP3 inflammasome activation in an epileptic rat model. Curr Neurovasc Res. 2018;15:186–92.

55. Meng XF, Tan L, Tan MS, Jiang T, Tan CC, Li MM, et al. Inhibition of the NLRP3 inflammasome provides neuroprotection in rats following amygdala kindling-induced status epilepticus. J Neuroinflammation. 2014;17(11):212.

56. Mohseni-Moghaddam P, Sadr SS, Roghani M, Arabzadeh S, Khamse S, Zamani E, et al. Huperzine a ameliorates cognitive dysfunction and neuroinflammation in kainic acid-induced epileptic rats by antioxidant activity and NLRP3/caspase-1 pathway inhibition. Clin Exp Pharmacol Physiol. 2019;46:360–72.

57. Tan CC, Zhang JG, Tan MS, Chen H, Meng DW, Jiang T, et al. NLRP1 inflammasome is activated in patients with medial temporal lobe epilepsy and contributes to neuronal pyroptosis in amygdala kindling-induced rat model. J Neuroinflammation. 2015;12:18.

58. Ulusoy C, Vanli-Yavuz EN, Sanli E, Timirci-Kahraman O, Yilmaz V, Bebek N, et al. Peripheral blood expression levels of inflammasome complex components in two different focal epilepsy syndromes. J Neuroimmunol. 2020;347:577343.

59. de Brito C, Toscano E, Leandro Marciano Vieira E, Boni Rocha Dias B, Vidigal Caliari M, Paula Goncalves A, et al. NLRP3 and NLRP1 inflammasomes are up-regulated in patients with mesial temporal lobe epilepsy and may contribute to overexpression of caspase-1 and IL-beta in sclerotic hippocampi. Brain Res. 2021;1752:147230.

60. Jang J, Park S, Jin Hur H, Cho HJ, Hwang I, Pyo Kang Y, et al. 25-hydroxycholesterol contributes to cerebral inflammation of X-linked adrenoleukodystrophy through activation of the NLRP3 inflammasome. Nature communications. 2016;7:13129.

61. Wang H, Xu P, Liao D, Dang R, He X, Guo Y, et al. Association between NLPR1, NLPR3, and P2X7R Gene Polymorphisms with Partial Seizures. Biomed Res Int. 2017;2017:9547902.

62. Mohseni-Moghaddam P, Roghani M, Khaleghzadeh-Ahangar H, Sadr SS, Sala C. A literature overview on epilepsy and inflammasome activation. Brain res bull. 2021;172:229–35.

63. Lunemann JD, Malhotra S, Shinohara ML, Montalban X, Comabella M. Targeting inflammasomes to treat neurological diseases. Ann Neurol. 2021;90(2):177–88.

64. Bojja SL, Medhi B, Anand S, Bhatia A, Joshi R, Minz RW. Metformin ameliorates the status epilepticus- induced hippocampal pathology through possible mTOR modulation. Inflammopharmacology. 2021;29(1):137–51.

65. Rojas A, Amaradhi R, Banik A, Jiang C, Abreu-Melon J, Wang S, et al. A novel second-generation EP2 receptor antagonist reduces neuroinflammation and gliosis after status epilepticus in rats. Neurotherapeutics. 2021;18(2):1207–25.

66. Varvel NH, Espinosa-Garcia C, Hunter-Chang S, Chen D, Biegel A, Hsieh A, et al. Peripheral myeloid cell EP2 activation contributes to the deleterious consequences of status epilepticus. J Neurosci. 2021;41(5):1105–17.

67. Lee DS, Kim JE. Protein disulfide isomerase-mediated S-nitrosylation facilitates surface expression of P2X7 receptor following status epilepticus. J Neuroinflammation. 2021;18(1):14.

68. Kyriatzis G, Bernard A, Bole A, Pflieger G, Chalas P, Masse M, et al. Neurotensin receptor 2 is induced in astrocytes and brain endothelial cells in relation to neuroinflammation following pilocarpine-induced seizures in rats. Glia. 2021;69(11):2618–43.

69. Becker AJ. Review: Animal models of acquired epilepsy: insights into mechanisms of human epileptogenesis. Neuropathol Appl Neurobiol. 2018;44(1):112–29.

70. Janisset N, Romariz SAA, Hashiguchi D, Quintella ML, Gimenes C, Yokoyama T, et al. Partial protective effects of cannabidiol against PTZ-induced acute seizures in female rats during the proestrus-estrus transition. Epilepsy Behav. 2022;129:108615.

