

NORSE Bulletin

Vol 2, Issue 1 February 2021

Funding opportunity: 2021 AES-NORSE Institute Seed Grant (deadline: March 24, 2021)
The NORSE Institute seeks to support research related to the etiology of NORSE (including its subset, FIRES) and comparisons of treatment efficacy, especially immune treatments, in patients of all ages. Because the grant is fully funded by the NORSE Institute, eligibility is expanded to include investigators at all stages of their careers. International investigators are welcome to apply. More information is available on the [AES Seed Grant Program page](#). Direct questions on submission requirements, etc. to grants@aesnet.org.

Access to remaining samples obtained as part of the CCEMRC NORSE study may be possible. Please direct sample queries to Lawrence J. Hirsch (lawrence.hirsch@yale.edu) before application is submitted to AES.

New and Ongoing Research

Recipient, Fall 2020 AES-NORSE Institute Seed Grant

In vitro model of FIRES for rapid selection of clinically effective drugs

Principal Investigator and Contact: Annamaria Vezzani, PhD, Laboratory Experimental Neurology, Head, Dept of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy. annamaria.vezzani@marionegri.it

In this proposal, we aim at refining and validating an in vitro slice model of acute seizures that rapidly progresses in a crescendo-like pattern to refractory status epilepticus with minimal or no response to conventional anti-seizure medications. Our intent is to set up a model for rapidly testing and selecting novel or repurposed drugs with potential therapeutic effect for stopping acute unremitting seizures in FIRES. This model will facilitate treatment's clinical translation.

Although the exact pathogenesis of FIRES remains elusive, experimental and clinical evidence strongly support the involvement of a dysregulated innate immune activation, triggered by the preceding febrile infection and leading to an unopposed pathological inflammatory state in the brain. This phenomenon may contribute to acute unremitting seizures in FIRES therefore promoting disease progression. Our in vitro model includes this critical inflammatory component and the refractory status epilepticus in a simplified system.

Specifically, we will determine (1) whether neuroinflammation induced by lipopolysaccharide (LPS) application to acute mouse temporal cortex-hippocampal slices exacerbates seizures and epileptiform discharges induced by zero (0)Mg²⁺ plus 4-aminopyridine (4-AP, a K⁺ channel blocker) in artificial CSF. (2) The 0Mg²⁺/4-AP model induces early recurrent seizure-like events (SLEs) sensitive to anti-seizure medications and late recurrent discharges (LRDs) that typically do not respond to anti-seizure medications. We will test whether neuroinflammation increases refractoriness to anti-seizure medications by converting drug-sensitive SLEs into drug-resistant events, and by inducing refractory status epilepticus. (3) We will assess if drug-resistant epileptiform activity in LPS+0Mg²⁺/4-AP slices is reduced by immunomodulatory drugs recently proven effective in some FIRES patients. If successful, this model will provide a new tool for fast selection of new treatments and identification of candidate molecular targets for controlling acute unremitting seizures in FIRES.

Virtual NORSE Scientific Symposium and Family Conference

Scientific Symposium on Neuro-Inflammation in NORSE and Related Conditions

Thursday, March 4, 2021

10:00 am – 12:30 pm Eastern Time

Target audience: Scientists and Clinicians

[Click here](#) to register in advance for the scientific symposium

Agenda

- 10:00 - 10:10 Introduction: Nicolas Gaspard MD, PhD (Université Libre de Bruxelles Hôpital Erasme) Nora Wong PhD (NORSE Institute) Lawrence Hirsch MD (Yale)
- 10:10 - 10:45 **Overview of what we know about inflammation in NORSE/FIRES:**
Annamaria Vezzani PhD (Mario Negri Institute) (25 min + 10 min Q&A)
- 10:45 - 11:20 **Single Cell RNA Sequencing: An Unbiased tool for Pathologic Characterization of Human Inflammatory Disease at a Molecular Level:**
David Hafler MD (Yale) (25 min + 10 min Q&A)
- 11:20 - 11:30 10-minute break
- 11:30 - 12:10 Data blitz/current related projects: 10 min each (7 min + 3 min Q/A)
Charles L. Howe PhD (Mayo Clinic) Insights from Immuno-profiling
Sookyong Koh MD, PhD (Emory --> U. Nebraska) Working towards Novel Murine Models of FIRES/NORSE
Olga Taraschenko MD, PhD (U. Nebraska) The future of interleukin-based therapies for NORSE: anakinra-loaded nanoparticles
Michael Wilson MD (UCSF) Insights from metagenomics and antibody screening

12:10 - 12:25 Discussion: 15 mins

12:25 - 12:30 Closing remarks: Lawrence Hirsch MD

*See articles relevant to Vezzani – Hafler talk on page 5.

