



Idiopathic Generalized Epilepsy Ictogenesis and Epileptogenesis: a Cross-disciplinary Discussion from Molecule to Human Brain

American Epilepsy Society Annual Meeting 2008
Investigators' Workshop
Seattle, WA
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- [Comments and Discussion page](#) link to [AES2008 Idiopathic Generalized Epilepsy IW](#) group on Facebook. Facebook username needed, but free to join.
 - ☐ Provide feedback on the workshop
 - ☐ Continue the scientific discussion
- [American Epilepsy Society](#) home page and link to annual meeting

Investigators' Workshop Abstract

This session is designed to be a participatory workshop focused on addressing questions of ictogenesis and epileptogenesis in idiopathic generalized epilepsy (IGE) via a cross-disciplinary approach. Four investigators from the fields of molecular neuroscience, thalamocortical network physiology, transgenic animal physiology/behavior, and human/animal neuroimaging will serve as workshop speakers. To provide a basis for discussion, the speakers will use the first half of their presentation time to describe the relevant work from their respective laboratories. In the second half of their allotted presentation time, the speakers and workshop attendees will discuss how the results obtained in the speaker's experimental system address questions of IGE ictogenesis and epileptogenesis and complement the work done in other experimental systems. Participants will also use this time to "workshop" new experiments that could be performed within the speaker's area of scientific expertise that would answer questions deemed important to IGE investigators from all disciplines.

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Workshop Speakers

speaker	title	background references suggested by speaker
 <u>Martin J. Gallagher MD, PhD</u>	workshop coordinator	N/A
 <u>Robert L. Macdonald MD, PhD</u>	GABA _A Receptor Mutations and IGEs	<p>Kang,J. and Macdonald, RL, (2004), The GABA_A receptor γ2 subunit R43Q mutation linked to childhood absence epilepsy and febrile seizures causes retention of α1β2γ2S receptors in the endoplasmic reticulum, <u>J Neurosci</u>, 8672-7</p> <p>Feng H-J, Kang J-Q, Song L and Macdonald RL, (2006), The δ subunit susceptibility variants E177A and R220H associated with complex epilepsy alter channel gating and cause endoplasmic reticulum retention of α4β2δ GABA_A receptors. <u>J Neurosci</u>, 1499-1506</p> <p>Gallagher, MJ, Ding, L, Maheshwari, A, and Macdonald, RL, (2007), The GABA_A receptor α1 subunit epilepsy mutation A322D inhibits transmembrane helix formation and causes proteasomal degradation, <u>Proc Natl Acad Sci USA</u>,12999-13004</p>
 <u>John R. Huguenard, PhD</u>	Circuits and Receptors Underlying Absence Seizures	<p>Beyer, B, Deleuze, C, Letts, VA, Mahaffey,CL, Boumil, RM, Lew, T, Huguenard, JR & Frankel, WN, (2008), Absence seizures in C3H/HeJ and knockout mice caused by mutation of the AMPA receptor subunit Gria4. <u>Hum Mol Genet.</u>, 1738-49</p> <p>Huguenard JR, McCormick DA, (2007), Thalamic synchrony and dynamic regulation of global forebrain oscillations. <u>Trends Neurosci</u>, 350-6</p>
 <u>Steven Petrou, PhD</u>	Mouse Models of Familial Epilepsy – a Genes to Behaviour Perspective	<p>Tan HO, Reid CA, Single FN, Davies PJ, Chiu C, Murphy S, Clarke AL, Dibbens L, Krestel H, Mulley JC, Jones MV, Seeburg PH, Sakmann B, Berkovic SF, Sprengel R, Petrou S, (2007), Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy <u>Proc Natl Acad Sci U S A</u>, 17536-41</p> <p>Chiu C, Reid CA, Tan HO, Davies PJ, Single FN, Koukoulas I, Berkovic SF, Tan SS, Sprengel R, Jones MV, Petrou S, (2008), Developmental impact of a familial GABA_A receptor epilepsy mutation, <u>Ann Neurol</u>, 284-93</p>



Hal Blumenfeld MD, PhD

Neuroimaging and IGE:
from Animal Models to Human Patients

Nersesyan H, Hyder F, Rothman D, Blumenfeld H, (2004), Dynamic fMRI and EEG recordings during spike-wave seizures and generalized tonic-clonic seizures in WAG/Rij rats, J Cereb Blood Flow Metab, 589-99.

Blumenfeld H, Klein JP, Schridde U, Vestal M, Rice T, Khera DS, Bashyal C, Giblin K, Paul-Laughinghouse C, Wang F, Phadke A, Mission J, Agarwal RK, Englot DJ, Motelow J, Nersesyan H, Waxman SG, Levin AR, (2008), Early treatment suppresses the development of spike-wave epilepsy in a rat model. Epilepsia,, 400-9

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Summary of Workshop Discussion

I would really like to thank all the speakers for their efforts. I was really pleased with the content of the talks and with the discussion. It is very difficult to have a true workshop in such a large meeting room. Nonetheless, I think it worked out pretty well. As would be expected, there were many specific questions that pertained directly to the individual talks. However there were several workshop-like ideas that developed and I'll list a few of them here. So I don't overburden our web guru, Dr. John Fang, with endless updates to this page (thanks for your help, John!) I'll defer most of the commentary to the Comments and Discussion page.

- √ Utilizing molecular neuroscience techniques to probe one of the surprising results observed in the knock-in mice.
 - ∅ How do missense mutations in epilepsy genes alter targeting of the affected protein to the axon initial segment? Would this occur in neuronal culture? Perhaps we can overexpress recombinant and appropriately tagged or chimeric wild type or mutant protein in neurons and determine the domains/binding partners of the wild type and mutant proteins.
- √ Testing the effect of augmented AMPAergic signaling in stargazin and Gria4 mice using behavioral and EEG data
 - ∅ What would be the effect of administering AMPAergic drugs? Would they augment cognition? Would they be pro-convulsant?
- √ Using fMRI/ DTI to explore connectivity in monogenic epilepsy
 - ∅ It is of interest. DTI has been done in mice. fMRI is a little more difficult due to mouse anesthesia.
- √ Utilizing molecular techniques with thalamocortical recordings to determine distribution of AMPA receptor compensation.
 - ∅ EM is definitely of interest. Molecular studies are also planned to determine the mechanism of compensation.

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