71. Zhong R, Chen Q, Li M, Zhang X, Lin W. Elevated blood C-reactive protein levels in patients with Epilepsy: A Systematic Review and Meta-Analysis. Front. Neurol. 2019;10:974.

72. Tao H, Gong Y, Yu Q, Zhou H, Liu Y. Elevated serum matrix metalloproteinase-9, interleukin-6, hypersensitive C-reactive protein, and homocysteine levels in patients with epilepsy. J Interferon Cytokine Res. 2020;40:152–8.

73. Meguid NA, Samir H, Bjorklund G, Anwar M, Hashish A, Koura F, et al. Altered S100 calcium-binding protein B and matrix metallopeptidase 9 as biomarkers of mesial temporal lobe Epilepsy with hippocampus sclerosis. J Mol Neurosci. 2018;66:482–91.

74. Simoes PSR, Zanelatto AO, Assis MC, Varella PPV, Yacubian EM, Carrete H, et al. Plasma kallikrein-kinin system contributes to peripheral inflammation in temporal lobe epilepsy. J Neurochem. 2019;150:296–311.

75. Sangeetha A, Bobby Z, Wadwekar V, Nisha Y. Atherogenic risk factors among young Indian adults with Epilepsy on Treatment with phenytoin: need for novel therapeutic strategies. Neurol India. 2021;69:957–61.

76. Conte G, Menendez-Mendez A, Bauer S, El-Naggar H, Alves M, Nicke A, et al. Circulating P2X7 receptor signaling components as diagnostic biomarkers for temporal lobe Epilepsy. Cells. 2021;9:2444.

77. Kegler A, Caprara ALF, Pascotini ET, Arend J, Gabbi P, Duarte M, et al. Apoptotic markers are increased in epilepsy patients: a relation with manganese superoxide dismutase Ala16Val polymorphism and seizure type through IL-1β and IL-6 pathways. Bio Med Res Int. 2020;2020:6250429.

78. Peltola J, Laaksonen J, Haapala AM, Hurme M, Rainesalo S, Keranen T. Indicators of inflammation after recent tonic-clonic epileptic seizures correlate with plasma interleukin-6 levels. Seizure. 2002;11:44–6.

79. Toledo A, Orozco-Suarez S, Rosetti M, Maldonado L, Bautista SI, Flores X, et al. Temporal lobe epilepsy: Evaluation of central and systemic immune-inflammatory features associated with drug resistance. Seizure. 2021;91:447–55.

80. Gao F, Gao Y, Zhang SJ, Zhe X, Meng FL, Qian H, et al. Alteration of plasma cytokines in patients with active epilepsy. Acta Neurol Scand. 2017;135:663–9.

81. Chen JR, Jin MF, Tang L, Liu YY, Ni H. Acute Phase Serum Leptin, Adiponectin, Interleukin-6, and Visfatin are altered in Chinese children with febrile seizures: a cross-sectional study. Front Endocrinol. 2020;11:531.

82. Kamasak T, Dilber B, Yaman SO, Durgut BD, Kurt T, Coban E, et al. HMGB-1, TLR4, IL-1R1, TNF-alpha, and IL-1beta: novel epilepsy markers? Epileptic Disord. 2020;22(1):183–93.

83. Kan M, Song L, Zhang X, Zhang J, Fang P. Circulating high mobility group box-1 and toll-like receptor 4 expressions increase the risk and severity of epilepsy. Braz J Med Biol Res. 2019;52:e7374.

84. Wu Y, Zhang Y, Zhu S, Tian C. MiRNA-29a serves as a promising diagnostic biomarker in children with temporal lobe epilepsy and regulates seizure-induced cell death and inflammation in hippocampal neurons. Epileptic Disord. 2021;23(6):823–32.

85. Zhu M, Chen J, Guo H, Ding L, Zhang Y, Xu Y. High mobility group protein B1 (HMGB1) and interleukin-1beta as prognostic biomarkers of Epilepsy in children. J Child Neurol. 2018;33:909–17.

86. Kegler A, Pascotini ET, Caprara ALF, Arend J, Gabbi P, Duarte MM, et al. Relationship between seizure type, metabolic profile, and inflammatory markers in blood samples of patients with epilepsy. Epileptic Disord. 2021;23(1):74–84.

87. Ouedraogo O, Rebillard RM, Jamann H, Mamane VH, Clenet ML, Daigneault A, et al. Increased frequency of proinflammatory CD4 T cells and pathological levels of serum neurofilament light chain in adult drug-resistant epilepsy. Epilepsia. 2021;62:176–89.