One hour break: Family Conference begins. **Use Family Conference registration link below.*

Family Conference: What Happened – The Who, What, and Why of NORSE and FIRES

Thursday, March 4, 2021

1:30 pm - 3:45 pm Eastern Time

Target audience: Patients/Families, Clinicians and Scientists

[Click here](#) to register in advance for the Family Conference meeting

Agenda

1:30 - 1:40 Introduction to the NORSE Institute and Family Registry: Nora Wong PhD (NORSE Institute)

1:40 - 1:50 Current definition of NORSE and FIRES: Lawrence Hirsch MD (Yale)

1:50 - 2:05 Who gets NORSE and FIRES and what are the causes? Coral Stredny MD (Boston Children's Hospital)

2:05 - 2:20 Why do people die from NORSE and FIRES? Olga Taraschenko MD, PhD (U. Nebraska) and Sookyong Koh MD, PhD (Emory --> U. Nebraska)

2:20 - 2:35 The role of inflammation and emerging treatment options for NORSE and FIRES: Eric Payne MD (Alberta Children's Hospital, Canada)

2:35 - 2:45 Panel Question and Answer

2:45 - 2:55 Break

Doctor-Family-Patient Communication

2:55 - 3:10 Challenges in communication during times of uncertainty: Teneille Gofton MD (Western University, Canada)

3:10 - 3:25 How physicians can improve – Personal communication experiences.

Two family perspectives: Natalee Gibson and Jason Hallett

3:25 - 3:45 Breakout Sessions in groups of 10 people

Opportunity for feedback to physicians: How do families want information

communicated to them and what do families want physicians and scientists to study?

*Day 2 of Family Conference continues the next day.

Family Conference: Loss, Survival, and Hope

Friday, March 5, 2021

10:00 am– 12:30 pm Eastern Time

Target audience: Patients/Families, Clinicians and Scientists

[Click here](#) to register in advance for the Family Conference meeting

Agenda

- 10:00 - 10:05 Welcome: Nora Wong PhD (NORSE Institute)
- 10:05 - 10:20 What happens to people who survive? Krista Eschbach MD
(Children's Hospital Colorado)
- 10:20 - 10:35 Decision making and the role of Palliative Care: Teneille Gofton MD
(Western University, Canada)
- 10:35 - 10:50 Preparing for the future and discharge planning guide: Erica Sieg PsyD
(Northwestern)
- 10:50 - 11:00 10-minute break
- 11:00 - 11:30 Breakout Sessions: Resources and support moving forward
***Please identify which breakout session you will attend at time of registration.**

1. Parents of children who survived NORSE / FIRES
 - o Moderators: Raquel Farias-Moeller MD (Medical College of Wisconsin) and Coral Stredny
2. Adult survivors and their adult family members
 - o Moderators: Erica Sieg and Lawrence Hirsch
3. Resources and support for bereavement
 - o Moderators: Teneille Gofton and Kellie Jankowski (Epilepsy Foundation)
4. Support for children / teens / young adults (siblings and children of those affected by NORSE / FIRES)
 - o Moderator: Lauren Treat MD (Children's Hospital Colorado)

- 11:30 - 11:40 Summary of Breakout Sessions
Primary moderator from each session to give overview
- 11:40 - 12:15 Current and Emerging Research
Nicolas Gaspard MD, PhD (Université Libre de Bruxelles – Hôpital Erasme, Belgium)
Multi-center NORSE study
Teneille Gofton MD Family Registry
Sookyong Koh MD PhD (Emory --> U. Nebraska) and Olga Taraschenko MD PhD
(U. Nebraska) Basic research in NORSE
Lawrence Hirsch MD Biorepository
- 12:15 - 12:30 Final discussion and questions – Goals for the Future
Moderator: Krista Eschbach MD

Questions: Contact Yashwanth Pulluru
yashwanth.pulluru@yale.edu

NORSE Family Registry - Spanish and French translations about to launch.

Principal Investigator and Contact: Teneille Gofton, MD (Western University, London, Ontario, Canada) Teneille.gofton@lhsc.on.ca

Co-investigators: Nicolas Gaspard, MD, PhD (Erasmie Hospital, Brussels) Lawrence J. Hirsch, MD (Yale) Marissa Kellogg, MD (OHSU) Sara Hocker, MD (Mayo Clinic)

Project coordinator: Karnig Kazazian, karnig.kazazian@lhsc.on.ca

The goal of the NORSE Family Registry is to build a broader understanding of the patient profile, trajectories and outcomes of NORSE. Survivors, substitute/surrogate decision makers or physicians (with patient/SDM permission) can enter data directly into this international, online registry using REDCap. Variables include demographics, past medical history, types of investigations and treatments during the acute phase, and clinical and quality of life outcomes in the acute and post-acute phases. Access through the [NORSE Institute website](#).

Articles relevant to scientific symposium:

Pappalardo JL, Zhang L, Pecsok MK, Perlman K, Zografou C, Raddassi K, Abulaban A, Krishnaswamy S, Antel J, van Dijk D, Hafler DA. **Transcriptomic and clonal characterization of T cells in the human central nervous system.** Sci Immunol. 2020 Sep 18;5(51):eabb8786. doi: 10.1126/sciimmunol.abb8786. PMID: 32948672.