88. Saengow VE, Chiangjong W, Khongkhatithum C, Changtong C, Chokchaichamnankit D, Weeraphan C, et al. Proteomic analysis reveals plasma haptoglobin, interferon-gamma, and interleukin-1beta as potential biomarkers of pediatric refractory epilepsy. Brain Dev. 2021;43:431–9.

89. Raoof R, Bauer S, el Naggar H, Connolly NMC, Brennan GP, Brindley E, et al. Dual-center, dual-platform microRNA profiling identifies potential plasma biomarkers of adult temporal lobe epilepsy. EBioMedicine. 2018;38:127–41.

90. Asadi-Pooya AA, Tajbakhsh A, Savardashtaki A. MicroRNAs in temporal lobe epilepsy: a systematic review. Neurol Sci. 2021;42:571–8.

91. Evers KS, Hugli M, Fouzas S, Kasser S, Pohl C, Stoecklin B, et al. Serum neurofilament levels in children with febrile seizures and in controls. Front Neurosci. 2020;14:579958.

92. Mazdeh M, Omrani MD, Sayad A, Komaki A, Arsang-Jang S, Taheri M, et al. Expression analysis of cytokine coding genes in epileptic patients. Cytokine. 2018;110:284–7.

93. Basnyat P, Pesu M, Soderqvist M, Gronholm A, Liimatainen S, Peltola M, et al. Chronically reduced IL-10 plasma levels are associated with hippocampal sclerosis in temporal lobe epilepsy patients. BMC Neurol. 2020;12(20):241.

94. Mochol M, Tauboll E, Aukrust P, Ueland T, Andreassen OA, Svalheim S. Interleukin 18 (IL-18) and its binding protein (IL-18BP) are increased in patients with epilepsy suggesting low-grade systemic inflammation. Seizure. 2020;80:221–5.

95. Ethemoglu O, Calik M, Koyuncu I, Ethemoglu KB, Gocmen A, Guzelcicek A, et al. Interleukin-33 and oxidative stress in epilepsy patients. Epilepsy Res. 2021;17(176):106738.

96. Alvim MKM, Morita-Sherman ME, Yasuda CL, Rocha NP, Vieira EL, Pimentel-Silva LR, et al. Inflammatory and neurotrophic factor plasma levels are related to epilepsy independently of etiology. Epilepsia. 2021;10:2385–94.

97. Liu Z, Xian H, Ye X, Chen J, Ma Y, Huang W. Increased levels of NLRP3 in children with febrile seizures. Brain Dev. 2020;42:336–41.

98. Bakhtadze S, Geladze N, Khachapuridze N. Inflammation in childhood epilepsy syndromes. Georgian Medical News. 2021;312:88–92.

99. Hogg MC, Raoof R, El Naggar H, Monsefi N, Delanty N, O'Brien DF, et al. Elevation in plasma tRNA fragments precede seizures in human epilepsy. J Clin Invest. 2019;129:2946–51.

100. Choi J, Kim SY, Kim H, Lim BC, Hwang H, Chae JH, et al. Serum alpha-synuclein and IL-1beta are increased and correlated with measures of disease severity in children with epilepsy: potential prognostic biomarkers? BMC Neurol. 2020;9(20):85.

101. Yamaguchi H, Nishiyama M, Tomioka K, Hongo H, Tokumoto S, Ishida Y, et al. Growth and differentiation factor-15 as a potential prognostic biomarker for status-epilepticus-associated-with-fever: a pilot study. Brain Dev. 2021;44(3):210–20.

102. He C, Su C, Zhang W, Zhou Q, Shen X, Yang J, et al. Modulatory Potential of LncRNA Zfas1 for inflammation and neuronal apoptosis in temporal lobe epilepsy. Yonsei Med J. 2021;62:215–23.

103. Tegeler C, O'Sullivan JL, Bucholtz N, Goldeck D, Pawelec G, Steinhagen-Thiessen E, et al. The inflammatory markers CRP, IL-6, and IL-10 are associated with cognitive function-data from the Berlin aging study II. Neurobiol Aging. 2016;38:112–7.

104. Giudici KV, de Souto BP, Guerville F, Beard J, Araujo de Carvalho I, Andrieu S, et al. Associations of C-reactive protein and homocysteine concentrations with the impairment of intrinsic capacity domains over a 5-year follow-up among community-dwelling older adults at risk of cognitive decline (MAPT Study). Exp Gerontol. 2019;127:110716.

105. Arce Renteria M, Gillett SR, McClure LA, Wadley VG, Glasser SP, Howard VJ, et al. C-reactive protein and risk of cognitive decline: the REGARDS study. PloS one. 2020;15:e0244612.

106. Sethwala AM, Goh I, Amerena JV. Combating inflammation in cardiovascular disease. Heart Lung Circ. 2021;30(2):197–206.

107. Markozannes G, Koutsioumpa C, Cividini S, Monori G, Tsilidis KK, Kretsavos N, et al. Global assessment of C-reactive protein and health-related outcomes: an umbrella review of evidence from observational studies and Mendelian randomization studies. Eur J Epidemiol. 2021;36:11–36.

108. Si S, Li J, Tewara MA, Xue F. Genetically determined chronic low-grade inflammation and hundreds of health outcomes in the UK Biobank and the FinnGen population: a phenome-wide Mendelian randomization study. Front Immunol. 2021;12:720876.

109. McFadyen JD, Zeller J, Potempa LA, Pietersz GA, Eisenhardt SU, Peter K. C-reactive protein and its structural isoforms: an evolutionary conserved marker and central player in inflammatory diseases and beyond. Subcell Biochem. 2020;94:499–520.

110. Zeinolabediny Y, Kumar S, Slevin M. Monomeric C-reactive protein - a feature of inflammatory disease associated with cardiovascular pathophysiological complications? In vivo. 2021;35:693–7.

111. Nass RD, Wagner M, Surges R, Holdenrieder S. Time courses of HMGB1 and other inflammatory markers after generalized convulsive seizures. Epilepsy Res. 2020;162:106301.

112. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of sepsis: time for a reappraisal. Crit Care. 2020;24:287.

113. Murakami H, Naraba H, Gondo T, Mochizuki M, Nakano H, Takahashi Y, et al. Diagnostic value of serum procalcitonin in patients with convulsion in emergency department, an observational study. Antibiotics (Basel). 2020;9(10):683.

114. Park JH, Kim DH, Jang HR, Kim MJ, Jung SH, Lee JE, et al. Clinical relevance of procalcitonin and C-reactive protein as infection markers in renal impairment: a cross-sectional study. Crit Care. 2014;18(6):640.

115. Simon L, Saint-Louis P, Amre DK, Lacroix J, Gauvin F. Procalcitonin and C-reactive protein as markers of bacterial infection in critically ill children at onset of systemic inflammatory response syndrome. Pediatr Crit Care Med. 2008;9(4):407–13.

116. Trachtman R, Murray E, Wang CM, Szymonifka J, Toussi SS, Walters H, et al. Procalcitonin differs in children with infection and children with disease flares in juvenile idiopathic arthritis. J Clin Rheumatol. 2021;27(3):87–91.

117. Cantarin-Extremera V, Castano-De La Mota C, Alvarez-Coca J, Rojas MR, Gutierrez-Solana LG, Garcia Penas JJ, et al. Procalcitonin, a high acute phase reactant in antiepileptic hypersentivity syndrome in pediatric age. Eur J Paediatr Neurol. 2012;16:200–2.

118. Peng F, Chang W, Xie JF, Sun Q, Qiu HB, Yang Y. Ineffectiveness of procalcitonin-guided antibiotic therapy in severely critically ill patients: A meta-analysis. Int J Infect Dis. 2019;85:158–66.

119. Kyriazopoulou E, Poulakou G, Giamarellos-Bourboulis EJ. Biomarkers in sepsis: can they help improve patient outcome? Curr Opin Infect Dis. 2021;34(2):126–34.

120. Bohosova J, Vajcner J, Jabandziev P, Oslejskova H, Slaby O, Aulicka S. MicroRNAs in the development of resistance to antiseizure drugs and their potential as biomarkers in pharmacoresistant epilepsy. Epilepsia. 2021;62:2573–88.

121. Whitlock JH, Soelter TM, Williams AS, Hardigan AA, Lasseigne BN. Liquid biopsies in epilepsy: biomarkers for etiology, diagnosis, prognosis, and therapeutics. Hum Cell. 2021;35(1):15–22.

122. Wang Y, Chen Y, Hua Y, Xu L, Zhu M, Zhao C, et al. Circulating microRNAs from plasma small extracellular vesicles as potential diagnostic biomarkers in pediatric epilepsy and drug-resistant epilepsy. Front Mol Neurosci. 2022;15:823802.

123. Lukawski K, Czuczwar SJ. Emerging therapeutic targets for epilepsy: preclinical insights. Expert Opin Ther Targets. 2022;26(3):193–206.

124. Qi L, Yan Y, Chen B, Cao J, Liang G, Xu P, et al. Research progress of circRNA as a biomarker of sepsis: a narrative review. Ann Transl Med. 2021;9:720.