Vezzani A, Balosso S, Ravizza T. **Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy.** Nat Rev Neurol. 2019 Aug;15(8):459-472. doi: 10.1038/s41582-019-0217-x. Epub 2019 Jul 1. PMID: 31263255.

Vezzani A, Dingledine R, Rossetti AO. **Immunity and inflammation in status epilepticus and its sequelae: possibilities for therapeutic application.** Expert Rev Neurother. 2015;15(9):1081-92. doi: 10.1586/14737175.2015.1079130. PMID: 26312647; PMCID: PMC4767891.

van Baalen A, Vezzani A, Häusler M, Kluger G. **Febrile Infection-Related Epilepsy Syndrome: Clinical Review and Hypotheses of Epileptogenesis.** Neuropediatrics. 2017 Feb;48(1):5-18. doi: 10.1055/s-0036-1597271. Epub 2016 Dec 5. PMID: 27919115.

Koh S, Wirrell E, Vezzani A et al. **Proposal to optimize evaluation and treatment of Febrile infection-related epilepsy syndrome (FIRES): A Report from FIRES workshop.** Epilepsia Open. First published: 20 November 2020 <https://doi.org/10.1002/epi4.12447>

Recommended by Our Readers

Lai YC, Muscal E, Wells E, Shukla N, Eschbach K, Hyeong Lee K, Kaliakatsos M, Desai N, Wickström R, Viri M, Freri E, Granata T, Nangia S, Dilena R, Brunklaus A, Wainwright MS, Gorman MP, Stredny CM, Asiri A, Hundallah K, Doja A, Payne E, Wirrell E, Koh S, Carpenter JL, Riviello J. **Anakinra usage in febrile infection related epilepsy syndrome: an international cohort.** Ann Clin Transl Neurol. 2020 Dec;7(12):2467-2474. doi: 10.1002/acn3.51229. Epub 2020 Dec 4. PMID: 33506622; PMCID: PMC7732241.

Taraschenko O, Fox H, Zekeridou A, Pittock S, Eldridge E, Farukhuddin F, Al-Saleem F, Devi Kattala C, Dessain S, Casale G, Willcockson G and Dingleline R, **Seizures and memory impairment induced by patient-derived anti-NMDA receptor antibodies in mice are attenuated by anakinra, an interleukin-1 receptor antagonist**
Epilepsia, in press

Horino A, Kuki I, Inoue T, Nukui M, Okazaki S, Kawawaki H, Togawa M, Amo K, Ishikawa J, Ujiro A, Shiomi M, Sakuma H. **Intrathecal dexamethasone therapy for febrile infection-related epilepsy syndrome.** Ann Clin Transl Neurol. 2021 Feb 5. doi: 10.1002/acn3.51308. Online ahead of print. <https://onlinelibrary.wiley.com/doi/10.1002/acn3.51308>

Kim HJ, Lee SA, Kim HW, Kim SJ, Jeon SB, Koo YS. **The timelines of MRI findings related to outcomes in adult patients with new-onset refractory status epilepticus.** Epilepsia. 2020 Aug;61(8):1735-1748. doi: 10.1111/epi.16620. Epub 2020 Jul 27. PMID: 32715470.

Tan TH, Perucca P, O'Brien TJ, Kwan P, Monif M. **Inflammation, ictogenesis, and epileptogenesis: An exploration through human disease.** Epilepsia. 2020 Dec 14. doi: 10.1111/epi.16788. Epub ahead of print. PMID: 33316111.

Matthews E, Alkhachroum A, Massad N, Letchinger R, Doyle K, Claassen J, Thakur KT. **New-onset super-refractory status epilepticus: A case series of 26 patients.** Neurology. 2020 Oct 20;95(16):e2280-e2285. doi: 10.1212/WNL.0000000000010787. Epub 2020 Sep 17. PMID: 32943479; PMCID: PMC7713780.

Dono F, Carrarini C, Russo M, De Angelis MV, Anzellotti F, Onofri M, Bonanni L., **New-onset refractory status epilepticus (NORSE) in post SARS-CoV-2 autoimmune encephalitis: a case report.** Neurol Sci. 2021 Jan;42(1):35-38. doi: 10.1007/s10072-020-04846-z. Epub 2020 Nov 3. PMID: 33145624; PMCID: PMC7608104.

Resources for your patients and families

- **NORSE and FIRES in plain English:** Families can hear a September 2020 podcast done with ILAE that features Dr Lawrence Hirsch and Dr Nicolas Gaspard discussing NORSE awareness and research.
<https://www.newswise.com/articles/new-onset-refractory-status-epilepticus-norse-awareness-and-research>
- **An updated report for the lay reader:** Written by Dr Nicolas Gaspard and Dr Lawrence Hirsch and posted on NORD's website Oct 2020:
<https://rarediseases.org/rare-diseases/new-onset-refractory-status-epilepticus-norse/>.
- **A 2020 discharge planning guide:** Written by neuropsychologist, Dr. Erica Sieg,
<http://www.norseinstitute.org/discharge-planning-guide>
- **An explanation of our online NORSE Family Registry.**
<http://www.norseinstitute.org/norse-registry-2>