125. Gomes-Duarte A, Bauer S, Veno MT, Norwood BA, Henshall DC, Kjems J, et al. Enrichment of circular RNA expression deregulation at the transition to recurrent spontaneous seizures in experimental temporal lobe epilepsy. Front Genet. 2021;12:627907.

126. Hong X, Li S, Wang J, Zhao Z, Feng Z. Circular RNA circFADS2 is overexpressed in sepsis and suppresses LPS-induced lung cell apoptosis by inhibiting the maturation of miR-15a-5p. BMC Immunol. 2021;22(1):29.

127. Beltran-Garcia J, Osca-Verdegal R, Nacher-Sendra E, Pallardo FV, Garcia-Gimenez JL. Circular RNAs in sepsis: biogenesis, function, and clinical significance. Cells. 2020;9:1544.

128. Pawar K, Shigematsu M, Sharbati S, Kirino Y. Infection-induced 5′-half molecules of tRNAHisGUG activate toll-like receptor 7. PLoS Biol. 2020;18:e3000982.

129. Ivanov P. Emerging roles of tRNA-derived fragments in viral infections: the Case of respiratory syncytial virus. Mol Ther. 2015;23:1557–8.

130. Phizicky EM, Hopper AK. tRNA biology charges to the front. Genes Dev. 2010;24:1832–60.

131. McArdle H, Hogg MC, Bauer S, Rosenow F, Prehn JHM, Adamson K, et al. Quantification of tRNA fragments by electrochemical direct detection in small volume biofluid samples. Sci Rep. 2020;10:7516.

132. Alter AS, Dhamija R, McDonough TL, Shen S, McBrian DK, Mandel AM, et al. Ictal onset patterns of subdural intracranial electroencephalogram in children: how helpful for predicting epilepsy surgery outcome? Epilepsy Res. 2019;149:44–52.

133. Biondi A, Laiou P, Bruno E, Viana PF, Schreuder M, Hart W, et al. Remote and long-term self-monitoring of electroencephalographic and noninvasive measurable variables at home in patients with epilepsy (EEG@HOME): protocol for an observational study. JMIR Res Protoc. 2021;10:e25309.

134. Scholten K, Meng E. A review of implantable biosensors for closed-loop glucose control and other drug delivery applications. Int J Pharm. 2018;544:319–34.

135. Mirza KB, Golden CT, Nikolic K, Toumazou C. Closed-loop implantable therapeutic neuromodulation systems based on neurochemical monitoring. Front Neurosci. 2019;13:808.

136. Lai YC, Muscal E, Wells E, Shukla N, Eschbach K, Hyeong Lee K, et al. Anakinra usage in febrile infection related epilepsy syndrome: an international cohort. Ann Clin Transl Neurol. 2020;7:2467–74.

137. Kenney-Jung DL, Vezzani A, Kahoud RJ, LaFrance-Corey RG, Ho ML, Muskardin TW, et al. Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol. 2016;80:939–45.

138. Dilena R, Mauri E, Aronica E, Bernasconi P, Bana C, Cappelletti C, et al. Therapeutic effect of Anakinra in the relapsing chronic phase of febrile infection-related epilepsy syndrome. Epilepsia Open. 2019;4:344–50.

139. Jyonouchi H, Geng L. Resolution of EEG findings and clinical improvement in a patient with encephalopathy and ESES with a combination of immunomodulating agents other than corticosteroids: A case report. Epilepsy Behav Rep. 2020;14:100379.

140. Kern-Smith E, Chen DF, Koh S, Dutt M. The cat's out of the bag: a rare case of new-onset refractory status epilepticus (NORSE) due to Bartonella henselae. Seizure. 2020;81:241–3.

141. Yang JH, Nataraj S, Sattar S. Successful Treatment of pediatric FIRES with anakinra. Pediatr Neurol. 2021;114:60–1.

142. Sa M, Singh R, Pujar S, D'Arco F, Desai N, Eltze C, et al. Centromedian thalamic nuclei deep brain stimulation and Anakinra treatment for FIRES - Two different outcomes. Eur J Paediatr Neurol. 2019;23:749–54.

143. L'Erario M, Roperto RM, Rosati A. Sevoflurane as bridge therapy for plasma exchange and anakinra in febrile infection-related epilepsy syndrome. Epilepsia Open. 2021;6:788–92.

144. Westbrook C, Subramaniam T, Seagren RM, Tarula E, Co D, Furstenberg-Knauff M, et al. Febrile infection-related epilepsy syndrome treated successfully with anakinra in a 21-year-old woman. WMJ. 2019;118:135–9.

145. Mochol M, Tauboll E, Sveberg L, Tennoe B, Berg Olsen K, Heuser K, et al. Seizure control after late introduction of anakinra in a patient with adult onset Rasmussen's encephalitis. Epilepsy Behav Rep. 2021;16:100462.

146. Stredny CM, Case S, Sansevere AJ, Son M, Henderson L, Gorman MP. Interleukin-6 blockade with tocilizumab in anakinra-refractory febrile infection-related Epilepsy syndrome (FIRES). Child Neurology Open. 2020;7:2329048X20979253.

147. Yamaguchi Y, Furukawa K, Yamamoto T, Takahashi Y, Tanaka K, Takahashi M. Multifocal encephalopathy and autoimmune-mediated limbic encephalitis following tocilizumab therapy. Intern Med. 2014;53:879–82.

148. Randell RL, Adams AV, van Mater H. Tocilizumab in refractory autoimmune encephalitis: a series of pediatric cases. Pediatr Neurol. 2018;86:66–8.

149. Lee WJ, Lee ST, Shin YW, Lee HS, Shin HR, Kim DY, et al. Teratoma removal, steroid, IVIG, rituximab and tocilizumab (T-SIRT) in anti-NMDAR encephalitis. Neurotherapeutics. 2021;18:474–87.

150. Lee WJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, et al. Tocilizumab in autoimmune encephalitis refractory to rituximab: an institutional cohort study. Neurotherapeutics. 2016;13:824–32.

151. Benucci M, Tramacere L, Infantino M, Manfredi M, Grossi V, Damiani A, et al. Efficacy of tocilizumab in limbic encephalitis with anti-CASPR2 antibodies. Case Rep Neurol Med. 2020;2020:5697670.

152. Osminina M, Geppe N, Afonina E. Scleroderma "en coup de sabre" with Epilepsy and uveitis successfully treated with tocilizumab. Reumatologia Clinica. 2020;16:356–8.

153. Leo A, Nesci V, Tallarico M, Amodio N, Gallo Cantafio EM, de Sarro G, et al. IL-6 receptor blockade by tocilizumab has anti-absence and anti-epileptogenic effects in the WAG/Rij rat model of absence Epilepsy. Neurotherapeutics. 2020;17:2004–14.

154. Cantarin-Extremera V, Jimenez-Legido M, Duat-Rodriguez A, Garcia-Fernandez M, Ortiz-Cabrera NV, Ruiz-Falco-Rojas ML, et al. Tocilizumab in pediatric refractory status epilepticus and acute epilepsy: Experience in two patients. J Neuroimmunol. 2020;340:577142.

155. Zhu Y, Gou H, Ma L, Sun J, Hou Y, Li Y, et al. Effects of double-dose statin therapy for the prevention of post-stroke epilepsy: A prospective clinical study. Seizure. 2021;88:138–42.

156. Fang J, Tuo M, Ouyang K, Xu Y. Statin on post-stroke epilepsy: a systematic review and meta-analysis. J Clin Neurosci. 2021;83:83–7.

157. Zhao T, Ding Y, Feng X, Zhou C, Lin W. Effects of atorvastatin and aspirin on post-stroke epilepsy and usage of levetiracetam. Medicine. 2020;99:e23577.

158. Etminan M, Samii A, Brophy JM. Statin use and risk of epilepsy: a nested case-control study. Neurology. 2010;75:1496–500.

159. Xu T, Wang Y, Yuan J, Chen Y, Luo H. Statin use and the risk of post-stroke seizures: a meta-analysis. Seizure. 2020;83:63–9.

160. Liu Z, Li J, Yang F, Hu Y, Liu J, Hu H, et al. Sodium valproate combined with levetiracetam in pediatric epilepsy and its influence on NSE, IL-6, hs-CRP and electroencephalogram improvement. Exp Ther Med. 2020;20:2043–8.

161. Lagarde S, Villeneuve N, Trebuchon A, Kaphan E, Lepine A, McGonigal A, et al. Anti-tumor necrosis factor alpha therapy (adalimumab) in Rasmussen's encephalitis: an open pilot study. Epilepsia. 2016;57:956–66.

162. Akyuz E, Kullu I, Arulsamy A, Shaikh MF. Melatonin as an antiepileptic molecule: therapeutic implications via neuroprotective and inflammatory mechanisms. ACS Chem Neurosci. 2021;12:1281–92.

163. French JA, Cole AJ, Faught E, Theodore WH, Vezzani A, Liow K, et al. Safety and efficacy of Nataluzimab as adjunctive therapy for people with drug-resistant Epilepsy: a phase 2 study. Neurology. 2021;97(18):e1757–67.

164. Nosadini M, Thomas T, Eyre M, Anlar B, Armangue T, Benseler SM, et al. International consensus recommendations for the

treatment of pediatric NMDAR antibody encephalitis. Neurol Neuroimmunol Neuroinflamm. 2021;8(5):e1052.

165. Nosadini M, Eyre M, Molteni E, Thomas T, Irani SR, Dalmau J, et al. Use and safety of immunotherapeutic management of N-methyl-d-aspartate receptor antibody encephalitis: a meta-analysis. JAMA Neurol. 2021;78:1333–44.

166. Day AM, Hammill AM, Juhasz C, Pinto AL, Roach ES, McCulloch CE, et al. Hypothesis: presymptomatic treatment of Sturge-Weber syndrome with aspirin and antiepileptic drugs may delay seizure onset. Pediatr Neurol. 2019;90:8–12.

167. Sanghvi J, Mehta S, Mulye S. Paroxysmal vascular events in Sturge-weber syndrome: role of aspirin. J Pediatr Neurosci. 2014;9:39–41.

168. Triana Junco PE, Sanchez-Carpintero I, Lopez-Gutierrez JC. Preventive treatment with oral sirolimus and aspirin in a newborn with severe Sturge-weber syndrome. Pediatr Dermatol. 2019;36:524–7.

169. Lance EI, Sreenivasan AK, Zabel TA, Kossoff EH, Comi AM. Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes Journal of child neurology. 2013;28:213–8.

170. Bay MJ, Kossoff EH, Lehmann CU, Zabel TA, Comi AM. Survey of aspirin use in Sturge-Weber syndrome. J Child Neurol. 2011;26:692–702.

171. Nagib MM, Yu Y, Jiang J. Targeting prostaglandin receptor EP2 for adjunctive treatment of status epilepticus. Pharmacol Ther. 2020;209:107504.

172. Godfred RM, Parikh MS, Haltiner AM, Caylor LM, Sepkuty JP, Doherty MJ. Does aspirin use make it harder to collect seizures during elective video-EEG telemetry? Epilepsy Behav. 2013;27:115–7.

173. Morris G, O'Brien D, Henshall DC. Opportunities and challenges for microRNA-targeting therapeutics for epilepsy. Trends Pharmacol Sci. 2021;42:605–16.

174. Nishibori M, Mori S, Takahashi HK. Anti-HMGB1 monoclonal antibody therapy for a wide range of CNS and PNS diseases. J Pharmacol Sci. 2019;140:94–101.

175. Agarwal S, Vyas P, Nirwan N, Vohora D. Effect of lacosamide on neuroinflammation-mediated seizures comorbid with depression in C57BL/6 mice- role of kynurenine pathway. Epilepsy Behav. 2021;123:108262.

176. Torun IE, Kilinc YB, Kilinc E. Endogenous and exogenous serotonin, but not sumatriptan, ameliorate seizures and neuroinflammation in the pentylenetetrazole-induced seizure model in rats. Arq Neuropsiquiatr. 2022;80:48–55.

177. Bortoletto R, Balestrieri M, Bhattacharyya S, Colizzi M. Is it time to test the antiseizure Potential of Palmitoylethanolamide in human studies? A Systematic Review of Preclinical Evidence. Brain Sci. 2022;12:101.

178. Singh T, Thapliyal S, Bhatia S, Singh V, Singh M, Singh H, et al. Reconnoitering the transformative journey of minocycline from an antibiotic to an antiepileptic drug. Life Sci. 2022 Mar;293:120346.

179. Salam MT, Mirzaei M, Ly MS, Nguyen DK, Sawan M. An implantable closedloop asynchronous drug delivery system for the treatment of refractory epilepsy. IEEE Trans Neural Syst Rehabil Eng. 2012;20:432–42.

180. Amsen D, de Visser KE, Town T. Approaches to determine expression of inflammatory cytokines. Methods Mol Biol. 2009;511:107–42.

181. Numis AL, Fox CH, Lowenstein DJ, Norris PJ, Di Germanio C. Comparison of multiplex cytokine assays in a pediatric cohort with epilepsy. Heliyon. 2021;7:e06445.

182. Hao Z, Wang Z, Li Y, Zhu Y, Wang X, De Moraes CG, et al. Measurement of cytokine biomarkers using an aptamer-based affinity graphene nanosensor on a flexible substrate toward wearable applications. Nanoscale. 2018;29(10):21681–8.

183. Letchumanan I, Arshad MKM, SCB G. Nanodiagnostic attainments and clinical perspectives on C-reactive protein: cardiovascular disease risks assessment. Curr Med Chem. 2020;28(5):986–1002.

184. Poudineh M, Maikawa CL, Ma EY, Pan J, Mamerow D, Hang Y, et al. A fluorescence sandwich immunoassay for the real-time continuous detection of glucose and insulin in live animals. Nat Biomed Eng. 2021;5:53–63.

185. Ghasemi A, Akbari E, Imani R. An overview of engineered hydrogel-based biomaterials for improved beta-cell survival and insulin secretion. Front Bioeng Biotechnol. 2021;9:662084.

186. Risvoll GB, Thorsen K, Ruoff P, Drengstig T. Variable setpoint as a relaxing component in physiological control. Physiol Rep. 2017;5:e13408.

187. Liu G, Xiao R, Xu L, Cai J. Minireview of Epilepsy detection techniques based on electroencephalogram signals. Front Syst Neurosci. 2021;15:685387.

188. Dave D, Erraguntla M, Lawley M, DeSalvo D, Haridas B, McKay S, et al. Improved low-glucose predictive alerts based on sustained hypoglycemia: model development and validation study. JMIR Diabetes. 2021;29(6):e26909.

189. Kodama S, Fujihara K, Shiozaki H, Horikawa C, Yamada MH, Sato T, et al. Ability of current machine learning algorithms to predict and detect hypoglycemia in patients with diabetes mellitus: meta-analysis. JMIR diabetes. 2021;6(1):e22458.

190. Luan S, Schooler LJ, Gigerenzer G. A signal-detection analysis of fast-and-frugal trees. Psychol Rev. 2011;118:316–38.

191. Basu T, Maguire J, Salpekar JA. Hypothalamic-pituitary-adrenal axis targets for the treatment of epilepsy. Neurosci Lett. 2021;746:135618.

192. Nabavi Nouri M, Zak M, Jain P, Whitney R. Epilepsy Management in Tuberous Sclerosis Complex: existing and evolving therapies and future considerations. Pediatr Neurol. 2022;126:11–9.

193. Koh S, Dupuis N, Auvin S. Ketogenic diet and neuroinflammation. Epilepsy Res. 2020;167:106454.

194. Aronica E, Bauer S, Bozzi Y, Caleo M, Dingledine R, Gorter JA, et al. Neuroinflammatory targets and treatments for epilepsy validated in experimental models. Epilepsia. 2017;58(Suppl 3):27–38.

195. Rodriguez-Acevedo AJ, Gordon LG, Waddell N, Hollway G, Vadlamudi L. Developing a gene panel for pharmacoresistant epilepsy: a review of epilepsy pharmacogenetics. Pharmacogenomics. 2021;22:225–34.

196. Xu C, Gong Y, Wang Y, Chen Z. New advances in pharmacoresistant epilepsy towards precise management-from prognosis to treatments. Pharmacol Ther. 2021;28:108026.

197. Loscher W, Potschka H, Sisodiya SM, Vezzani A. Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. Pharmacol Rev. 2020;72:606–38.

198. Bourgeois-Tardif S, De Beaumont L, Rivera JC, Chemtob S, Weil AG. Role of innate inflammation in traumatic brain injury. Neurol Sci. 2021;42:1287–99.

199. Macdonald TT. Inside the microbial and immune labyrinth: totally gutted. Nat Med. 2010;16:1194–5.

200. Nailwal NP, Doshi GM. Role of intracellular signaling pathways and their inhibitors in the treatment of inflammation. Inflammopharmacology. 2021;29:617–40.

201. Zarrin AA, Bao K, Lupardus P, Vucic D. Kinase inhibition in autoimmunity and inflammation. Nat Rev Drug Discov. 2021;20:39–63.

202. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21:677–87.

203. Shi X, Tan S. NLRP3 inflammasome in sepsis (review). Mol Med Rep. 2021 Jul;24:514.

204. Wu D, Chen Y, Sun Y, Gao Q, Li H, Yang Z, et al. Target of MCC950 in inhibition of NLRP3 inflammasome activation: a literature review. inflammation. 2020;43:17–23.

205. Dinarello CA. Treatment of Inflammatory Diseases with IL-1 Blockade. Curr Otorhinolaryngol Rep. 2018;6:1–14.

206. Simonato M, Agoston DV, Brooks-Kayal A, Dulla C, Fureman B, Henshall DC, et al. Identification of clinically relevant biomarkers of epileptogenesis - a strategic roadmap. Nat Rev Neurol. 2021;17:231–42.